THIRTEENTH EDITION

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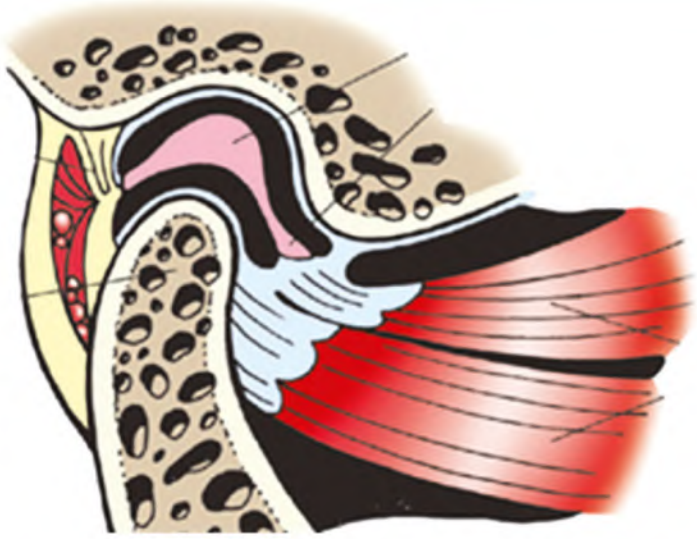
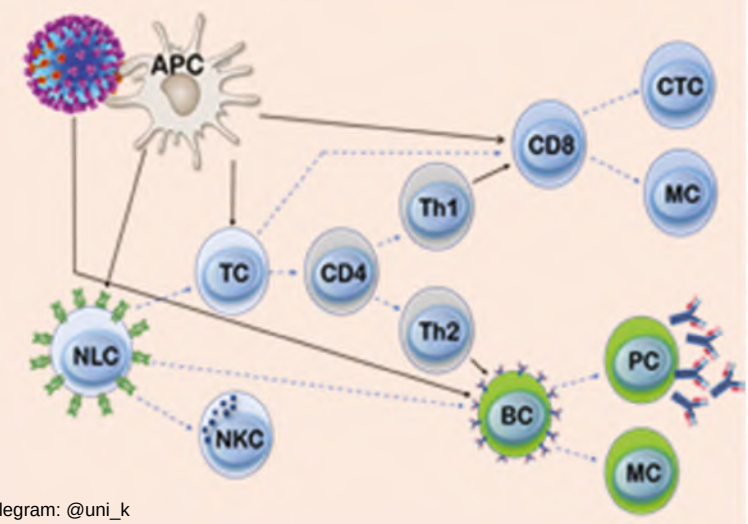
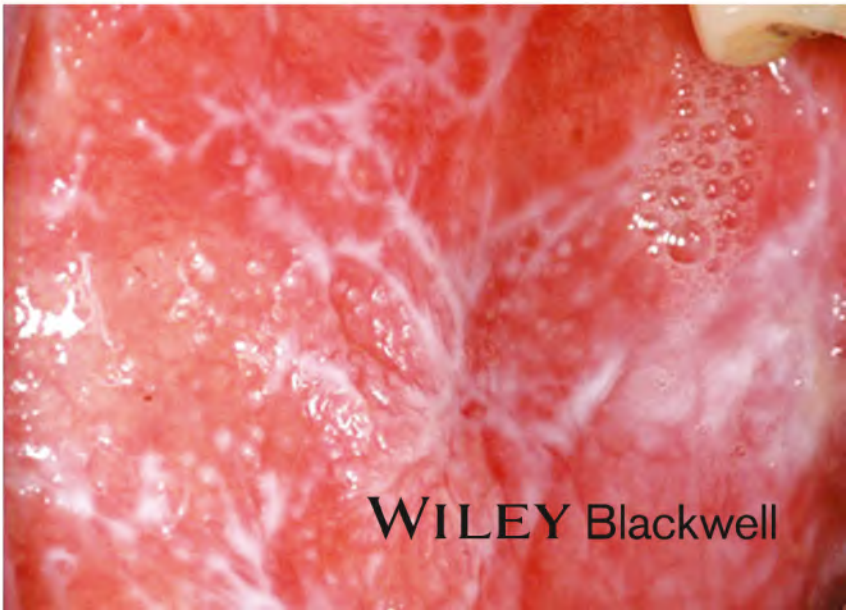


BURKET'S ORAL MEDICINE





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Burket's Oral Medicine

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Thirteenth Edition

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Lester W. Burket DDS, MD
1907–1991

Dr. Lester W. Burket, widely considered the father of Oral Medicine, wrote the first edition of this groundbreaking text, Oral Medicine Diagnosis and Treatment, published in 1946.

Dr. Burket was trained in dentistry at the University of Pennsylvania and medicine at Yale. He was one of the first to stress the importance of the knowledge of medicine to the practice of dentistry, the role dentists could play in the diagnosis and management of diseases of the mouth and jaws, and the benefit to patients from close collaboration of dentists and physicians.

In addition to his devotion to teaching, he founded the Department of Oral Medicine at the School of Dental Medicine at the University of Pennsylvania, and served as Department Chair from 1944 to 1972, while also serving as Dean of the dental school from 1951 to 1972.

Dr. Burket would be pleased to see the scope of the present text as well as the international group of authors writing the thirteenth edition of his classic text.

"The good physician treats the disease; the great physician treats the patient who has the disease."

Sir William Osler

We have found Oral Medicine to be an extraordinarily rewarding career, and for this we are grateful to the pioneers of the field for their vision, creativity, and dedication to their work. They established oral medicine as a specialty at the interface of dentistry and medicine, and we owe them a huge debt. It is therefore to Lester Burket and the other leaders of the past in academics, clinical practice, and research who mentored and guided us that we dedicate this book. We also dedicate it to current and future practitioners of Oral Medicine around the world who share our professional fulfillment in this developing specialty, and especially to our families who have supported us throughout the years.

Michael Glick
Martin S. Greenberg
Peter B. Lockhart
Stephen J. Challacombe

Contents

Preface

It is with great pleasure that we share this thirteenth edition of the classic text *Burket's Oral Medicine* with students, residents, and professional colleagues around the world. This edition reflects the scope of modern oral medicine in both the content and the international nature of many new contributors.

Two experienced editors with international reputations for clinical and academic excellence, Dr. Peter Lockhart and Dr. Stephen Challacombe, have been added as Editors to this new edition, which has contributed to expanding the scope of the text and the diversity of the authors.

As the volume and availability of both basic and clinical biomedical information are growing at an ever-increasing pace, we realize that today's students, teachers, and practitioners of oral medicine must broaden the scope of their knowledge to increase their competence as clinicians, academics, and researchers. The chapters from the 12th edition describing oral mucosal and salivary gland disease, orofacial pain, TMD, and dental management of medically complex patients have been expanded and updated. In addition, the 13th edition contains chapters not found in traditional books in this discipline, including chapters on clinical research, pediatric oral medicine, psychiatry and psychology, geriatric oral medicine, laboratory medicine, and appraising and interpreting the biomedical literature.

With more than 80 authors from across the globe, we have broadened the scope and approach to ensure that this text is highly relevant to teaching and practice in many different countries and clinical settings.

Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe

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1

Introduction to Oral Medicine and Oral Diagnosis: Patient Evaluation

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Oral medicine, as defined by the American Academy of Oral Medicine, is "the specialty of dentistry responsible for the oral health care of medically complex patients and for the diagnosis and management of medically related disorders or conditions affecting the oral and maxillofacial region." Definitions vary in different parts of the world, but most include the diagnosis and nonsurgical management of oral mucosal and salivary gland disease, orofacial pain, and dental treatment of patients with medical disorders.

The overall goal for all oral healthcare professionals is to deliver and maintain optimal health for their patients. A recent definition was approved by the World Dental Parliament in 2016, which expanded the definition to include three different domains: disease and condition status, psychosocial status, and physiologic function.[1] The inclusion of a psychosocial status and physiologic function deviates from traditional definitions that mainly focused on the presence or absence of disease, and, further, it promotes the inclusion of patient values and preferences, as well as elevates the importance of subjective findings. This approach is more aligned with a person-centered care approach that emphasizes a patient's problem in the context of behavioral, socioeconomic, and environmental aspects, and their impact on the patient and on the care that needs to be delivered.[2–4] This definition has also been the underlying framework to establish outcomes that can be used to measure the oral status of an individual.[5]

Given the nature, complexity, and potential systemic implications for some oral conditions, coupled with an aging population with multimorbidities (multimorbidities do not identify an index disease, while comorbidities focus on an index disease and other diseases) and individuals taking numerous medications, all oral healthcare clinicians are required to enhance their knowledge of many aspects of medicine. Therefore, what previously was considered the purview of oral healthcare professionals with hospital-based

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training has become increasingly more important in general and specialty dental practice.

Advances in clinical practice are influencing many aspects of patient care, from our initial contact with a patient, through medical history-taking, diagnosis, and treatment options. For example, electronic health records (EHRs) allow for sharing health information among multiple clinicians caring for the same patient and can provide point-of-care algorithms for eliciting and using health information. Modern imaging techniques, such as computerized tomography scans (CTs) and magnetic resonance imaging (MRI), provide more detailed information and are a means to acquire more sophisticated data, but require enhanced training for accurate interpretation. Nevertheless, one of the most important skills for accurate diagnosis and management remains an experienced clinician with highly developed skills of listening and examination.

The initial encounter with a patient may influence all subsequent care. The skilled, experienced practitioner has learned to elicit the subjective (i.e., history-taking) and objective (e.g., clinical, laboratory) findings and other necessary information required for an accurate diagnosis. This process is an art, as well as a skill. Although mastering a patient evaluation can be assisted by specific clinical protocols, the experienced practitioner will add their own skills and experience to the diagnostic methodology.

A variety of accessible sources of healthcare information are now readily available to patients, and many will use this information to self-diagnose, as well as demand specific treatments. As a person-centered approach is encouraged, where a patient's preferences and values will influence care, the practitioner must listen to the patient to understand their needs, fears, and wishes and address them to arrive at an appropriate treatment plan that results in informed, scientific, and evidence-based choices. Furthermore, part of a shared decision-making approach includes the responsibility of the oral healthcare professional to educate their patient about the implications and consequences of a diagnosis and subsequent treatment. Creating an environment for effective communication between provider and patient has been shown to improve health outcomes.[6]

The process of obtaining, evaluating, and assessing a patient's oral and overall health status can arbitrarily be divided into seven major, sometimes overlapping, parts:

1) History and examination.
2) Establishing a differential diagnosis.
3) Obtaining necessary consultations, as well as appropriate laboratory tests, such as specific blood investigations, a biopsy, and imaging studies, all based upon the initial differential diagnosis.
4) Final diagnosis.
5) Formulating a plan of action.
6) Initiating treatment.
7) Follow-up assessment of response to treatment.

INFORMATION GATHERING

An appropriate interpretation of the information collected through a medical history and patient examination achieves several important objectives. It affords an opportunity for:

- Gathering the information necessary for establishing a diagnosis for the patient's chief complaint.
- Assessing the influence of the patient's systemic health on their oral health.
- Detecting other systemic health conditions of which the patient may not be aware.
- Providing a basis for determining whether dental treatment might impact the patient's systemic health.
- Giving a basis for determining necessary modifications to routine dental care.
- Monitoring medical conditions of relevance to the maxillofacial condition.

Medical History

Obtaining an appropriate and accurate medical history is a critical first step for all patient care. It begins with a systematic review of the patient's chief or primary complaint, a detailed history related to this complaint, information about past and present medical conditions, pertinent social and family histories, and a review of symptoms by organ system. A medical history also includes biographic and demographic data used to identify the patient.

There is no universally agreed method for obtaining a medical history, but a systematic approach will help the practitioner to gather all necessary information without overlooking important facts. The nature of the patient's oral health visit (i.e., initial dental visit, complex diagnostic problem, emergency, elective continuous care, or recall) often dictates how the history is obtained. The two most common means of obtaining initial patient information are a patient self-administered preprinted health questionnaire, or recording information during a systematic health interview without the benefit of having the patient fill out a questionnaire. The use of self-administered screening questionnaires is the most common method in dental settings. This technique can be useful in gathering background medical information, but the accurate diagnosis of a specific oral complaint requires a history of the present illness and other verbal information. While the basic information for a past medical history may be obtained by a questionnaire, a vital

part of the evaluation of a patient with a complex diagnostic problem is the history of the present illness, which is a combination of science and art and should be taken directly by the clinician.

The challenge in any healthcare setting is to use a questionnaire that has enough items to obtain the essential medical information, but is not too long to deter a patient's willingness and ability to fill it out. These questionnaires should be constructed in a manner that allows the clinician to query the patient about the most essential and relevant required information, yet provides a starting point for a dialogue with the patient about other pertinent information not included on the health form. Preprinted self-administered or online health questionnaires are readily available, standardized, and easy to administer and do not require significant "chair time." They give the clinician a starting point for a dialogue to conduct more in-depth medical queries, but are restricted to the questions chosen on the form and are therefore limited in scope. The questions on the form can be misunderstood by the patient, resulting in inaccurate information, and they require a specific level of reading comprehension. Preprinted forms cover broad areas without necessarily focusing on particular problems pertinent to an individual patient's specific medical condition. Therefore, the use of these forms requires that the provider has sufficient background knowledge to understand the reasons for the questions on the forms. Furthermore, the provider needs to realize that a given standard history form necessitates timely and appropriate follow-up questions, especially when positive responses have been elicited. An established routine for performing and recording the history and examination should be followed conscientiously.

The oral healthcare professional has a responsibility to obtain relevant medical and dental health information, yet the patient cannot always be relied upon to know this information or to provide an accurate and comprehensive assessment of their medical or dental status.

All medical information obtained and recorded in an oral healthcare setting is considered confidential and may in many jurisdictions constitute a legal document. Although it is appropriate for the patient to fill out a history form in the waiting room, any discussion of the patient's responses must take place in a private setting. Furthermore, access to the written or electronic (if applicable) record must be limited to personnel who are directly responsible for the patient's care. Any other release of private information should be approved, in writing, by the patient and that approval retained by the dentist as part of the patient's medical record.

Given that medical status and medication regimens often change, a patient's health status or medication regimen should be reviewed at each office visit prior to initiating dental care. The monitoring of patients' compliance with suggested medical treatment guidelines and prescribed medications is part of the oral healthcare professional's responsibilities. The following strategies are common to nearly all methods of history-taking:

- Review available patient information prior to meeting the patient.
- Greet the patient; use the patient's name; ensure privacy; sit rather than stand, preferably at eye level; maintain eye contact as often as possible; listen carefully to the patient's concerns; do not rush the interview process.
- Do not concentrate chiefly on entering the information into an electronic health record, as this may distract you from listening to pertinent information.
- Use the patient's own words (in quotation marks) to describe the primary reason(s) to seek care/consultation; i.e., be absolutely clear about the patient's chief complaint(s).
- Use open-ended questions to encourage open dialogue with the patient. Although all information should be collected in a systematic fashion, the order is not as important as is initiating a dialogue with the patient about their health.
- Create a timeline of the reported patient-related events. An accurate chronology is an extremely important element to establish or deny a causative relationship.

The medical history traditionally consists of the following subcategories:

- *Identification*—name, date and time of the visit, date of birth, gender, ethnicity, occupation, contact information of a primary care provider (physician and, if applicable, dentist), referral source.
- *Chief complaint (CC)*—the main reason for the patient seeking care or consultation and the length of time these symptoms have been present, recorded in the patient's own words.
- *History of present illness (HPI)*—taking an effective HPI takes experience and is often the key to making an accurate differential diagnosis. It includes a chronologic account of events; state of health before the presentation of the present problem; description of the first signs and symptoms and how they may have changed; description of occurrences of amelioration or exacerbation; previous clinicians consulted, prior treatment, and degree of the response to previous treatment. For those who favor mnemonics, the nine dimensions of a medical problem can be easily recalled using OLD CHARTS (Onset, Location/radiation, Duration, Character, Habits, Aggravating factors, Reliving factors, Timing, and Severity).[7]
- *Review of systems (ROS)*—identifies symptoms in different body systems (Table 1-1). The ROS is a comprehensive and systematic review of *subjective* symptoms affecting different bodily systems. It is an essential component for

Table 1-1 Review of Systems (ROS): A systematic approach to ascertain mostly subjective symptoms associated with the different body systems.

General: Weight changes, malaise fatigue, night sweats
Head: Headaches, tenderness, sinus problems
Eyes: Changes in vision, photophobia, blurring, diplopia, spots, discharge
Ears: Hearing changes, tinnitus, pain, discharge, vertigo
Nose: Epistaxis, obstructions
Throat: Hoarseness, soreness
Respiratory: Chest pain, wheezing, dyspnea, cough, hemoptysis
Cardiovascular: Chest pain, dyspnea, orthopnea (number of pillows needed to sleep comfortably), edema, claudication
Dermatologic: Rashes, pruritus, lesions, skin cancer (epidermoid carcinoma, melanoma)
Gastrointestinal: Changes in appetite, dysphagia, nausea, vomiting, hematemesis, indigestion, pain, diarrhea, constipation, melena, hematochezia, bloating, hemorrhoids, jaundice
Genitourinary: Changes in urinary frequency or urgency, dysuria, hematuria, nocturia, incontinence, discharge, impotence
Gynecologic: Menstrual changes (frequency, duration, flow, last menstrual period), dysmenorrhea, menopause
Endocrine: Polyuria, polydipsia, polyphagia, temperature intolerance, pigmentations
Musculoskeletal: Muscle and joint pain, deformities, joint swellings, spasms, changes in range of motion
Hematologic: Easy bruising, epistaxis, spontaneous gingival bleeding, increased bleeding after trauma
Lymphatic: Swollen or enlarged lymph nodes
Neuropsychiatric: Syncope, seizures, weakness (unilateral and bilateral), changes in coordination, sensations, memory, mood, or sleep pattern, emotional disturbances, history of psychiatric therapy

identifying patients with a disease that may affect dental treatment or associated symptoms that will help determine the primary diagnosis. For example, a patient with skin, genital, or conjunctival lesions who also has oral mucosal disease, or a patient with anesthesia, paresthesia, or weakness who also presents with orofacial pain. The clinician records both negative and positive responses. Direct questioning of the patient should be aimed at collecting additional data to assess the severity of a patient's medical conditions, monitor changes in medical conditions, and assist in confirming or ruling out those disease processes that may be associated with patient's symptoms.

- *Past medical history (PMH)* (may not have been revealed in systems review)—general health; immunizations; major adult illnesses; any surgical operations (date, reason, and outcome); medications (prescribed medications, over-the-counter medications, supplements) and home remedies; allergies.
- *Personal and social history (SH)*—birthplace; marital status; children; habits (tobacco use, alcohol use, recreational drug use); occupation; religion (if it may have an impact on therapy); sexual history if relevant to complaint.
- *Family history (FH)*—health or cause of death of parents, siblings, and children. The FH should also include diseases important to the patient's chief compliant, including genetic disorders; and common diseases, such as cardiovascular diseases or diabetes mellitus.

Patient Examination

The examination of the patient represents the second stage of the evaluation and assessment process. An established routine for examination decreases the possibility of missing important findings (signs).

A routine head and neck examination should be carried out at least annually or at each recall visit. This includes a thorough inspection (and when appropriate palpation, auscultation, or percussion) of the exposed surface structures of the head, neck, and face and a detailed examination of the oral cavity, dentition, oropharynx, and adnexal structures. Laboratory studies and additional special examination of other organ systems may be required for the evaluation of patients with orofacial pain, oral mucosal disease, or signs and symptoms suggestive of otorhinologic or salivary gland disorders, or signs or symptoms suggestive of a systemic etiology. A less comprehensive but equally thorough inspection of the face and oral and oropharyngeal mucosae should be carried out at each visit and the tendency to focus on only the tooth or jaw quadrant in question should be strongly resisted.

Each visit should be initiated by a deliberate inspection of the entire face and oral cavity prior to intraoral examination. The importance of this approach in the early detection of head and neck cancer cannot be overstated (see Chapter 7, Oral and Oropharyngeal Cancer).

Examination carried out in the dental office (surgery) is traditionally restricted to that of the superficial tissues of the oral cavity, head, and neck and the exposed parts of the extremities. On occasion, evaluation of an oral lesion logically leads to an inquiry about similar lesions on other skin or mucosal surfaces or about the enlargement of other regional groups of lymph nodes. Although these inquiries can usually be satisfied directly by questioning the patient, the oral health professional may also quite appropriately request permission from the patient to examine axillary nodes or other skin surfaces, provided

that the examination is carried out competently and there is adequate privacy for the patient. A male oral health professional should have a female assistant present in the case of a female patient; a female oral health professional should have a male assistant present in the case of a male patient. Similar precautions should be followed when it is necessary for a patient to remove tight clothing for accurate measurement of blood pressure. A complete physical examination should not be attempted when facilities are lacking or when religious or other customs prohibit it, or when no chaperone is present.

The degree of responsibility accorded to the oral health professional in carrying out a complete physical examination varies among institutions, hospitals, states, and countries.

The examination procedure in a dental office setting may include any or all of the following six areas:

- Registration of vital signs (respiratory rate, temperature, pain level, pulse, and blood pressure).
- Examination of the head, neck, and oral cavity, including salivary glands, temporomandibular joints, and head and neck lymph nodes.
- Lesions of the oral mucosa should have a detailed description including location, size, color, ulceration and induration, and an assessment of the severity made. Detailed descriptions of specific diseases presenting as ulcers, blisters, or white or red lesions can be found in Chapters 3–7.
- Assessment of cranial nerves, particularly when the patient presents with nondental orofacial pain, weakness, anesthesia, or paresthesia.
- Examination of other organ systems, when appropriate.
- Ordering indicated laboratory studies.

Consultations

Requesting Consultations from Other Clinicians

The overall purpose of a consultation is to clarify issues or help with diagnosis or management. Oral medicine clinicians are involved with two major types of consultations: those that they initiate for their own patients as a request from another healthcare professional; and those in response to a request for help with a patient of another healthcare professional.

Consent from the patient is needed before a consultation is initiated. All verbal and written consultation should be documented in the patient's record. A consultation letter should identify the patient and contain a brief overview of the patient's pertinent medical history and a request for relevant and specific information. The written request should be brief and should specify the particular concern and items of information needed from the consultant (Box 1-1).

Patients who may need medical consultation include:

- Those with known medical problems who are scheduled for either inpatient or outpatient dental treatment and cannot adequately describe all of their medical problems.
- Those with abnormalities detected during history-taking, on physical examination, or through laboratory studies.
- Those who have a higher risk for the development of a particular medical problem (e.g., diabetes with increased risk of atherosclerotic cardiovascular disease).
- Those for whom additional medical information is required that may impact the provision of dental care or assist in the diagnosis of an orofacial problem.
- Those with an orofacial disorder, which may also affect other parts of the body. For example, oral lesions may also involve the skin and conjunctiva.
- Those who are being considered for a medication that may have an adverse effect on another medical problem, such as diabetes or hypertension, or drug interactions.

Requests for consultation should include the problem and the specific questions to be answered and should be transmitted to the consultant in writing. Adequate details of the planned oral or dental procedure, include, as appropriate:

- Estimated risk of clinically significant bleeding.
- Assessment of time and stress to the patient.
- Expected period of post-treatment disability.
- Details of the particular symptom, sign, or laboratory abnormality that gave rise to the consultation.

Medically complex patients may have a medical condition that suggests the need for an opinion from the patient's physician as to risks involved in an invasive or stressful dental procedure, too often referred to as "clearing the patient for dental care."[8] In many cases, the physician is provided with too little information about the nature of the proposed dental treatment (type of treatment, amount of local anesthetics, anticipated bleeding, etc.) to help in this regard. Physicians cannot be expected to understand the nature of dental procedures and they should not be asked to "clear" patients for dental treatment. They should be contacted for pertinent medical information that will help the oral healthcare provider make the decision as to the appropriateness of the dental treatment plan. The response of a given patient to specific dental interventions may be unpredictable, particularly patients with comorbidities and those taking one or more medications. A physician's advice and recommendation may be helpful in managing a patient, but the responsibility to provide safe and appropriate care lies ultimately with the clinician performing the procedure.[9] Another health professional cannot from a legal standpoint "clear" a patient for any dental procedure and thus a request for "medical clearance" should be avoided.[8]

Box 1-1 Oral Medicine Inpatient Consultation

Patient: BRADLEY, BOB **MRN:** 0002222222
Age: 36 years **Sex:** Male **DOB:** 5/4/1983
Oral Medicine Resident: Dr. Alexandra Howell

Requesting Service: Hematology **Attending Physician:** INPATIENT HEMATOLOGY
Reason for Admission: LEUKOCYTOSIS; THROMBOCYTOPENIA
Date of Admission: 01/24/2020 **Hospital Day:** 2

Reason for Consult: Hospital dentistry consult requested by Dr. Green for oral evaluation and to rule out oral infection prior to immunosuppressive chemotherapy.
Source of History: Patient and medical record.

Chief Complaint: Patient not aware of any problems with his mouth in the past 6 months. He denies active dental pain but says that his "enamel keeps chipping off."

History of Present Illness:
Patient is a 36 y/o male with past medical history of chronic acid reflux who presented to our Emergency Room on January 24 with right-sided abdominal & flank pain and decreased urine output. He was found to have an acute kidney injury with hyperkalemia. CT of his abdomen/pelvis showed hydronephrosis/hydroureter and splenomegaly. CBC revealed white blood cell count of 53.9, hemoglobin of 10, and platelets 29,000. He was transferred to the inpatient hematology service for further evaluation and management of acute T-cell ALL and tumor lysis.

Health Status
Allergies: None known
Current Medications:
allopurinol 300mg per 1 tablet ORAL daily
hydroxyurea (Hydrea) 1,000 mg per 2 capsules ORAL q8h
sevelamer (sevelamer carbonate 800 mg oral tablet) 800 mg per 1 tablet ORAL TIDWM (3 times a day with meals)
Labs from 01/25/2020: ANC = 3150; INR=1.2; aPTT = 32.8; ALT/AST = 26/28.

Past Medical History: No active or resolved past medical history items have been selected or recorded. Patient states he has not seen a dentist in 10+ years.

Family History: Cancer—mother. Diabetes mellitus—father.

Extraoral examination: No trismus or swelling noted. Significant lymphadenopathy in postauricular area bilaterally.

Intraoral examination: Very poor oral hygiene with heavy plaque and calculus. Rampant dental caries with several retained root tips and fractured teeth. Noted a draining sinus tract/fistula on the buccal gingiva of lower left first molar (root tip) with moderate swelling and erythema. Also noted possible sinus tract above tooth #8.

Review/Management: Reviewed soft tissue neck CT. Relevant dental findings include numerous dental caries and extensive periodontal disease with periapical lucencies involving the mandibular left second molar, mandibular left first molar, mandibular right first molar, and multiple maxillary and mandibular incisors. Multiple root tips, and grossly enlarged and erythematous gingiva.

Impression: Diagnosis: dental caries, root tips, and advanced periodontal disease. Multiple draining sinus tracts/fistulas of the buccal gingiva. Posterior auricular bilateral lymphadenopathy R>L, moderate sized.

Recommendations: Patient does have clear signs of active dental infection. Recommend patient be transported to the dental clinic by wheelchair for a comprehensive clinical examination, full mouth series of radiographs and a Panorex for full treatment planning. We have tentatively scheduled him for the dental clinic on Monday morning, 1/27/20 at 10:00 am, pending medical stability. Treatment recommendations will be available following our department case conference on Tues 1/28/20.

Responding to Consult Requests from Other Clinicians

There are three major categories of oral medicine consultations:

- Diagnosis and nonsurgical treatment of orofacial disorders, including oral mucosal disease, temporomandibular and myofascial dysfunction, chronic lesions involving the maxilla and the mandible, orofacial pain, dental anomalies, maxillary and mandibular bone lesions, salivary gland disorders, and disorders of oral sensation, such as dysgeusia, dysesthesia, and glossodynia.
- Dental treatment of patients with medical problems that affect the oral cavity or for whom modification of standard dental treatment is required to avoid adverse events.
- Opinion on the management of dental disease that does not respond to standard treatment, such as rampant dental caries or periodontal disease in which there is a likelihood of a systemic etiologic cofactor.

In response to a consultation request, the diagnostic procedures outlined in this chapter may be followed, with the referral problem listed as the chief complaint and with supplementary questioning (i.e., history of the present illness) directed to the exact nature, mode of development, prior diagnostic evaluation/treatment, and associated symptomatology of the primary complaint. An examination of the head, neck, and oral cavity is important and should be fully documented, and the ROS should include an exploration of any associated symptoms and including pertinent negatives. When pertinent, existing laboratory, radiographic, and medical records should be reviewed and documented in the consultation record, and any additional testing or specialized examinations should be ordered.

A comprehensive consultation always includes a written report of the consultant's examination, usually preceded by a history of the problem under investigation and any items from the medical or dental history that may be relevant to the problem. A formal diagnostic summary follows, together with the consultant's opinion on appropriate treatment and management of the issue. Other previously unrecognized abnormalities or significant health disorders should also be communicated to the referring clinician. When a biopsy or initial treatment is required before a definitive diagnosis is possible, and when the terms of the consultation request are not clear, a discussion of the initial findings with the referring clinician is appropriate before proceeding. Likewise, the consultant usually discusses the details of their report with the patient, unless the referring dentist specifies otherwise. In community practice, patients are sometimes referred for consultation by telephone or are simply directed to arrange an appointment with a consultant and acquaint them with the details of the problem at that time; a written report is still necessary to clearly identify the consultant's recommendations, which otherwise may not be transmitted accurately by the patient. The details of an oral consultation must be documented on the patient's chart.

An important responsibility for hospital-based dentists is responding to consults from medical and surgical services. It is not at all uncommon for hospitalized patients to have routine maxillofacial problems (e.g., toothache) that have nothing to do with their reason for hospitalization. More commonly, patients may have a wide variety of problems that are directly related to their medical condition or its treatment (e.g., mucositis secondary to cancer chemotherapy) or require a dental exam to eliminate a possible source of infection during cancer chemotherapy.[9]

In hospital practice, the dental consultant is always advisory to the patient's attending physician; the recommendations listed at the end of the consultation report are suggestions and not *orders,* and are not implemented unless authorized by the attending physician. For some oral lesions and mucosal abnormalities, a brief history and examination of the lesion will readily identify the problem, and only a short report is required; this accelerated procedure is referred to as a limited consultation (Box 1-2).

Both custom and health insurance reimbursement systems recognize the need of individual practitioners to request the assistance of a colleague who may have more experience with the treatment of a particular clinical problem or who has received advanced training in a medical or dental specialty pertinent to the patient's problem. However, this practice of specialist consultation is usually limited to defined problems, with the expectation that the patient will return to the referring primary care clinician once the nature of the problem has been identified (diagnostic consultation) and appropriate treatment has been prescribed or performed (consultation for diagnosis and treatment).

ESTABLISHING A DIFFERENTIAL AND FINAL DIAGNOSIS

Before establishing a final diagnosis, the clinician often needs to formulate a differential diagnosis based on the history and physical examination findings. The disorders included in the differential diagnosis will determine which laboratory tests, such as biopsies, blood tests, or imaging studies, are required to reach a final diagnosis.

Box 1-2 Outpatient Oral Medicine Consultation

Date: _____

To: John Doe MD

From: Robert Dent DMD

Patient Name and Date of Birth

The patient is a 19-year-old female sent for a consultation for evaluation of recurring oral ulcerations, which have been increasing in severity for the past 5 months.

The patient has a history of occasional oral ulcers since age 10 with 2 to 3 ulcers occurring 3 to 4 times yearly and lasting 8 to 10 days. Five months ago, she began to experience 5 to 10 ulcers each month lasting 2 to 3 weeks. Each episode has been treated with prednisone 30 mg once daily for 5 to 7 days. The lesions heal with this regimen, but recur in 3 to 4 weeks.

The patient denies conjunctival lesions, although on 2 occasions during the past 3 months she had a vaginal ulcer. She has acne-type facial lesions since taking prednisone monthly.

Her past medical history is remarkable for depression. She denies hospitalizations or surgery and has no known drug allergies.

She takes Lexapro for depression, but no medications other than prednisone for oral ulcers.

Her review of systems is remarkable for weekly episodes of intestinal cramping and diarrhea. She denies GI bleeding or black tarry stools. The remainder of the review of systems is noncontributory except for the skin and vaginal lesions noted above.

The family history is significant for her mother and maternal grandmother having a history of recurring oral ulcers during adolescence. Her father is of Japanese descent and her mother is Caucasian.

She is currently a college student and denies smoking or use of recreational drugs.

The examination showed multiple acne-like lesions of the skin of the face.

There was no cervical lymphadenopathy or salivary gland enlargement.

Cranial nerves II–XII were grossly intact.

The oral mucosa had 5 shallow ulcers 5 mm to 8 mm in diameter surrounded by inflammation: two involving the left lateral tongue, one on the dorsal tongue, and one involving the left buccal mucosa. No vesicles or white lesions were present.

Impressions

1) Recurrent aphthous ulcers; increasing in severity during the past 5 months
2) R/O Behçet's disease
3) R/O Lupus
4) R/O celiac disease
5) R/O blood dyscrasia

Plan:

1) Order the following laboratory studies: CBC, CMP, ANA, ESR, tTG-IgA
2) Dermatology consult for evaluation of skin and vaginal lesions, and pathergy test
3) Ophthalmology consult to rule out uveitis or retinal vasculitis suggestive of Behçet's disease
4) GI consultation
5) Biopsies of oral ulcer for routine histology and lupus band test
6) Begin treatment with Clobetasol propionate gel, 0.05% directly to lesions tid
7) If the above laboratory tests and consultations are normal and there is inadequate benefit from topical steroids, consider a trial of pentoxifylline or colchicine

The rapidity and accuracy with which a diagnosis or set of diagnoses can be achieved depend on the history and examination data that have been collected and on the clinician's knowledge and ability to match these clinical data with suspected disease processes. Experienced clinicians with a more extensive knowledge of physiology and maxillofacial disease, and a broader knowledge of the relevant literature, can more rapidly establish a differential and diagnosis. Such "mental models" of disease syndromes also increase the efficiency with which experienced clinicians gather and evaluate clinical data and focus supplemental questioning and testing at all stages of the diagnostic process.

For effective treatment, as well as for health insurance and medicolegal reasons, it is important that a diagnosis (or diagnostic summary) is entered into the patient's record, following the detailed history and physical, radiographic, and laboratory examination findings. This may be a provisional diagnosis dependent on the results of investigation. When more than one health problem is identified, the diagnosis for the primary complaint is usually listed first. Previously diagnosed conditions that remain as actual or potential problems are also included, with the qualification "by history," "previously diagnosed," or "treated" to indicate their status. Problems that were identified but not clearly diagnosed during the current evaluation can also be listed with the comment "to be ruled out." Since oral medicine is concerned with problems that may be modified or linked to concurrent systemic diseases, it is common for the list of diagnoses to include both the oral problem such as a lesion or pain and systemic problems of actual or potential significance in the etiology or management of the oral problem. Items in the medical history that do not relate to the current problem and are not of major health significance usually are not included in the diagnostic summary. For example, for a presenting complaint of pain and swelling in the left side of the face in a 62-year-old female, a diagnosis list might read as follows:

Current:	1)	Alveolar abscess, mandibular left first molar
	2)	Rampant generalized dental caries secondary to radiation-induced salivary hypofunction
	3)	Hyperglycemia; R/O diabetes
Previous	4)	Carcinoma of the tonsillar fossa, by history, excised and treated with 65 Gy 2 years ago
	5)	Cirrhosis and prolonged prothrombin time, by history

A definite diagnosis cannot always be made, despite a careful review of all history, clinical, and laboratory data. In such cases, a descriptive term (rather than a formal diagnosis) may be used for the patient's symptoms or lesion, with the added word "idiopathic," "unexplained," or (in the case of symptoms without apparent physical abnormality) "functional" or "symptomatic." If a note is written prior to a definitive diagnosis, a clinician may list a descriptive term such as chronic oral ulcer with the diseases that must be "ruled out" (R/O) listed, from most to least likely. For example:

oral ulcer from chronic trauma
R/O squamous cell carcinoma
R/O granulomatous disease

The clinician must decide which terminology to use in conversing with the patient and whether to clearly identify this diagnosis as "undetermined." It is important to recognize the undiagnosed nature of the patient's problem and to schedule additional evaluation, by referral to another consultant, additional testing, or placement of the patient on recall for follow-up studies.

Unfortunately, there is no generally accepted system for identifying and classifying diseases, and diagnoses are often written with concerns related to third-party reimbursement and to medicolegal and local peer review, as well as for the purpose of accurately describing and communicating the patient's disease status. Within different specialties, attempts have been made to achieve conformity of professional expressions and language.

Some standardization of diagnoses has been achieved in the United States as a result of the introduction in 1983 of the diagnosis-related group (DRG) system as an obligatory cost-containment measure for the reimbursement of hospitals for inpatient care. However, groupings are mostly based on medical diagnoses, such as the *International Classification of Diseases, Tenth Revision* (ICD-11).[10] The DRG system is designed for fiscal use rather than as a system for the accurate classification of disease. It also emphasizes procedures rather than diseases and has a number of serious flaws in its classification and coding system. The ICD system, by contrast, was developed from attempts at establishing an internationally accepted list of causes of death and has undergone numerous revisions in the past 160 years since it was first suggested by Florence Nightingale; it is maintained by the World Health Organization. It relates to the various emphases placed on clinical, anatomic, biochemical, and perceived etiologic classification of disease at different times and different locations. However, the categories for symptoms, lesions, and procedures applicable to oral cavity conditions are limited and often outdated.

The patient (or, when appropriate, a responsible family member or guardian) should also be informed of the diagnosis, as well as the results of the examinations and tests carried out. Because patients' anxieties frequently emphasize the possibility of a potentially serious diagnosis, it is important to point out (when the facts allow) that the biopsy specimen revealed no evidence of a malignant growth, the blood test revealed no abnormality, and no evidence of

diseases, such as diabetes, anemia, leukemia, or other cancer, was found. Equally important is the necessity to explain to the patient the nature, significance, and treatment of any lesion or disease that has been diagnosed.

FORMULATING A PLAN OF ACTION

Medical Risk Assessment

Medical risk assessment of patients before oral or dental treatment offers the opportunity for greatly improving dental services for patients with complex health conditions. It requires considerable clinical training and understanding of the natural history and clinical features of systemic disease. It is hoped that revisions in dental pre-doctoral training will recognize this need and provide greater emphasis on both the pathophysiology of systemic disease and the practical clinical evaluation and management of medically complex patients.

The information gathering described above is also designed to help the oral health professional:

- Recognize a general health status that may affect dental treatment.
- Make informed judgments on the risk of dental procedures.
- Identify the need for medical consultation to provide assistance in ascertaining the presence of a systemic disease that may be associated with an oral pathology or that may adversely impact on the proposed dental treatment.

Reaching the end point of the diagnostic process and the formulation of a plan of action are usually not a simple process. In order to minimize any adverse events, an assessment of any special risks associated with a patient's compromised medical status that could be triggered by the planned anesthetic, diagnostic, or medical or surgical treatment procedure must be entered in the patient record, usually as an addendum to the plan of treatment. This process of medical risk assessment is the responsibility of all clinicians prior to initiating any treatment or intervention and applies to outpatient as well as inpatient situations.

A routine of initial history-taking and physical examination is essential for all dental patients, as even the apparently healthy individual may, on evaluation, be found to have a history or examination findings of sufficient significance to require a modification to the plan of treatment, a change to a medication, or deferring dental treatment until additional diagnostic data are available. To respect the familiar medical axiom *primum non nocere* (first, do no harm), all procedures carried out and all prescriptions given to a patient should be preceded by conscious consideration of the potential risk of the planned procedure. Establishing a formal medical risk assessment ensures a continuous evaluation process. A summary of the medical risk assessment, delineating potential risks from the proposed plan of action, should be entered in the patient record.

The Medical Complexity Status (MCS) was specifically developed for dental patients and has been used successfully for patients with medical problems ranging from nonsignificant to very complex diseases and conditions.[11] The MCS protocol is based on the premise that complications will rarely arise during provision of routine dental care in an outpatient setting to patients with stable or controlled medical conditions. However, modification of dental care may still be necessary in some circumstances and should be based on the level of the anticipated complication. The MCS classification and protocol, with examples, are described in more detail in Table 1-2.

Modification of Dental Care for Medically Complex Patients

Although there are many different medical conditions that may require modification of dental care, and protocols for a wide variety of situations, the assessment of risk to medically complex patients follows similar guidelines. It is helpful to focus on the following three questions, which will change according to the severity of the underlying disease or condition:

- What is the likelihood that the patient will experience an adverse event due to dental treatment?
- What are the nature and severity of the potential adverse event?
- What is the most appropriate setting in which to treat the patient?

Each of these questions can be subdivided into smaller entities, which will facilitate the assessment of the patient.

The four major concerns that must be addressed when assessing the likelihood of the patient experiencing an adverse event are:

- Potential for impaired hemostasis from medications or disease.
- Potential susceptibility to infection, both maxillofacial and distant to the oral cavity (e.g., infective endocarditis).
- Drug actions and interactions.
- Patient's ability to tolerate the stress and trauma of the dental procedure.

Patients are designated to an MCS category at their initial dental visit, which may be modified during subsequent visits

Table 1-2 Medical complexity status classification and protocol.

Major categories
MCS 0 Patients with no medical problems
MCS 1 Patients with controlled or stable medical conditions
MCS 2 Patients with uncontrolled or unstable medical conditions
MCS 3 Patients with medical conditions associated with acute exacerbation, resulting in high risk of mortality
Subcategories
A No anticipated complications
B Minor complications are anticipated. "Minor complications" are defined as complications that can be successfully addressed in the dental chair
C Major complications are anticipated. "Major complications" are defined as complications that should be addressed by a medical provider and may sometimes require a hospital setting
Examples of different MCS categories
MCS–0
A healthy patient
MCS–1A
A patient with controlled hypertension (No modifications to routine dental care are necessary)
MCS–1B
A patient with epilepsy (petit mal) that is controlled with medications (The patient's epilepsy status is controlled, but if the patient has a seizure, it will pass without any interventions from the oral healthcare practitioner. It would be pertinent to avoid any dental treatment that may bring about a seizure)
MCS–1C
A patient with a penicillin allergy (The allergy will not change a stable condition, but if penicillin is given, a major complication may ensue)
MCS–2A
A patient with hypertension and a blood pressure of 150/95 mm Hg but without any target organ disease (see Chapter 14, "Diseases of the Cardiovascular System") (The patient's hypertension is by definition not controlled, i.e., it is above 140/90 mm Hg. Yet this level of blood pressure, in an otherwise healthy patient, does not justify instituting any dental treatment modifications)
MCS–2B (see Chapter 22, "Disorders of the Endocrine System and of Metabolism")
A patient with diabetes mellitus and a glycosylated hemoglobin of 11% (Because of the patient's poor long-term glycemic control, the patient may be more susceptible to infections and poor wound healing. Dental modifications, such as possible antibiotics before a surgical procedure, may be indicated)
MCS–2C
A patient with uncompensated congestive heart failure (Because of the patient's compromised medical condition, it is important to avoid placing the patient in a supine position in the dental chair as this may induce severe respiratory problems)
MCS–3
A patient with unstable angina

according to the patient's changing medical status. Based on several critical items—MCS category, experience of the oral healthcare professional, the patient's ability to tolerate dental care, adequacy of the dental facility—a determination of where the patient is best treated should be made:

- A non-hospital-based outpatient setting.
- A hospital-based outpatient setting.
- An inpatient short-procedure unit setting.
- An inpatient operating room setting. Most medically complex patients can be safely treated when the factors mentioned earlier have been addressed.

A plan of treatment of this type, which is directed at the causes of the patient's symptoms rather than at the symptoms themselves, is often referred to as rational, scientific, or definitive (in contrast to symptomatic, which denotes a treatment plan directed at the relief of symptoms, irrespective of

their causes). The plan of treatment (similar to the diagnostic summary) should be entered in the patient's record and explained to the patient in detail. This encompasses the procedure, chances for improvement or cure (prognosis), potential complications and side effects, and number of appointments and expense. As initially formulated, the plan of treatment usually lists recommended procedures for the control of current disease as well as preventive measures designed to limit the recurrence or progression of the disease process over time. For medicolegal reasons, the treatment that is most likely to eradicate the disease and preserve as much function as possible (i.e., the ideal treatment) is usually entered in the chart, even if it is clear that compromises may be necessary to obtain the patient's consent to treatment.

It is also unreasonable for the clinician to prejudge a patient's decision as to how much time, energy, and expense should be expended on treating the patient's disease or how much discomfort and pain the patient is willing to tolerate. Patient involvement in decisions regarding the treatment plan—shared decision-making—is necessary to help achieve a satisfactory outcome. Such an approach has been promulgated by the Institute of Medicine as "patient-centered care" and is defined as "Providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions."[12]

The plan of treatment may be itemized according to the components of the diagnostic summary and is usually written prominently in the patient record to serve as a guide for the scheduling of further treatment visits. If the plan is complex or if there are reasonable treatment alternatives, a copy should also be given to the patient to allow consideration of the various implications of the plan of treatment that they have been asked to agree. Modifications of the ideal plan of treatment, agreed on by patient and clinician, should also be entered in the chart, together with a signed disclaimer from the patient if the modified plan of treatment is likely to be significantly less effective or unlikely to eradicate a major health problem.

Numerous protocols have been proposed to facilitate efficient and accurate preoperative assessment of medical risk. Many of the earlier guides were developed for the assessment of risks associated with general anesthesia or major surgery and focus on mortality as the dependent variable. All too often, these were adopted for risk assessment associated with invasive dental procedures performed under local or regional anesthesia. Of these, the most commonly used is the American Society of Anesthesiologists (ASA) Physical Scoring System (Table 1-3).[13] Although scores such as the ASA classification are commonly included in the preoperative evaluation of patients admitted to hospitals for dental surgery, they use relatively broad risk categories, and their applicability to both inpatient and outpatient dental procedures is limited. Importantly, the ASA score was developed for and is used to assess a patient's ability to tolerate general anesthesia and should therefore not be used to predict complications associated with dental surgery in the outpatient setting.

Table 1-3 American Society of Anesthesiologists (ASA) physical status classification system.

ASA I	A normal healthy person
ASA II	A patient with a mild disease
ASA III	A patient with a severe systemic disease
ASA IV	A patient with a severe systemic disease that is a constant threat to life
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes

In the event of an emergency, precede the number with an "E."
Adapted from American Society of Anesthesiologists. *ASA Physical Status Classification System*. https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system. Accessed September 22, 2020.

Monitoring and Evaluating Underlying Medical Conditions

Several major medical conditions can be monitored by oral healthcare personnel.[14] Signs and symptoms of systemic conditions, the types of medications taken, and the patient's compliance with medications can reveal how well a patient's underlying medical condition is being controlled. Signs of medical conditions are elicited by physical examination, which includes measurements of blood pressure and pulse, or laboratory or other diagnostic evaluations. Symptoms are elicited through an ROS, whereby subjective symptoms that may indicate changes in a patient's medical status are ascertained. A list of the patient's present medications, changes in medications and daily doses, and a record of the patient's compliance with medications usually provide a good indicator of how a medical condition is being managed. The combined information on signs, symptoms, and medications is ultimately used to determine the level of control and status of the patient's medical condition.

CLINICAL OUTCOMES AND ORAL DISEASE SEVERITY SCORING

All fields in medicine work toward evidence-based therapy. It is regarded as essential for the advancement of any field, including oral medicine, that there is continuous assessment of the results of treatment, so leading to progress in management. However, it is true that many treatments for oral

diseases are not evidence based, even those regarded as standard therapies. Until the last few years, there had been a lack of any method to routinely assess disease severity and thus to quantify responses to therapies. This led to the obvious need to devise and validate oral disease severity scores for a variety of conditions seen in routine clinical practice, which could also be used for assessing treatment responses. The accepted principle in medicine and surgery is that the response to therapy should be assessed in every single patient seen. This can be performed both from the perspective of the clinician (disease severity scores) and from the patient (patient-reported outcome measures or PROMs).

Disease severity scoring systems are tools that can help clinicians assess both the severity of the objective clinical findings as well as the subjective features of the disease, including its impact on patients' lives. There are three essential aspects that are important in defining the "intensity of the disease": clinical score measuring the level of inflammation, area, and specific clinical features (e.g., ulceration); subjective reporting of pain that the disease is inflicting; and a questionnaire relating to how the condition affects patients' functioning and their lives, known as oral health-related quality of life (OHRQoL).[15] There are now several validated and universally used tools for oral diseases that should be used at every patient visit.

Oral Disease Severity Scoring

The benefits of a scoring system for mucosal disease severity are that (1) they can indicate the severity of disease; (2) they are needed to indicate the efficacy of any treatments; (3) they may distinguish between or reveal subgroups of activity; (4) they may assist in deciding to implement or withhold treatment; and (5) they are a routine clinical audit tool that can also be used for research.

Any such oral disease scoring systems (ODSS) much be objective, must be reproducible, should be easy to use, and should be widely applicable. Fortunately, such ODSSs have been created, validated, and are in use for recurrent aphthous ulceration, oral lichen planus pemphigus, mucous membrane pemphigoid, orofacial granulomatosis, and dry mouth assessment.[15–20] Although additional work is required before these scoring systems are universally accepted and utilized, the principle of assessing disease severity at each clinical consultation is regarded as good clinical practice. See Chapter 4 for more on oral disease severity scoring.

Patient-Reported Outcome Measures and Oral Mucosal Disease

Alongside oral disease severity scoring, it is important to record PROMs. Whereas ODSSs are physician records of disease severity that allow clinical assessment of response to treatment, patient-reported outcomes record outcomes from a patient's perspective and are equally important in overall outcome success. On occasion, the PROMs score will demonstrate satisfaction at the outcome, even though the ODSS may be unchanged or vice versa. There are now simple, validated systems for PROMs[15] and it is appropriate for both to be recorded.

THE DENTAL AND MEDICAL RECORD

The patient's record is customarily organized according to the components of the history, physical examination, diagnostic summary, plan of treatment, and medical risk assessment described previously in this chapter. Test results (diagnostic laboratory tests, radiographic examinations, and consultation and biopsy reports) are filed after this, followed by dated progress notes recorded in sequence. Separate sheets are incorporated into the record for the following: (1) a summary of medications prescribed for or dispensed to the patient; (2) a description of surgical procedures; (3) the anesthetic record; (4) a list of types of radiographic exposures; and (5) a list of the patient's problems and the proposed and actual treatment. This pattern of organization of the patient's record may be modified according to local custom and to varying approaches to patient evaluation and diagnostic methodology taught in different institutions.

In recent years, educators have explored a number of methods for organizing and categorizing clinical data, with the aim of maximizing the matching of the clinical data with the "mental models" of disease syndromes referred to earlier in this chapter. The problem-oriented record (POR) and the condition diagram are two such approaches; both use unique methods for establishing a diagnosis and also involve a reorganization of the clinical record.

Problem-Oriented Record

The POR focuses on problems requiring treatment rather than on traditional diagnoses. It stresses the importance of complete and accurate collecting of clinical data, with the emphasis on recording abnormal findings rather than on compiling the extensive lists of normal and abnormal data that are characteristic of more traditional methods (consisting of narration, checklists, questionnaires, and analysis summaries). Problems can be subjective (symptoms), objective (abnormal clinical signs), or otherwise clinically significant (e.g., psychosocial) and need not be described in prescribed diagnostic categories. Once the patient's problems have been identified, priorities are established for further diagnostic evaluation or treatment of each problem.

These decisions (or assessments) are based on likely causes for each problem, risk analysis of the problem's severity, cost and benefit to the patient as a result of correcting the problem, and the patient's stated desires. The plan of treatment is formulated as a list of possible solutions for each problem. As more information is obtained, the problem list can be updated, and problems can be combined and even reformulated into recognized disease categories.

The POR is helpful in organizing a set of complex clinical data about an individual patient, maintaining an up-to-date record of both acute and chronic problems, ensuring that all of the patient's problems are addressed, and ensuring that preventive as well as active therapy is provided. Furthermore, the POR facilitates interprofessional communication and is a foundation for collaborative practice and teaching.[21,22] It is also adaptable to computerized patient-tracking programs. However, without any scientifically based or accepted nomenclature and operational criteria for the formulation of the problem list, data cannot be compared across patients or clinicians. An additional concern that has been put forward is the reliance on a POR to "automatically" generate a diagnosis.[23] Although the POR will allow for a systematic approach to delineate specific problems, clinicians need to be able to synthesize findings into an appropriate diagnosis.[24]

Despite these shortcomings, two features of the POR have received wide acceptance and are often incorporated into more traditionally organized records: the collection of data and the generation of a problem list. The value of a problem list for individual patient care is generally acknowledged and is considered a necessary component of the hospital record in institutions accredited by the Joint Commission on Accreditation of Healthcare Organizations. Furthermore, the use of a problem-oriented approach may enhance the utilization of and satisfaction with EHRs.[25]

SOAP Note

The SOAP note concept, as well as POR, was initially proposed by Dr. Lawrence ("Larry") Weed in the 1960s and has ever since been a mainstay in teaching and clinical care.[26,27] The purpose of this type of documentation was to provide a clinician with a systematic and structured method—a checklist—to record patient findings. The SOAP note is also used for communication between healthcare professionals and as a teaching aid.

The four components of a problem—Subjective, Objective, Assessment, and Plan—constitute the SOAP mnemonic for organizing progress notes or summarizing an outpatient encounter (see Box 1-3). The components of the mnemonic are as follows:

- *S or Subjective*—the patient's experience, complaint, symptoms, and medical history (a brief review of the chief complaint, HPI, PMH, ROS, current medications, and allergies).
- *O or Objective*—the general clinical examination (physical examination, vital signs); review of laboratory data, imaging results, other diagnostic data; review of documentation from other healthcare providers; and a focused evaluation of the chief complaint or the area of the procedure to be undertaken.

Box 1-3 SOAP Note: Example: A progress note placed in a patient's chart after an oral medicine evaluation

Date _____

S—The patient is a 32-year-old women with a history of multiple sclerosis and recent increasing loss of visual acuity and muscle weakness, with sudden onset of severe but brief episodes of pain involving the left mandibular region. She was admitted by Neurology for evaluation and treatment with intravenous methylprednisone and interferon.

O—Touching lower left lip or gingiva in the region of the mental foramen triggers brief electric shock-like pain.
Extraoral exam reveals no lymphadenopathy, major salivary gland tenderness, or enlargement.
Intraoral exam shows no mucosal lesions or masses in the area of the left mandible. Teeth are not tender to percussion and no dental caries, fractured teeth, or removable prosthesis noted.
Panoramic radiography of the left mandible showed no dental or bony pathology.
A recent MRI of the brain, reviewed with radiology, demonstrated a demyelinating plaque involving the left trigeminal nerve root.

A—Trigeminal neuralgia secondary to multiple sclerosis, no evidence of an oral source for her pain.

P—Current plan includes a trial of carbamazepine or oxcarbazepine.

*Signature*_____

- *A or Assessment*—a synthesis of the subjective and objective findings to arrive at a diagnosis (problem list and differential diagnosis) for the specific problem being addressed.
- *P or Plan*—the need for additional information (e.g., laboratory tests, consultations); referrals; treatment recommendation; patient education for the purpose of shared decision-making.

The SOAP note is a useful tool for organizing progress notes in the patient record for routine office procedures and follow-up appointments. It is also quite useful in a hospital record when a limited oral medicine consultation must be documented. However, in order for other healthcare professionals to more easily retrieve the most relevant information, it might be better to reorganize and document the SOAP note as an ASOP note (Assessment, Plan, Subjective, Objective). One significant drawback with the SOAP framework is the lack of a temporal or time component. This can be remedied by including a time component before consecutive SOAP notes. For example, "The present SOAP note is recorded 14 days following the last SOAP note. During this time the following changes have occurred: ...."

Confidentiality

Patients provide dentists and physicians with confidential dental, medical, and psychosocial information, on the understanding that the information (1) may be necessary for effective diagnosis and treatment; (2) will remain confidential; and (3) will not be released to other individuals without the patient's specific permission. This information may also be entered in the patient's record and shared with other clinical personnel involved in the patient's treatment, unless the patient specifically requests otherwise. Patients are willing to share such information with their dentists and physicians only to the extent that they believe that this contract is being honored.

There are also specific circumstances in which the confidentiality of clinical information is protected by law and may be released to authorized individuals only after compliance with legally defined requirements for informed consent (e.g., psychiatric records and confidential HIV-related information). Conversely, some medical information that is considered to be of public health significance is a matter of public record when reported to the local health authorities (e.g., clinical or laboratory confirmation of reportable infectious diseases such as syphilis, hepatitis, or AIDS). Courts may also have the power to subpoena medical and dental records under defined circumstances, and records of patients participating in clinical research trials may be subject to inspection by a pharmaceutical sponsor or an appropriate drug regulatory authority. Dentists are generally authorized to obtain and record information about a patient to the extent that the information may be pertinent to the diagnosis of oral disease and its effective treatment.

Conversations about patients, discussion with a colleague about a patient's personal problems, and correspondence about a patient should be limited to those occasions when information essential to the patient's treatment has to be transmitted. Lecturers and writers who use clinical cases to illustrate a topic should avoid mention of any item by which a patient might be identified and should omit confidential information. Conversations about patients, however casual, should never be held where they could possibly be overheard by unauthorized individuals, and discussion of patients with nonclinical colleagues, friends, family, and others should always be avoided and should never include confidential patient information.

Informed Consent

Prior consent of the patient is needed for all diagnostic and treatment procedures, with the exception of those considered necessary for treatment of a life-threatening emergency in a comatose patient.[28] In dentistry, such consent is more often implied than formally obtained, although written consent is generally considered necessary for surgical procedures (however minor), for the administration of general anesthetics, and for clinical research.

Consent of the patient is often required before clinical records are transmitted to another dental office or institution. In the United States, security control over electronic transmission of patient records has since 1996 been governed by the Health Insurance Portability and Accountability Act (HIPAA). The creation and transmission of electronic records are an evolving process that is mainly dependent on technological advances and fast movement of the integration of electronic patient information.[29]

There may also be specific laws that discourage discrimination against individuals infected with infectious diseases, such as HIV, by requiring specific written consent from the patient before any HIV-related testing can be carried out and before any HIV-related information can be released to insurance companies, other practitioners, family members, and fellow workers.[30] Oral healthcare professionals treating patients whom they believe may be infected with HIV must therefore be cognizant of local law and custom when they request HIV-related information from a patient's physician, and they must establish procedures in their own offices to protect this information from unauthorized release. In response to requests for the release of psychiatric records or HIV-related information, hospital medical record departments commonly supply the practitioner with the necessary additional forms for the patient to sign before the records are released. Psychiatric information that is released is usually restricted to the patient's diagnoses and medications.

TELEHEALTH/TELEDENTISTRY

Telehealth has been defined as "communication and information technologies [used] to provide or support long-distance clinical health care, patient and professional health-related education, public health, and health administration."[31] Although sometimes used interchangeably, several designations, such as telemedicine, mHealth, and eHealth, have been used to described how to interact and provide care when there is no direct physical contact—remotely—between providers and patients. According to some definitions, telehealth refers to a broad scope of remote healthcare services that may include nonclinical services, while telemedicine specifically refers to remote clinical services.[32] mHealth is usually employed to describe technology used by patients to capture their own health data with the help of apps on devices such as smartphones and tablets, while eHealth mostly refers to utilizing the internet and similar technology.

One of the major drawbacks for the utilization of teledentistry in oral medicine is the inability to perform a clinical examination that includes components such as touch and palpation. In telemedicine there are already armamentaria that aim to overcome these types of limitations. For example, there exist electronic stethoscopes, dermatoscopes, and scales, as well as tele-ophthalmoscopes, video-otoscopes, and digital endoscopes.[33] However, studies have been performed where individuals can take pictures with their smartphones and share these images with a specialist who can make differential diagnoses and determine the need for additional studies, such as biopsies. This technology has enabled early detection of oral cancer, as well as HIV-associated lesions, among individuals in areas without immediate access to specialists.[34,35] Another study using a mobile telemedicine system to diagnose oral mucosal lesions remotely showed a high degree of accuracy, demonstrating the potential for future use of this technology in oral medicine.[36]

The need to develop better, more reliable, and validated technology for oral medicine purposes will enhance our ability to provide care to individuals not only in remote areas, but also during circumstances where person-to-person interactions are being discouraged due to, for example, a pandemic. The Covid-19 pandemic has substantially increased the routine use of telemedicine by many clinicians, including oral medicine specialists. It is expected that as these clinicians become experienced using telemedicine, its use will continue to expand in clinical practice.

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2

Overview of Clinical Research

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Evidence-based practice uses current scientific evidence to guide clinical decision-making. In dentistry, this practice integrates the dental professional's clinical expertise, the patient's needs and preferences, and the most current, clinically relevant evidence.[1] Oral health clinical research seeks to improve the evidence base to allow dental professionals and patients to make informed clinical care decisions. The purpose of this chapter is to provide a brief overview of types of research involving human subjects and the features of good clinical research, including ethical and regulatory considerations.

DEFINITIONS OF HUMAN SUBJECTS AND CLINICAL RESEARCH

The US Department of Health and Human Services (Title 45 Code of Federal Regulations (CFR) Part 46)[2] defines a human subject as "a living individual about whom an investigator (whether professional or student) conducting research: obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens." Research involving human subjects must be reviewed by the overseeing Institutional Review Board (IRB), or an equivalent ethics committee or board in countries outside of the US, to seek approval or determination of exemption prior to enrolling research participants. Human subjects research includes all research in which investigators interact directly with subjects to collect research data, including survey research, and research utilizing existing data/biospecimens from human subjects if at least one member of the research team has the ability to link data/biospecimens to identifiable information.[3] For human subjects research utilizing existing data/biospecimens, an IRB or equivalent ethics committee will make a determination about whether the study would be exempt or non-exempt depending upon the role of the study team member who has access to identifiable information.

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Human subjects are also sometimes referred to as "participants," and both terms will be used throughout this chapter.

"Clinical research" can be broadly defined as patient-oriented research. Many types of studies are included under this definition, including studies of human disease mechanisms, natural history studies of disease, epidemiologic studies, prognostic studies, studies of technologies or procedures used to diagnose, prevent, or treat human diseases, outcomes research, and health services research. Clinical research can be broadly categorized as observational or interventional research. In observational studies, participants are identified as belonging to study groups and are assessed for biomedical or health outcomes. Participants may receive diagnostic, preventive, therapeutic, or other types of interventions as "standard of care," but the investigator does not assign the participants to a specific group. Interventional research, or clinical trials, involves prospective assignment of participants to one or more interventions to test the effect of the intervention(s) on the disease or condition. "Intervention" includes anything that can alter the course of a disease, such as a pharmaceutical agent, a medical device, a surgical technique, a behavioral intervention, or a public health program. Clinical research studies, whether observational or interventional, require approval by an IRB or equivalent ethics board/committee and provision of informed consent by the study participants.

STUDY DESIGNS

Several types of designs are available to study diseases and conditions and collect research information. The study designs described below are commonly employed in clinical research.

Case Report and Case Series

A case report (singular) or case series (plural) is a description of one or several individuals with a disease or condition of interest. A case report can offer insights into diagnosis and management of a disease or condition by providing details about the patient's clinical presentation, diagnostic work-up, differential diagnoses, final diagnosis, management, and current disposition. Examples include descriptions of: orofacial manifestations of a patient with a systemic disease and strategies to manage the disease, unusually shaped teeth in a child or children with a genetic syndrome, or an adult presenting with orofacial pain from an unusual source such as a metastatic tumor and the diagnostic approach to determine the pain etiology. The description should be complete enough for use by another clinician who may evaluate a similar case. If the study is a case series, the same diagnostic criteria should be used to group the cases together for a report.

Case series can be very valuable in the description of new diseases or conditions. A good example is the large case series describing 63 cases of osteonecrosis of the jaw (ONJ) associated with the use of bisphosphonates.[4] While the report of this emerging clinical condition suggested a relationship to use of bisphosphonate medication, an obvious limitation of this study design is the lack of a population of individuals without the disease or condition, or a "control" group. Other limits of a case series include the fact that most data are obtained via a retrospective review of existing clinical records. This introduces the potential for recall bias as the researchers are "looking back" at events and extracting record information, which often is a mixture of complete and incomplete facts. Also, the information is recorded for clinical care and not research purposes. Therefore, clinicians will use varying methods to evaluate patient outcomes, such as a non-healing extraction site. If the patients were evaluated as part of a research study, the study team would use a predefined set of criteria to determine study inclusion and judge clinical outcomes and would collect a predefined set of information from the patients such as current and past medications.

Cross-Sectional Studies

Cross-sectional studies are employed frequently in clinical research. Research participants are evaluated at one time point and are not followed over time, creating a dataset that is a "snapshot" of the condition under study. Prevalence studies use cross-sectional designs that describe the population under study, derive a representative sample of that population and define the characteristics under study to establish the prevalence of a disease or condition in a population.[5] For example, the prevalence of oral human papillomavirus (HPV) infection in unvaccinated men and women has been estimated through the National Health and Nutrition Examination Survey (NHANES) 2009–2016.[6] The NHANES study uses a statistically representative sample of the civilian non-institutionalized US population. Many factors must be considered when designing a cross-sectional prevalence study. First, it is not usually feasible to examine an entire population of individuals with a disease or condition. Therefore, the sample being examined should represent the entire population at risk and not only those most severely affected. In the example of ONJ, patients with small non-healing affected sites that healed in two to three months without any intervention should be included as well as those with large lesions that persisted for months, to represent the entire spectrum of the disease. Second, all research participants should be evaluated using the same, standardized methods (read "Outcome Assessment" below). Prevalence studies require very large sample sizes and, therefore, may need to be conducted at more than one

study site (multi-centered) to achieve adequate enrollment. When the number of individuals with the disease of interest is very limited, it may not be possible to conduct a prevalence study.[5]

Cross-sectional studies may also be utilized to assess relationships between an exposure or risk factor and the presence of disease. Because research participants are evaluated at one time point, causal inferences cannot be drawn between the risk factor and disease, representing a major limitation of this study design. Using the example of periodontal disease and cardiovascular disease, some cross-sectional studies have suggested an association between the two conditions. It is important to recognize that the two conditions can occur together in a person because of a common underlying etiology, such as smoking, environmental exposures, and/or limited access to the health care system.[7] Cross-sectional studies linking these conditions do not prove that one causes the other. The temporal relationship, that is, which condition occurs first, cannot be determined from a cross-sectional study. Nevertheless, such cross-sectional designs have value in research, particularly to develop hypotheses for future studies. An initial relationship between a risk factor and presence of disease may be established in a cross-sectional study before consideration of a more resource-intensive study design in which risk factors for disease can be evaluated over time. When establishing initial relationships using a cross-sectional design, the biologic plausibility between the risk factor(s) and disease and potential biases due to data collection at one time point should be described. For example, when exploring the relationship between periodontal disease and cardiovascular disease, study participants may report healthy behaviors such as frequent flossing if they have started to alter their oral health behaviors.

Case-Control Studies

A case-control study is an observational study in which the objective is to evaluate persons with the disease or outcome of interest (cases) and compare them with another group of persons without the disease or outcome (controls) to determine if certain exposures (such as being a current smoker or taking a specific medication) or characteristics are associated with the disease or lack of disease. If the exposure is found more frequently in the cases, it is termed a "risk factor" for having the disease. Sometimes the exposure is found more frequently in the control group, suggesting it might be a "protective factor" that helps protect against a disease. Because this design evaluates individuals with and without the disease or outcome of interest, it may be used to assess the presence or absence of disease, but not development of the disease. There are critical design issues that must be considered in a case-control study.[5] The exposure and disease in both cases and controls should be assessed in the same manner. Patients who have a severe disease may experience recall bias in that they remember more or over-report past exposures or symptoms than generally healthy controls because they are seeking an explanation for why they have a disease. The cases need to represent the entire population of those with the disease, and the controls must be selected from the same population as the cases and should have the same prognostic characteristics. Finally, most experts recommend evaluating at least an equal number of controls as cases and matching cases and controls on variables that may differentially affect the exposure and disease. Selection of controls for a case-control study can be difficult and can introduce bias into the study if not chosen carefully, as discussed at length in the literature.[8–10] A case control study performed across three dental practice-based research networks assessed risk factors for ONJ.[11] ONJ cases were defined as having maxillary or mandibular exposed bone of any size that clinically appeared necrotic, without regard to duration or size. For each case, three controls with no current or previous history of bone necrosis were selected from the same dental practice where a case was diagnosed. Risk factors were ascertained in cases and controls, and the odds of having ONJ in patients who took bisphosphonates was compared to the odds of having ONJ in those who did not take bisphosphonate medication.

Case-control studies are particularly beneficial when studying rare diseases. If the disease of interest is sufficiently rare, such as salivary gland cancers, it may be safe to assume that a sample of cases is representative of the entire population of those with the disease. Findings in case-control studies are typically reported as the odds ratio of the exposure, whereas cohort study (see below) findings are expressed in terms of the relative risk of exposure. Case-control study results cannot be reported as the relative risk, because the investigator determines, and can arbitrarily change, the disease prevalence within the study by setting the number of study participants with and without the disease or outcome of interest. When interpreting the results of case-control studies, limitations in assessing temporality between the exposure and disease and the confidence interval of the association should be considered before making conclusions about the validity (a term used to describe how well the study measures that which it is intended to measure) of the results. A finding of a "dose-response" (in which increasing levels of the exposure such as pack-years of smoking are associated with increasing rates of the disease or condition) increases the strength of the evidence.

Because of criticisms about potential bias arising from control selection in case-control studies, researchers may choose to utilize more than one control population when

designing studies. In a classic example from the medical literature, the relation between estrogen use and endometrial cancer was established using a well-designed case-control study design and two control populations.[12] Cases of endometrial cancer admitted to hospitals (451 cases) were matched to two sets of control populations admitted to hospitals without endometrial cancer, one taken from those seeking gynecological services (442 cases) and another from those who did not seek gynecological services (446 controls). The choice for selection of two hospital control populations was to offset concerns about surveillance bias; that is, that estrogen users may be under greater surveillance for disease development.

Longitudinal Cohort Studies

Longitudinal cohort studies allow the opportunity to collect data over time. The purpose of this study design is to assess associations between an exposure or risk factor and subsequent development of disease or to determine outcomes of standard of care treatment. When performed prospectively to assess associations between an exposure and disease, a representative sample of the population of interest is assessed for an exposure at the beginning of the study, and then new cases of disease accrue during a period of follow-up evaluation. At the end of the study, the differences in exposures between those with and without the disease are evaluated. In some cases, a single population is observed over a period of time to observe the natural incidence of a condition or the natural history of a disease. For example, a study of Swedish adolescents estimated the incidence of temporomandibular disorder (TMD) pain. All individuals aged 12 to 19 years in all Public Dental Service clinics in a Swedish county from 2000 to 2003 were followed over 3 years for development of TMD pain.[13] Research participants with TMD were evaluated for differences that distinguished them from participants without TMD. In this study, TMD incidence was found to be greater in older children and in girls. More frequently, research participants may be selected for a particular exposure, along with a comparable group of controls without the exposure, and both groups are followed over time for development of disease.[14] An example of a longitudinal cohort study examining outcomes of treatment is a study of 372 individuals with head and neck cancer who were enrolled prior to undergoing radiation treatment and followed to determine the rate of oral complications such as oral mucositis, oral pain, and oral health-related quality of life.[15]

Cohort studies may also be retrospective, in which the exposure was captured in a standardized manner in the past, disease status is determined at a point in time before the outcomes of interest developed, and participants are followed over time. This study design assumes that the participant population (exposed and unexposed participants) is representative of the general population, and exposure history is collected accurately. Definitions of disease outcome should be reliable and reproducible and held constant during the study duration. Standard criteria for determining the disease outcome should be applied to exposed and non-exposed participants to avoid bias.

One significant advantage of well-conducted prospective cohort studies over other study designs is that the exposure is collected in a standardized manner, and cases are incident (new cases). This design provides more information about the natural history of the disease, as well as direct estimates of incidence and relative risk.[5] Longitudinal cohort studies have the potential to initially or further establish the temporal relationship between exposure and disease and a dose-response relationship, both of which increase the strength of the study conclusions and may provide evidence about the association (or causality) between an exposure and disease. An important factor in prospective longitudinal cohort studies is the ability to retain the cohort over time. Participants who drop out of research studies may differ from those who remain and may introduce attrition biases into the population sample.

Longitudinal studies by their nature are resource intensive. Large sample sizes for rare diseases and long durations for chronic diseases may be required. Maintaining the use of consistent study methods, such as standardized collection of the exposure, and retaining research participants in the study are continual challenges.

Clinical Trials

The purpose of a clinical trial is to determine whether a particular intervention is associated with a change in a prespecified health-related outcome. A clinical trial involves prospective assignment into one or more intervention groups and assessment of an outcome measure.

Clinical trials can be classified into four phases (Phase I, II, III, or IV) or stages.[16] This step-wise approach reduces the potential for harm from a previously untested intervention and allows investigators to assess safety and determine potential efficacy of a new treatment while minimizing time and costs. A Phase I trial often is the "first-time in human" study, meaning trial participants are the first humans to receive the new drug or treatment. These studies are not randomized or blinded and are typically performed with a small number of participants. The primary goal is to evaluate the safety of the agent and determine a safe dose range for subsequent studies. A Phase II trial tests the new drug in individuals who are randomized to different treatments, with goals of determining potential efficacy and establishing a

more complete safety profile. Feasibility of using the treatment also can be determined. The Phase III trial enrolls hundreds or thousands of participants and is sometimes called a "pivotal study." These trials are designed to test efficacy in a much larger segment of the population with the disease or condition, and results are used to gain drug approval from government agencies. Phase III trials should generate generalizable results. Phase IV trials are post-marketing studies to determine how well a treatment found effective in a Phase III trial works in the community and to assess any side effects associated with its long-term use in the overall population.

A randomized controlled trial (RCT) compares participants receiving the intervention under study to a control group, such as participants receiving another treatment, usual care, placebo treatment, or no treatment. Potential study participants from a well-defined study population are assigned at random to receive or not receive the intervention(s) under study, and then well-defined endpoints are measured at a specific time point. Intervention efficacy is assessed by comparing the outcome measure between the intervention group(s) and the control. RCTs provide the strongest evidence for the causal nature of a modifiable factor (such as inflammation in a periodontal pocket), and the effect that modifying the factor has on disease outcomes (such as reduction in pocket depth).

A key component of RCTs is that research participants are assigned to one of the study arms at random to eliminate the potential for bias in treatment assignment. Random, concealed, or "blinded" allocation of treatment helps ensure that any baseline differences in the treatment groups arise by chance alone. The random allocation process involves generating an unpredictable random sequence and then implementing the sequence in a way that conceals the interventions until participants have been formally assigned to their groups. Both randomization and concealment are necessary to maximize validity in RCTs, and reproducibility of the allocation order and the concealment process are necessary to maintain integrity of the research study. Other important features of high-quality RCTs include independent or "blind" assessment of research endpoints and data analysis based upon the treatment assignment, also known as analysis by "intention to treat." Intention to treat analysis removes artifacts from the study that are caused by unequal attrition in the two study arms, or by treatment crossover.

There are three levels of concealing treatment (blinding) in an RCT: (1) participants are unaware of their study treatment group; (2) the investigators are unaware of the participant's study treatment group; and (3) the statistical analyses are conducted without knowledge of the groups' study treatment. Multiple levels of blinding can occur in an RCT and should be considered when feasible. Recent oral health RCTs that followed the strict principles of clinical trials were two Phase III studies testing periodontal therapy as a treatment to prevent preterm birth[17] and to improve glycemic control.[18]

A limitation of the RCT study design is the concern about external validity, or the extent to which RCT results are applicable beyond the research study. In addition, RCTs are expensive because of the logistics involved in sampling, blinding, treating, and following hundreds of participants; in addition, extremely large sample sizes are required to study rare outcomes. Consequently, some research questions may be more appropriately addressed using other study designs.

Systematic Reviews

A systematic review is a structured process of comprehensively reviewing published research studies focused on a research question in which inclusion and exclusion criteria for study selection are established *a priori*. The purpose of the systematic review is to determine the "state of the science" by objectively identifying, appraising, selecting, and synthesizing high-quality research evidence. Such reviews may also elucidate a paucity of high-quality evidence and, therefore, identify research questions to be addressed in future studies. For more information about systematic reviews, see Chapter 29: How to identify, interpret and apply the scientific literature to practice.

ISSUES IN THE DESIGN, IMPLEMENTATION, AND QUALITY OF CLINICAL RESEARCH

Clinical research, regardless of its type, is a scientific study. Therefore, investigators must take care to conduct studies that minimize bias and maximize reproducibility. Many factors should be considered when designing and implementing clinical studies, including the type of study design, sample size, research participant selection, methods to ascertain exposures and outcomes, ethical and human subjects concerns, and analytical approaches. Below are short descriptions of some of the features of clinical research to consider when designing clinical research studies.

Study Design

Investigators should employ a study design that is suitable and most appropriate for answering the clinical research question of interest. In general, investigators should review the literature on the topic of interest, define the purpose of the study and hypothesis to be tested, and then use the

strongest research design that is acceptable and feasible to address the research question.

Sample Size

When designing clinical research studies, an important consideration is the required number of study participants to draw meaningful statistical conclusions. The sample size depends upon the variability of the data and the effect size, or the difference between values.[25] Analyses should be conducted to determine the sample size needed to accomplish the goals of the study. For longitudinal studies, sample size calculations should take into account study participant attrition over time. Many clinical studies suffer from small sample sizes, and this issue is often a reason why studies are excluded from evidence-based reviews.[26]

Selection of Disease and Control Groups

Another critical factor to consider when designing a study is the definition and selection of the disease and control groups. The disease or case group should be carefully defined to include those individuals with the disease or condition of interest, but without other conditions or variables that may affect the validity of the study results.

Many clinical studies include a control group to compare study outcomes between the case or disease population and those who do not have the outcome of interest or do not receive the intervention being tested. For these studies, the control group should be clearly defined to include those individuals who are similar to the case or test group in many aspects so that there are minimal differing variables between the comparison groups.[8–10] Careful selection of control populations was described in the Case-Control Study section above. To guide control group selection, studies may match cases and controls based upon variables that may contribute to the exposure or disease presentation or severity such as gender, age, current/past smoking history, and setting where participants may be recruited for study participation, such as a tertiary care clinic. Controls should be chosen in the same manner as cases to ensure they have the same likelihood of having the exposure of interest.[8–10] For example, if cases are patients with head and neck cancer being recruited from a radiation oncology clinic, controls should be patients recruited from the same clinic, who are undergoing treatment for another condition.

Potential for Bias

When designing and conducting a research study, there are numerous types of bias that must be considered to maintain the validity of study results. Bias can occur at any phase of research, including decisions related to the study design, implementation of study procedures, methods of data collection, the process of data analysis, and publication of study results.[27] Some bias is inevitable and inherent in certain study designs, and the investigator must show that efforts have been undertaken to lessen the impact of study bias.

Methods to avoid selection bias in observational studies include enrolling consecutive individuals reporting to a clinic who meet inclusion criteria, or recruiting individuals from an existing large population using consistent recruitment criteria for all individuals. RCTs use randomization and allocation procedures for treatment arm assignment to avoid bias.

Other biases can occur during data collection. The use of objective, validated measures for outcome assessment and independent data collectors will reduce these biases (see section Outcome Assessment below). Some biases can be addressed through data analyses, such as accounting for potential confounders and effect modifiers.

Outcome Assessment

Study outcomes or endpoints used in a clinical study or trial must be measurable, reliable (consistent and repeatable), and valid to document disease prevalence and/or progression or determine the efficacy of the intervention being tested. The outcome must be reproducible, and there should be published evidence of its validity. For example, if the goal of a study is to quantify oral cancer pain, the investigator should use a validated instrument to collect pain measures appropriate for the population being studied. In this example, an appropriate instrument would be a pain scale that had been tested previously in a population for whom cancer pain had been assessed and for whom the cultural values related to expression of pain had been similar.

Methods for ascertainment of study outcomes also need to be standardized. Examiners should be calibrated, by having them each examine the same group of patients to measure outcome assessment agreement with each other (inter-rater reliability) and having them examine a set of patients repeatedly to measure their outcome assessment agreement with themselves (intra-rater reliability).[28] Studies that assess caries and periodontal disease over time usually conduct calibration sessions annually or prior to a wave of study visits, during which examiners are calibrated to a gold standard examiner and compared numerically using percentage agreement or kappa scores.[17,29]

Loss to Follow-up and Retention

When planning research studies that intend to follow research participants over time, significant efforts should be

made to retain those participants in the study. Minimizing loss to follow-up is critical to maintaining valid study results. Aside from the concern about missing data, when study participants are lost over time, there is no way to know if they exhibit characteristics that may be different from those who have been retained in the study, such as having more or less severe disease. Both simple and sophisticated analytic methods are available to model missing data, but these cannot protect against bias created by research participant loss. One can look at how participants lost to follow-up differ from those retained and undertake bootstrapping or other rigorous sensitivity analyses to impute missing data and establish a range for the study outcome.[30–32] However, these analytic methods have limitations that should be considered and should not replace the need for rigorous approaches to retain the study population.

Retention strategies should be planned prior to implementing the clinical study and should be tracked carefully throughout the study. If retention efforts are not producing the desired results, strategies should be reassessed and improved during the study's data collection phase.

Retention strategies that can be considered when designing a study include:

- Having a run-in period at the beginning of a study to eliminate those who will be lost or cannot comply.
- Obtaining reliable, complete participant contact information that may include alternate phone numbers, email and physical addresses.
- Obtaining names and contact information for designated family or friends who could be contacted for information on missing participants.
- Sending out communications such as newsletters and educational pieces that inform study participants of new findings in the field or progress of the study, as allowable.
- Sending out reminders such as birthday cards, text messages, phone messages, postcards, or letters.
- Having dedicated and professional study staff with low turnover to establish rapport with study participants.
- Employing outreach workers to find those who may be lost to follow-up.
- Having the data center follow-up individuals via phone or email should they fail to respond to contacts made by the clinic or site. It is possible the participant has a personal reason for not continuing in the study.
- Reviewing death records and registries to account for those missing due to demise.
- Reviewing public media to search for obituaries and accidents.
- Offering study visits during hours that accommodate participants; this may include early mornings, evenings, or weekends.
- Scheduling study visits with other necessary patient care to minimize the number of trips to the study site.
- Creating satellite clinics or sites near where patients are situated so they are not required to travel as much. Venues for data collection may include visits to participants' homes, churches, schools' or worksites to allow study visits to be less disruptive to participants' lives.
- Establishing methods for remote data collection when the study data and outcomes are suitable for such methods.
- Providing incentives that make it easier to participate in the study such as
  - child care
  - paid transportation to the site
  - remuneration as deemed appropriate by the IRB.

Prior to implementing retention strategies in a research study, they should be presented to the IRB for their approval. Further, with the exception of review of public information such as death registries or public media, strategies to obtain follow-up data from participants require participant consent to prevent privacy infringement. An engaged, informed, and interested study population is far more likely to be retained than one who is not.[31]

Analytical Issues

It is impossible in this limited space to discuss all the analytical issues of clinical studies. Important topics include prespecified analysis plans, avoidance of unsupported multiple comparisons, and attention to clinical significance of outcomes. Unless a study is fully hypothesis-generating and exploratory, the principal study hypothesis, sample size, power, and statistical analyses should be prespecified to protect against *ad hoc* analyses that attempt to make provocative conclusions from the data. It is tempting to conduct analyses for which the study was not specifically designed, and it is unusual for convincing, robust conclusions to be drawn from such *a posteriori* analysis. Another threat to the validity of analyses is multiple comparisons, or making too many comparisons for the study sample size. This will quickly undermine study power. Although many statistical corrections are available for multiple comparisons, there is no perfect method and, as such, this approach should be avoided unless necessary. One should also predefine endpoints that will represent clinical significance in the study findings, independent of statistical significance. A common mistake is to conflate statistical significance with clinical significance. For example, an epidemiologic study may result in a caries prevalence difference of 0.1 surfacing between sample groups. Because of a large sample size, the difference may be

statistically significant, but the clinical significance of the finding is questionable. The articulation of planned study analyses can be included in the protocol or in a separate statistical analysis plan depending on the complexity of the planned analyses.[33]

Generalizability and Representativeness

Generalizability of study results and representativeness of the study population are important considerations for any clinical research study. The convenience of conducting a study in a setting such as an academic health center may limit study participant selection and would limit generalizability of study findings to the population with a disease or condition. Similarly, it may be convenient to enroll patients who present to a tertiary clinic, but those study participants may not represent the race, ethnicity, and/or age of individuals in the population with the disease or condition of interest. Consequently, when planning a clinical study, the setting and population from which potential participants will be recruited must be considered as related to representativeness of the study sample and generalizability of study findings.

For example, observational studies of select patient groups often draw conclusions about the condition from small numbers of patients who are in active treatment in one medical center and who have the most severe disease. However, the patients evaluated in the study may not represent all patients in the general population. A single center study does have value in generating new hypotheses for more research, but the studies would need to be replicated in larger, more representative samples to improve generalizability of research results.[25] Studies of rare diseases can be difficult because few patients with the condition of interest are available for study. To overcome this problem, multi-center registries can be established that enroll and follow patients with a particular condition. Examples include the chromosome 22q11.2 deletion syndrome registry that has characterized the highly variable spectrum of the clinical consequences associated with this deletion in over 1400 affected individuals[34] and the international registry to assess safety of denosumab, an antiresorptive drug associated with ONJ.[14]

Concern about representativeness has also occurred in clinical trials with the use of restrictive inclusion/exclusion criteria. To determine if a new drug or technique is effective for treating a disease, potential participants with coexisting conditions may be excluded, or study participation may be limited to a particular age group. This creates a potential for study results to be valid for only a population similar to those enrolled in the trial, which may be a smaller subset of individuals with disease. An example of this problem is clinical trials testing therapies for non-Hodgkins lymphoma (NHL). While the majority of patients with NHL are over the age of 65 years, older adults have been poorly represented in NHL RCTs.[35] Similarly, most RCTs testing caries preventive treatments studied children, though the therapies are recommended for adults.[36]

ETHICAL CONSIDERATIONS AND REGULATORY REQUIREMENTS

Regulatory requirements for research with human participants vary according to the type of study conducted and the region or country in which the research is conducted. In the United States, starting an interventional clinical trial to test the safety and efficacy of an investigational new drug for disease treatment will require an Investigational New Drug (IND) application filed with the United States Food and Drug Administration (FDA) and approval from an Institutional Review Board (IRB). In Canada, a Clinical Trial Application must be filed with Health Canada; an investigator must receive a No Objection Letter from Health Canada and IRB approval to begin a study. In the European Union, the trial of an investigational drug may be started after a Clinical Trial Authorization (CTA) dossier is authorized by a National Competent Authority and an Ethics Committee issues a positive opinion. For a simple observational study intended, for example, to identify risk factors for a disease or condition, regulations for the protection of human subjects must be followed. These may vary with the region or country in which the research is conducted.

For any research study that involves human participants, sponsors and investigators have an obligation to protect the participants, by weighing the foreseeable risks and anticipated benefits before initiating a study and by conducting the study with adequate rigor to produce scientifically valid results. The regulations and guidelines followed by clinical researchers today have their foundations in a variety of codes, resolutions, and guidelines adopted by national and international bodies, including the Nuremberg Code (1947),[37] the Declaration of Helsinki[38] (adopted in 1964 and amended several times through 2013), the Belmont Report prepared by the United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979),[39] the International Ethical Guidelines for Biomedical Research Involving Human Subjects published by the Council for International Organizations of Medical Sciences (CIOMS) (released 1993, most recently revised in 2016),[40] and the E6 Guideline for Good Clinical Practice developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[41]

Beginning in 1990, the ICH brought together representatives of the regulatory bodies and industry representatives from the European Union (EU), Japan, and the US. The mission of the ICH was to promote international harmonization of requirements, to streamline the process of conducting regulated clinical research in different countries. Providing a unified standard for technical requirements and acceptance of clinical data by the regulatory agencies of the participating jurisdictions was intended to facilitate the development and marketing pathway for new medical products. Topics covered by the ICH are categorized as Quality, Safety, Efficacy, and Multidisciplinary Guidelines, based on the criteria for approving new medicinal products. Guidelines in the Efficacy category deal with the design, conduct, safety, and reporting of clinical trials, and include the ICH Guideline for Good Clinical Practice[41] (ICH GCP E6), which was finalized in 1996 and amended in 2016. The Guideline defines Good Clinical Practice as "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects" and indicates that "compliance with this standard provides public assurance that the rights, safety and well-being of trial participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible."

Section 2 of the ICH E6 document lists the 13 principles of ICH GCP (see Table 2-1; also Table 2-2, Table 2-3), which emphasize ethical treatment of human subjects, sound science to justify and support a trial, and scientific rigor and quality in the conduct of the trial. Sections 3, 4, and 5 of the GCP document describe the responsibilities of the following entities involved in the conduct of a clinical trial:

- The IRB or Independent Ethics Committee (IEC) is defined as "an independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial." The IRB or IEC is expected to review and approve the trial protocol and amendments, the methods and material to be used in obtaining and documenting informed consent of trial participants, qualifications of the investigator, etc., and to conduct continuing review of the trial at least annually.
- The Investigator is defined as "a person responsible for the conduct of the clinical trial at a trial site." Investigator(s) should be "qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies)." The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. A qualified physician or dentist should be responsible for all trial-related

Table 2-1 The principles of good clinical practice.[41]

1	Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2	Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3	The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4	The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5	Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6	A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/ favorable opinion.
7	The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8	Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9	Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10	All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this guideline, irrespective of the type of media used.
11	The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12	Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13	Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

International Council for Harmonisation Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 9 November 2016.

Table 2-2 Data collection time points by study design.

Past	Present	Future
Cross-Sectional Study		
	• Exposure • Disease or Outcome	
Case-Control Study		
• Exposure	• Disease or Outcome	
Retrospective Cohort Study		
• Exposure	• Disease or Outcome	
Prospective Cohort Study		
	• Exposure	• Disease or Outcome
Clinical Trial		
	• Intervention	• Outcome

medical or dental decisions. Among the critical duties of the investigator are communication with the IEC/IRB, compliance with the protocol, accountability for the investigational product, proper conduct and documentation of the informed consent process, proper recording and reporting of trial data, and documentation and reporting of safety issues.

- The Sponsor is defined as "an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial." The sponsor is responsible for implementing a risk-based system to manage quality throughout all stages of the trial process, for using qualified individuals to design the trial, develop study documents, conduct the trial, manage the data, and provide safety oversight, for ensuring that adequate data are available to support use of an investigational product in the trial, for ensuring that an investigational product is manufactured in accordance with good manufacturing practice (GMP) standards, labeled appropriately and maintained under appropriate conditions, for submitting applications for investigational product use and information on safety issues to the proper regulatory authorities, and for monitoring the trial to ensure that the rights and well-being of participants are protected, that the trial data are accurate, complete and verifiable, and that the trial is conducted in compliance with the protocol, with GCP and with applicable regulatory requirements. Adherence to GCP is expected of all clinical research monitors and auditors appointed by the sponsor and all staff of contract research organizations to whom a sponsor transfers any study-related functions.

Sections 6 and 7 of the GCP Guidelines outline the critical components of a clinical protocol and an Investigator's Brochure for an investigational product. Section 8 summarizes the minimum essential documents "which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced." The list includes documents to be generated before the trial begins, during the clinical conduct of the trial and after completion or termination of the trial.

The importance of adhering to the principles of good clinical practice when conducting research with human participants is widely recognized. While the ICH GCP standards

Table 2-3 Strengths and weaknesses by study design.

Study Design	Strengths	Weaknesses
Cross-sectional	• Time and resource efficient • Can assess multiple exposures and confounders • Can assess multiple outcomes	• No temporality between exposure and outcome; causality between exposure and outcome cannot be assessed
Case-control	• Time and resource efficient • Can assess multiple exposures and confounders • Good for rare diseases	• Can assess one outcome only • Poor selection of controls can introduce selection bias • Potential to recall bias • No temporality between exposure and outcome
Retrospective and Prospective Cohort	• Can assess causality • Can assess multiple exposures • Can assess multiple outcomes • Ability to control for multiple confounders	• Time and resource intensive • Not ideal for rare diseases
Clinical Trial	• Ability to assess safety and efficacy of an intervention • Prospective assignment into study groups reduces potential bias • Strongest evidence for causality between a modifiable factor and outcome	• Time and resource intensive

were developed as guidelines, the principles have been incorporated into legal requirements in some countries (e.g., Japan, Australia, Canada). In the EU, the ICH GCP is considered a scientific guideline, but legal requirements for following good clinical practice are implemented in Directive 2001/20/EC and then in Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 ("approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use") and Directive 2005/28/EC ("laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use"). In addition, specific national laws apply within the EU member states (e.g., The Medicines for Human Use [Clinical Trials] Regulations 2004 and its amendments in the United Kingdom). In the US, the FDA endorsed the ICH E6 GCP and published it as a guidance document, with the statement that it "represents the agency's current thinking on good clinical practices." While FDA guidance documents are not legally binding, the principles of good clinical practice and human subjects protection have been incorporated into law in various parts of the U.S. (e.g., 45 CFR part 46 on Protection of Human Subjects, frequently referred to as the "Common Rule," which offers basic protections to human participants involved in biomedical or behavioral research conducted or supported by federal departments and agencies;[2] 21 CFR part 50 on Protection of Human Subjects and 21 CFR part 56 on IRBs; 21 CFR part 312 on Investigational New Drug Applications; 21 CFR part 314 on FDA approval to Market a New Drug; 21 CFR part 812 on Investigational Device Exemptions; 21 CFR part 814 on Premarket Approval of Medical Devices, etc.).

While the GCP guidance was developed for research using regulated investigational products (drugs, biologics, devices) in human participants, the introduction to ICH GCP guidance document states, "the principles established in this guidance may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects." Similarly, the World Health Organization (WHO) Handbook for Good Clinical Research Practice, states: "To the extent possible, the principles of GCP should generally apply to all clinical research involving human subjects, and not just research involving pharmaceutical or other medical products ... Although some principles of GCP may not apply to all types of research on human subjects, consideration of these principles is strongly encouraged wherever applicable as a means of ensuring the ethical, methodologically sound and accurate conduct of human subjects research."[2] Following the applicable parts of the GCP guidelines during the conduct of non-interventional studies provides a good starting point for complying with the variety of human subjects protection regulations that exist in countries around the world.

The US Common Rule (45 CFR 46, Subpart A),[2] which stipulates procedural requirements related to IRBs and informed consent, was recently revised for the first time since 1991.[43] The revisions have been adopted by the U.S. Department of Health and Human Services and 19 other Federal Departments and Agencies. These policy changes went into effect on January 21, 2019 in an effort to modernize and simplify the current system of oversight. The revisions are intended to better protect human participants involved in research, while reducing administrative burden placed on investigators. Broad categories for which revisions were adopted include:

- exempt research categories
- requirements for IRB continuing reviews
- informed consent
- single IRB requirements
- requirements for IRB reviews of grant applications and contract proposals.

The EU General Data Protection Regulation (GDPR) became effective on May 25, 2018.[44] The GDPR imposes rules to protect individuals' personal data. Its requirements for the processing of personal data have the potential to impact human participants research activities. While the GDPR applies directly to data controllers and data processors in the EU, it could also apply to data controllers and processors outside of the EU when monitoring data that tracks participants' behavior in the EU. For example, if a clinical study outside of the EU is using personal electronic devices (e.g., wearables or mobile devices) to track participants' health data, these data could be subject to the GDPR if a study participant is visiting the EU and transmits the data to the non-EU study location.

Clinical Trials Registration and Results Reporting

Due to concerns about selective reporting and publication bias resulting in publishing clinical trials with positive findings only and ethical considerations for clinical trial participants who have contributed to clinical trials that have not been published, the practice of clinical trial registration has been required in some circumstances and requested in others. Numerous clinical trials registries exist in many countries to facilitate registration of clinical trials prior to or soon after the first participant has been enrolled. Further, some registries allow for reporting of clinical trial results to offset the concerns about publication bias.

In the US, ClinicalTrials.gov, which is operated by the National Institutes of Health's (NIH) National Library of Medicine, launched in 2000 and provides a publicly accessible

platform for the public to access clinical trial information. The Food and Drug Administration Amendments Act of 2007 (FDAAA Section 801)[45] requires that studies that meet the definition of an "applicable clinical trial" (ACT) that were initiated or ongoing after the law came into effect must be registered on ClinicalTrials.gov. ACTs include the following: controlled clinical investigations (other than phase 1 investigations) of any FDA-regulated drug or biological product for any disease or condition, and certain studies of FDA-regulated medical devices, excluding small clinical trials to determine feasibility and certain clinical trials to test prototype devices, but including FDA-required pediatric postmarket surveillances of a device product. Further, the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11)[46] has been in effect since 2017 and clarifies that ACTs generally include interventional studies of FDA-regulated drug, biological, or device products that meet one of the following conditions: The trial has one or more US sites, the trial is conducted under an FDA IND application or IDE, or the trial involves a drug, biological, or device product that is manufactured in the US or its territories and is exported for research. The NIH Policy on Dissemination of NIH-Funded Clinical Trial Information[47] came into effect in January 2017 and requires clinical trials registration and results reporting for all clinical trials funded by NIH, regardless of whether they are subject to the Final Rule. Most NIH-funded trials must be registered and reported on ClinicalTrials.gov, with delayed enforcement of certain clinical trials.[48]

The International Committee of Medical Journal Editors (ICMJE) instituted a policy in 2005 that requires registration of a clinical trial in a public trials registry as a condition of consideration for publication in a journal that follows the ICMJE policy.[49] The ICMJE accepts registration in any registry that is recognized on the WHO International Clinical Trials Registry Platform[50] or in ClinicalTrials.gov.

SAFETY MONITORING

Safety reporting and safety oversight constitute study safety monitoring. Such monitoring must accommodate the nature of the clinical research being conducted. The goal of safety reporting and safety oversight is to protect the human participants from the risks that are intrinsic to participating in the research. It is also important for those reading the literature to know not only the benefits, but also the risks of a new therapy, whether a drug, procedure, or approach. Plans for safety monitoring should be commensurate with the risks and complexity of the study. The plans should include adequate processes to protect those participating in the research while not wasting precious resources collecting and reporting unnecessary or duplicative data. This section includes a brief overview of safety monitoring; references are provided for further reading.

Safety Reporting

The requirements and processes of safety reporting are governed by multiple regulations, guidances, and policies. Currently, clinical research funded by the US government must comply with safety reporting requirements specified by the Common Rule, 45 CFR 46,[2] and associated guidances and policies issued by the Office of Human Research Protections.[51] Studies governed by Food and Drug Law must comply with the requirements of the FDA.[52] There is overlap between some of the requirements as both have their basis in ICH guidance (see above). There are different regulations and guidances pertaining to studies that test biologics or drugs conducted under IND,[53] studies that do not require an IND but include marketed products, and studies that test devices and materials. When designing the study, it is important to determine whether the study requires an IND under 21 CFR 312[53] or Investigational Device Exemption (IDE) under 21 CFR 812.[54] Should an investigator be uncertain whether an IND or IDE is required, the appropriate agency can be contacted to obtain designation.[55–58]

Studies conducted under IND are required to collect "adverse events." Adverse events are any untoward medical occurrences associated with the use of the drug in humans, whether or not considered drug-related (21 CFR 312.32 (a)).[53] An important category of adverse event is a "Serious Adverse Event," which is generally reported to the FDA and IRBs in an expedited manner so that it can be acted upon quickly. Reporting of these events captures information suggesting that a drug poses a significant risk to human participants, and such reports require special scrutiny and attention. Adverse events are considered serious if they result in any of the following outcomes:

- death;
- an immediately life-threatening adverse event;
- an inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly or birth defect; or
- an important medical event that may not result in the above outcomes may be considered serious when, based upon appropriate medical judgment, it could jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the above outcomes. (21 CFR 312.32(a).[53]

Another important safety definition is "suspected adverse reaction," which means any adverse event for which there is

a "reasonable possibility" of a causal relationship between the drug and the adverse event (21 CFR 312.32(a)).[53] "Unexpected" is another term applied to adverse events. For regulatory purposes, unexpected means that the event has not been observed with drug use previously; that is, it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed, or it is not described in the general investigational plan or elsewhere in the IND application (21 CFR 312.32(a)). IND sponsors and investigators working under IND are required to have specific knowledge of any adverse events, including their type and severity, that have occurred with previous drug use so that they may recognize those events that require special focus, more detailed information, and expedited reported to the FDA and governing IRB.

The aforementioned safety reporting requirements are specific to drug and biologic studies under IND. For any federally funded study subject to the Common Rule, there is a requirement to capture and report "unanticipated problems involving risks to subjects or others," following specific requirements and time frames. An Unanticipated Problem meets all the following criteria:

- "unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized."

Unanticipated problems may or may not be either adverse events or serious adverse events. This definition can include events such as breach of participant privacy, or hazardous conditions or risks related to participating in the research that are not related to a drug.

Safety Oversight

For studies that involve only minimal risk for participants, oversight by the principal investigator is often adequate. However, studies of greater risk and complexity may either benefit from or require different or independent safety oversight structures. Most familiar are Data and Safety Monitoring Boards (DSMBs) or Committees (DSMCs), groups of independent experts who oversee reports of study conduct, data quality, and safety information. DSMBs are usually governed by a charter which outlines how frequently meetings occur, what sorts of data will be reviewed, whether special meetings should be convened to address certain important or unexpected events, how meetings will be conducted, what constitutes a quorum, and what sorts of recommendations are expected. DSMBs are an important oversight mechanism in the protection of human participant safety. Relevant expertise independent of the study and its investigators is critical to the proper functioning of a DSMB. Thus, DSMBs must be carefully constituted and supported to perform effectively.[59]

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3

Ulcerative, Vesicular, and Bullous Lesions

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Many ulcerative or vesiculobullous disease of the mouth have a similar clinical appearance. The oral mucosa is thin, and even slight trauma leads to rupture of vesicles and bullae forming eroded, red areas; a yellow fibrin membrane forms over the erosion and an ulcer develops. As such, vesiculo-bullous lesions that have a characteristic appearance on the skin (such as tense blisters of bullous pemphigoid) have a somewhat nonspecific appearance on the oral mucosa.

Taking a careful and detailed history often provides as much information as the clinical examination and guides the clinician during the clinical evaluation. Four pieces of information in particular help the clinician rapidly categorize a patient's disease and simplify the diagnosis: the length of time the lesions have been present (acute or chronic lesions), a past history of similar lesions (primary or recurrent disease, or episodic disease), the number of lesions present (single or multiple), and the location of lesions. In this chapter, the diseases are grouped according to the information just described. This information serves as a good starting point for the student who is just learning to diagnose these disorders, as well as for the experienced clinician who is aware of the potential diagnostic pitfalls.

A complete review of systems should be obtained for each patient, including questions regarding the presence of skin, eye, genital, pharyngeal, nasal, and rectal lesions as well as the presence of symptoms such as fever, joint pains, and muscle weakness to name a few. The clinical examination should include a thorough inspection of the exposed skin surfaces. Some knowledge of basic dermatology is helpful because many disorders occurring on the oral mucosa may also affect the skin.

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

Dermatologic lesions are classified according to their clinical appearance and include the following frequently used terms that are also applicable in the oral mucosa:

1) *Macules*. These are lesions that are flush with the adjacent mucosa and that are noticeable because of their difference in color from normal skin or mucosa. They may be red due to increased vascularity or inflammation, or pigmented due to the presence of melanin, hemosiderin, and foreign material (including the breakdown products of medications). A good example in the oral cavity is the melanotic macule.
2) *Papules*. These are lesions raised above the mucosal surface that are smaller than 1.0 cm in diameter (some use 0.5 cm for oral mucosal lesions). They may be slightly domed, or flat-topped. Papules are seen in a wide variety of diseases, such as the yellow-white papules of pseudomembranous candidiasis.
3) *Plaques*. These are raised lesions that are greater than 1 cm in diameter; they are essentially large papules.
4) *Nodules*. These lesions are present within the deep mucosa. The lesions may also protrude above the mucosa forming a characteristic dome-shaped structure. A good example of an oral mucosal nodule is the irritation fibroma.
5) *Vesicles*. These are small blisters containing clear fluid that are less than 1 cm in diameter.
6) *Bullae*. These are elevated blisters containing clear fluid that are greater than 1 cm in diameter.
7) *Erosions*. These are red lesions often caused by the rupture of vesicles or bullae, or trauma and are generally moist on the skin. However, they may also result from thinning or atrophy of the epithelium in inflammatory disease such as lichen planus. These should not be mistaken for ulcers, which are covered with fibrin and are yellow.
8) *Pustules*. These are blisters containing purulent material and appear yellow.
9) *Ulcers*. These are well-circumscribed, sometimes depressed lesions with an epithelial defect that is covered by a fibrin membrane, resulting in a yellow-white appearance. A good example is an aphthous ulcer.
10) *Purpura*. These are reddish to purple discolorations caused by blood from vessels leaking into the connective tissue. These lesions do not blanch when pressure is applied and are classified by size as petechiae (less than 0.3 cm), purpura (0.4–0.9 cm), or ecchymoses (greater than 1 cm).

The first section of this chapter describes acute multiple lesions that tend to occur only as a single episode; the second portion of the chapter covers recurring ulcerative conditions; the third portion presents conditions characterized by chronic, continuous multiple erosions and ulcers; and the final section describes diseases that present with single ulcers. It is hoped that classifying the disorders in this way will help the clinician avoid the common diagnostic problem of confusing acute viral infections with recurrent oral conditions, such as recurrent aphthous stomatitis, or disorders that present as chronic progressive disease, such as pemphigus.

THE PATIENT WITH ACUTE MULTIPLE LESIONS

The major diseases that cause acute multiple oral ulcers include viral and bacterial stomatitis, allergic and hypersensitivity reactions (particularly erythema multiforme and contact allergic stomatitis), and lesions caused by medications (such as cancer chemotherapy) (see Chapter 17, "Hematologic Diseases").

Herpes Simplex Virus Infection

Etiology and Pathogenesis

The Herpesviridae family of viruses contains eight different viruses that are pathogenic in humans with one affecting simians (Table 3-1). This chapter discusses only herpes simplex virus (HSV)-1 and varicella-zoster virus (VZV) which cause multiple ulcers, and cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections, which usually cause single ulcers. Herpes viruses have a common structure: an internal core containing the viral genome, an icosahedral nucleocapsid, the tegument, and an outer lipid envelope containing viral glycoproteins on its surface that are derived from host cellular membranes.[1] Nonetheless, each of the herpesviruses is distinct.

HSV-1, an α-herpesvirus, is a ubiquitous virus, and 54% of adults aged 14–49 between 2005–2014 in the United States are seropositive for it.[2] In general, infections above the waist are caused by HSV-1 and those below the waist by HSV-2, although with changing sexual practices, it is not uncommon to culture HSV-2 from oral lesions and vice versa.[3] The primary infection, which occurs on initial contact with the virus, is acquired by inoculation of the mucosa, skin, and eye with infected secretions. The virus then travels along the sensory nerve axons and establishes chronic, latent infection in the sensory ganglion (such as the trigeminal ganglion).[4] Extraneuronal latency (i.e., HSV remaining latent in cells other than neurons such as the epithelium) may play a role in recurrent lesions of the lips.[5] Recurrent HSV results when HSV reactivates at latent sites and travels centripetally to the mucosa or the skin, where it is directly cytopathic to epithelial cells, causing recrudescent HSV infection in the form of localized vesicles or ulcers.[6]

The most common sites of infection are the oral and genital mucosa and the eye. HSV infection of the cornea

Table 3-1 Herpesviridae that are pathogenic in humans.

Type of Human herpesvirus (HHV)	Primary infection	Recrudescent lesions in healthy hosts	Recrudescent lesions in immunocompromised hosts
Herpes simplex virus 1 (HHV-1)	Gingivostomatitis, keratoconjunctivitis, genital and skin lesions	Herpes labialis ("cold sores"), intraoral ulcers, keratoconjunctivitis, genital and skin lesions	Ulcers at any mucocutaneous site, usually large and persistent; disseminated infection
Herpes simplex virus 2 (HHV-2)	Genital and skin lesions, gingivostomatitis, keratoconjunctivitis, neonatal infections, aseptic meningitis	Genital and skin lesions gingivostomatitis, aseptic meningitis	Ulcers at any mucocutaneous site, usually large, persistent and dermatomal; disseminated infection
Varicella-zoster virus (HHV-3)	Varicella (chickenpox)	Zoster (shingles)	Disseminated infection
Cytomegalovirus (HHV-4)	Infectious mononucleosis, hepatitis, congenital disease		Retinitis, gastroenteritis hepatitis, severe oral ulcers
Epstein-Barr virus (HHV-5)	Infectious mononucleosis-like, hepatitis, encephalitis		Hairy leukoplakia, lymphoproliferative disorders, mucocutaneous ulcers
HHV-6	Roseola infantum, otitis media, encephalitis		Fever, bone marrow suppression
HHV-7	Roseola infantum		
HHV-8	Infectious mononucleosis-like, febrile exanthema		Kaposi sarcoma, lymphoproliferative disorders, bone marrow suppression

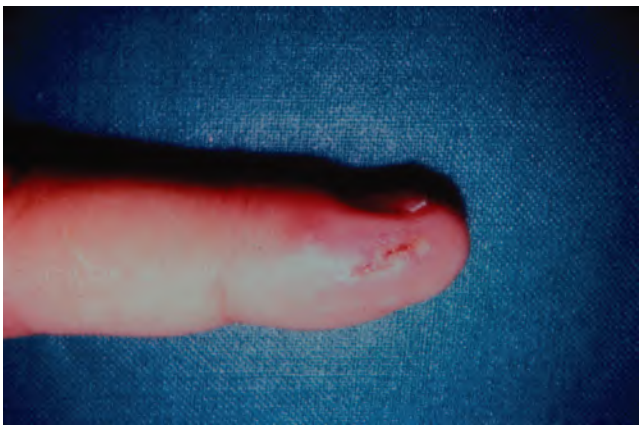

Figure 3-1 Primary herpetic whitlow on the finger of a dentist.

(keratitis) is a major cause of blindness in the world. HSV-1 or -2 may cause herpes whitlow, an infection of the fingers when virus is inoculated into the fingers through a break in the skin (Figure 3-1). This was a common occupational hazard (including within the dental profession) before the widespread use of gloves.[7,8] Other HSV-1 infections include herpes gladiatorum (infections of the skin spread through the sport of wrestling),[9] herpes encephalitis, HSV esophagitis, HSV pneumonia and neonatal and disseminated infection.[6]

HSV is an important etiologic agent in erythema multiforme, which is discussed below.[10,11] HSV has been recovered in the endoneurial fluid of 77% of patients with Bell palsy.[12] However, VZV has also been strongly implicated in the development of Bell palsy.[13] Treatment with antiviral therapy (especially with corticosteroids) within the first 48 hours resulted in better outcomes further supporting the concept of herpesvirus involvement in the pathogenesis of Bell palsy.[14] However, a recent study showed that approximately 60% of cases of Bell palsy were associated with HHV6, and only 13% with HSV.[15]

Clinical Manifestations

Primary Gingivostomatitis

The majority of primary HSV-1 infections are subclinical and generally occur in children and teenagers.[6,13] There is a 1- to 3-day viral prodrome of fever, loss of appetite, malaise, and myalgia that may also be accompanied by headache and nausea. Oral pain leads to poor oral intake, and patients may require hospitalization for hydration. The disease is self-limiting in otherwise normal patients and resolves within 10 to 14 days, typical for a viral illness.

Oral Findings

Within a few days of the prodrome, erythema and clusters of vesicles and/or ulcers appear on the keratinized mucosa of the hard palatal mucosa, attached gingiva and dorsum of the tongue, and the nonkeratinized mucosa of the buccal and labial mucosa, ventral tongue, and soft palate (Figures 3-2 and 3-3). Vesicles break down to form ulcers that are usually 1 to 5 mm and coalesce to form larger ulcers with scalloped borders and marked surrounding erythema. The gingiva is often

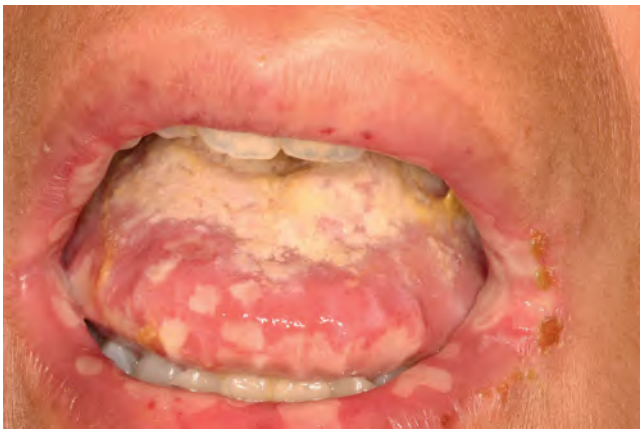

Figure 3-2 Primary herpetic gingivostomatitis with extensive involvement of the keratinized tissues of the tongue dorsum and nonkeratinized tissues of the ventral tongue and labial mucosa. *Source:* Courtesy of Dr. Nathaniel Treister, Boston, MA.

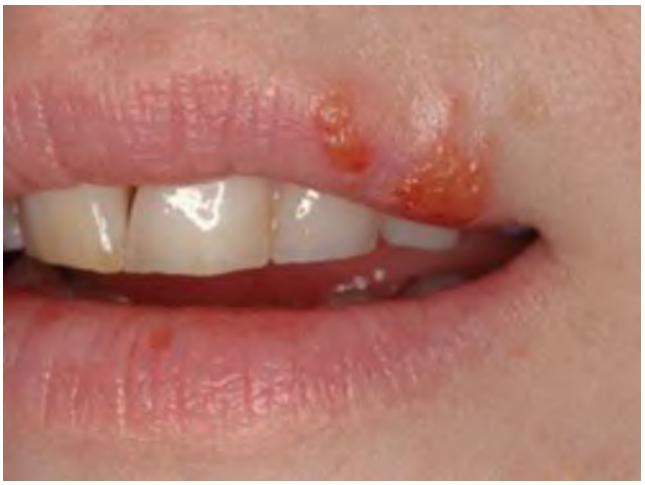

Figure 3-4 Clustered vesicles of recrudescent herpes labialis on vermilion.

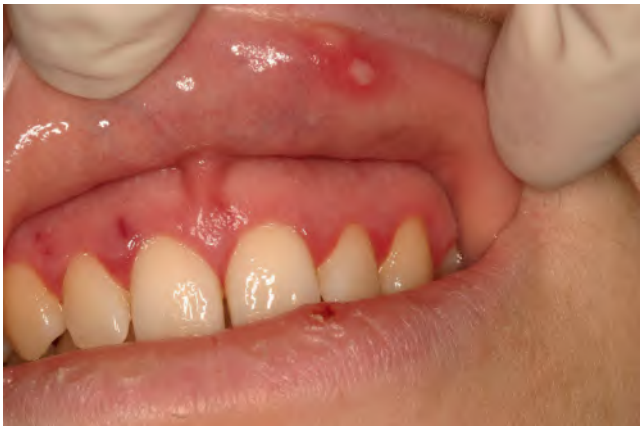

Figure 3-3 Primary herpetic gingivostomatitis with mild presentation: erythematous maxillary anterior gingiva with erythema and ulcer on upper labial mucosa and crusted lesion on lower lip.

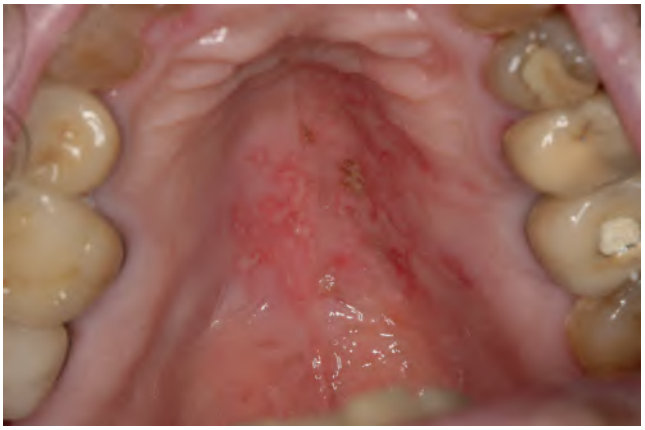

Figure 3-5 Recrudescent intraoral herpes simplex virus infection in an immunocompetent patient with clusters of small coalescent ulcers on the keratinized palatal mucosa.

erythematous, and the mouth is extremely painful, causing difficulty with eating. Pharyngitis causes swallowing difficulties. Primary HSV infection in adults follows a similar pattern.[16]

Recrudescent Oral HSV Infection

Reactivation of HSV may lead to asymptomatic shedding of HSV, in the saliva and other secretions, an important risk factor for transmission; it may also cause ulcers to form. Asymptomatic shedding of HSV is not associated with systemic signs and symptoms and occurs in 8 to 10% of patients following dental treatment.[17] The term *recrudescent HSV* should be used to refer to the actual ulcerations caused by reactivated virus. Fever, ultraviolet radiation, trauma, stress, and menstruation are important triggers for reactivation of HSV.

Recrudescent HSV on the lips is called recurrent herpes labialis (RHL) and occurs in 20 to 40% of the young adult population.[18,19] These are associated with a prodrome of itching, tingling, or burning approximately 50% of the time, followed in succession by the appearance of papules, vesicles, ulcers, crusting, and then resolution of lesions (Figure 3-4).[20] Pain generally is present only within the first 2 days. There is a suggestion that patients who do not experience a prodrome develop lesions from extraneural latent HSV within the epithelium and these lesions are less responsive to topical therapy.[21]

Recrudescent intraoral HSV (RIH) in the immunocompetent host occurs chiefly on the keratinized mucosa of the hard palatal mucosa, attached gingiva, and dorsum of the tongue.[22] They present as 1 to 5 mm single or clustered painful ulcers

with a bright erythematous border (Figure 3-5). One common presentation is the complaint of pain in the gingiva 1 to 2 days after a scaling and prophylaxis or other dental treatment. Lesions appear as 1 to 5 mm painful vesicles but more often ulcers on the marginal gingiva.

HSV in Immunocompromised Patients

In immunocompromised patients (such as those undergoing chemotherapy, who have undergone organ transplantation, or who have acquired immune deficiency syndrome [AIDS]), RIH infection may occur at any site intraorally and may form atypical-appearing ulcers that may be several centimeters in size and may last several weeks or months if undiagnosed and untreated (Figures 3-6 and 3-7).[23,24] In one study, 50% of patients with leukemia and 15% of patients who had undergone renal transplantation developed RIH infections.[25] Single RIH ulcers are indistinguishable from recurrent aphthous ulcers if they occur on a nonkeratinized site.[26] These ulcers are painful and similar to HSV lesions seen in immunocompetent patients except that they may be larger and often occur on nonkeratinized sites. They appear slightly depressed with raised borders. The presence of 1 to 2 mm vesicles or satellite ulcers at the edges of the main ulcer is a helpful sign.

If undiagnosed and left untreated, RIH infection may disseminate to other sites and cause morbidity in the immunocompromised population.[27] This is a particular problem in patients undergoing hematopoietic stem cell transplantation, where reactivation of HSV occurs in approximately 70% of patients, prompting prophylaxis in patients who are seropositive.[28,29]

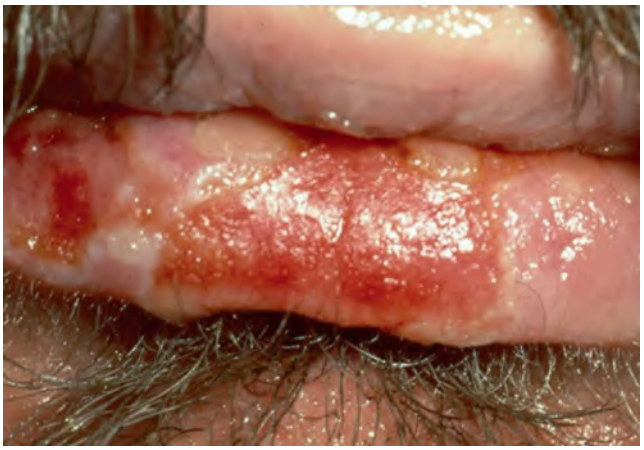

Figure 3-6 Recrudescent herpes simplex virus infection of the maxillary alveolar ridge mucosa in a patient with lymphoma.

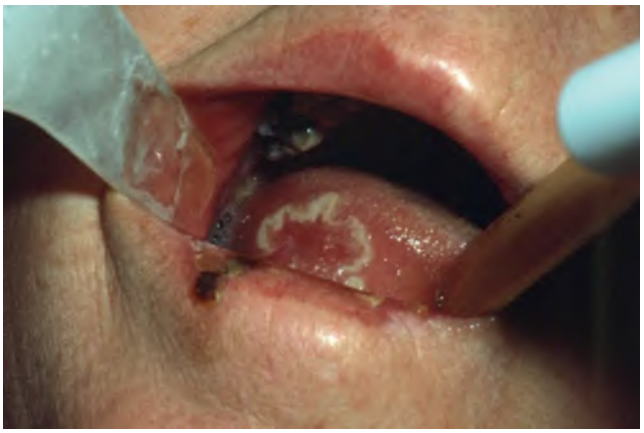

Figure 3-7 Recrudescent herpes simplex virus infection of the lateral tongue and oral commissure in a patient with leukemia postallogenic transplantation.

Differential Diagnosis

Coxsackievirus infections (especially hand-foot-and-mouth disease) may present with widespread ulcerations of the oral cavity mimicking primary herpetic gingivostomatitis, but ulcers are generally not clustered and generalized gingival inflammation usually is not present. Laboratory tests (see below) identifies HSV.

RIH infection in the immunocompetent patient on the gingiva may resemble a localized area of necrotizing ulcerative gingivitis (see below). Laboratory tests are positive for HSV, and lesions of necrotizing ulcerative gingivitis are widespread and diffuse rather than localized, as is often seen in RIH.

Traumatic ulcers on the palatal mucosa (such as from pizza burns) may resemble RIH.

RIH infection in the immunocompromised host may occur at any intraoral site and can be differentiated from aphthous ulcers because the latter are episodic.

In the immunocompromised population, ulcers secondary to CMV infection, fungal infection, and neutropenia must also be considered. Differentiation between these entities is accomplished by biopsy, culture, and blood tests.

Erythema multiforme, often triggered by a prior HSV infection may appear as multiple, coalescent ulcers (see below).

Laboratory Diagnosis

Diagnosis is by culture, antigen identification, or nuclei acid amplification techniques.[30] HSV isolation by cell culture with further herpes typing is the gold standard test for the diagnosis since it grows readily in tissue culture, although the quantity of virus falls precipitously once healing begins. The advantage of a culture is that it has high sensitivity and specificity and allows for amplification of virions, typing, and testing for sensitivity to antiviral drugs. The disadvantage is that it needs specialized equipment, is expensive, is dependent on proper transport of the culture, and may take up to several days for a final result, although use of centrifugation-enhanced (shell vial) culture has reduced culture time to 1–3 days. HSV that reactivates in

the saliva (asymptomatic shedding) will also grow in culture and results have to be interpreted with caution.

Antigen detection by direct or indirect immunofluorescence using fluorescein-labeled, type-specific monoclonal antibodies on smears and scrapings (e.g., from vesicles) or via enzyme inked immunoassay on swabs are an alternative to cultures and provide similar sensitivity and specificity very quickly. Nuclei acid amplification tests are now readily available commercially using real-time polymerase chain reaction (PCR) for detecting and quantifying HSV and this is now the standard of care in most medical centers. It is highly sensitive but will capture HSV in recrudescent active infections and from asymptomatic shedding.

HSV can be identified from scrapings from the base of lesions (especially vesicles) smeared onto glass slides. These can be stained with Wright, Giemsa (Tzanck preparation), or Papanicolaou stain to demonstrate the characteristic multinucleated giant cells or intranuclear inclusions as seen on histopathology (see below). However, this does not distinguish between HSV or VZV and an antigen detection technique, as noted above, must also be employed.

Primary HSV infection is associated with elevated immunoglobulin (Ig)M titers that occur within days, followed several weeks later by permanent IgG titers (seroconversion) that indicate previous infection but confer no protection against reactivation. Recurrent infection is associated with a rise in IgG antibody titer in acute and convalescent sera, but a fourfold rise (a criterion that indicates active infection) is seen in only 5% of patients. The assay for HSV IgM is not particularly reliable for diagnostic purposes and overall, the use of serology to diagnose recurrent infection is not advised.

HSV lesions are not generally biopsied because the clinical appearance and history are characteristic, and infection is readily confirmed with any of the techniques mentioned above when necessary. However, if a biopsy is obtained, it will show the presence of multi-nucleated giant epithelial cells at the edge of the ulcer. The nuclei exhibit typical molding and have a ground-glass appearance (Figure 3-8). Since intact epithelium is necessary for the diagnosis, a biopsy for a lesion suspicious for HSV must always include epithelium adjacent to the ulcer or there may be a false negative result.

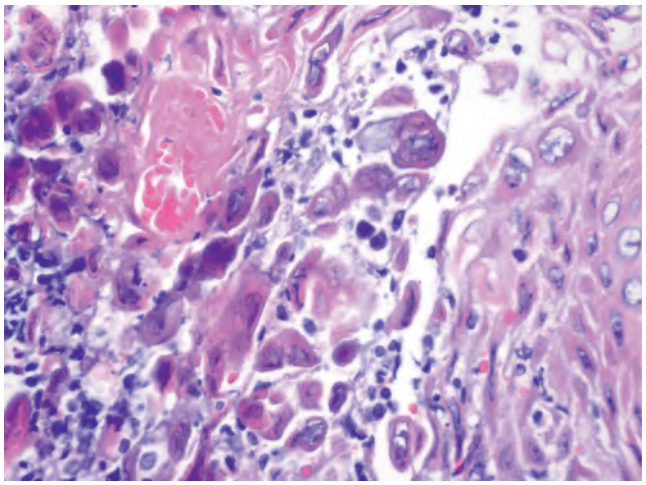

Figure 3-8 Biopsy of a herpes simplex virus ulcer demonstrating large epithelial cells with multiple ground-glass nuclei.

Table 3-2 Pain management and supportive care measures.

Pain Management
2% viscous lidocaine (swish 5 mL for 3–5 min. and spit out 4–5 times/d)
Liquid diphenhydramine (swish 5 mL for 3–5 min and spit out 5 4–5 times/d)
Combination of viscous lidocaine, diphenhydramine, and a covering agent (such as Kaopectate™ or Maalox™) in 1:1:1 ratio (swish 5 mL for 3–5 min and spit out)
0.1% diclonine hydrochloride
Benzydamine
Systemic analgesia
Supportive care
Hydration
Ice chips or popsicles
Soft bland diet
Antipyretics such as ibuprofen as needed (avoid aspirin products)*

*The use of aspirin products in children who have a viral illness (especially varicella infection, influenza, or coxsackievirus infection) has been associated with Reye syndrome, a potentially fatal condition characterized by fatty degeneration of the liver and encephalopathy.

Management

Primary HSV Infection

Management is directed toward pain control, supportive care, and definitive treatment (Table 3-2). In the past, healthy patients with primary herpetic gingivostomatitis were treated only with hydration and supportive measures. However, since the acyclovir family of drugs is inexpensive, safe, and readily available, it is appropriate to treat even primary infections definitively because it reduces viral shedding and infectivity.

Acyclovir inhibits viral replication and is activated by virally produced thymidine kinase. As such, it has little activity against nonvirally infected cells.[31] The use of acyclovir at 15 mg/kg five times a day in children reduces the duration of fever, reduces HSV shedding, halts the progress of lesions, improves oral intake, and reduces the incidence of hospital admissions.[32] Valacyclovir, the prodrug of

acyclovir, has three to five times the bioavailability of acyclovir and, together with famciclovir, are now widely used.

Recrudescent HSV

RHL can often be suppressed by reducing tissue damage, such as by using sunscreen.[33] Although RHL is self-limiting, the use of topical antiviral medications reduces shedding, infectivity, pain, and the size and duration of lesions. Topical antiviral medications such as 5% acyclovir cream,[34,35] 1% penciclovir cream,[36,37] and 10% docosanol cream are efficacious[38,39] if applied five to eight times a day (every two hours) at the first prodrome or sign of a lesion. Systemic therapy with valacyclovir (2 g 12 hours apart for one day) or famciclovir (1500 mg single dose) are both effective in aborting early lesions of RHL.[40] Suppression of HSV infection in patients who develop frequent episodes, large lesions, or erythema multiforme is effected with variable doses of acyclovir, valacyclovir and famciclovir.[41,42,43,44] Similar suppressive regimens can be used for patients susceptible to recrudescent HSV after dental procedures.[45]

HSV in Immunocompromised Patients

In general, HSV infections in immunocompromised hosts should be treated with systemic antivirals to prevent dissemination to other sites (e.g., HSV esophagitis) or systemically. The primary pathogen for herpes encephalitis and herpes pneumonitis is HSV-1. For patients undergoing hematopoietic cell transplantation, antiviral therapy such as acyclovir or valacyclovir at suppressive doses should be initiated for all patients who are HSV seropositive.[46] Resistance is seen in up to 6% of immunocompromised patients and usually stems from mutation of either virally-derived thymidine kinase that activates acyclovir, or from DNA polymerase.[47] In such cases, foscarnet or cidofovir are effective.[40] The dosage of the acyclovir family of drugs should be adjusted for age and renal health.

A number of vaccines and new therapies against HSV are currently under development.[48]

Varicella Zoster Virus (VZV) Infection

Biology and Pathogenesis

Primary infection with VZV, an α-herpesvirus, leads to varicella (chicken pox). As with all herpesviruses, the virus then becomes latent, usually in the dorsal root ganglia or ganglia of the cranial nerves.[49] Reactivation produces herpes zoster infection (HZI), commonly called shingles. The incidence of HZI increases with age and the degree of immunosuppression. There are 1.5 to 3 cases of HZI per 1000 subjects; this increases to 10 per 1000 in those over age 75 years.[50] Therefore, it is not uncommon to see HZI in the elderly, in patients undergoing cancer chemotherapy, in patients on chronic immunosuppressive drug therapy (such as those who have received organ transplants), and in patients with AIDS.[51] As with HSV, this virus is cytopathic to the epithelial cells of the skin and mucosa, causing blisters and ulcers. Transmission is usually by the respiratory route, with an incubation period of 2 to 3 weeks.[52]

Postherpetic neuralgia, a morbid sequela of HZI, is a neuropathy resulting from peripheral and central nervous system injury and altered central nervous system processing.[53]

Clinical Findings

Primary VZV or varicella infection generally occurs in the first two decades of life. The disease begins with a low-grade fever, malaise, and the development of an intensely pruritic, maculopapular rash, followed by vesicles that have been described as "dewdrop-like." These vesicles turn cloudy and pustular, burst, and scab, with the crusts falling off after 1 to 2 weeks. Lesions begin on the trunk and face and spread centrifugally. Central nervous system involvement may result in cerebellar ataxia and encephalitis.

Immunocompromised hosts usually experience more severe disease with more blisters, a bilateral distribution, a protracted course, and, not infrequently, with disseminated disease leading to encephalitis, hepatitis, and pneumonia. There is a significantly higher mortality rate.[54] Secondary bacterial infection by gram-positive cocci may have severe septic consequences.

Recrudescence of VZV leads to herpes zoster infection (HZI) or shingles which tends to occur in adult and starts with a prodrome of deep, aching, or burning pain, itching, and dysesthesia. There is usually little to no fever or lymphadenopathy. This is followed within 2 to 4 days by the appearance of crops of vesicles in a dermatomal or "zosteriform" pattern. This pattern describes the unilateral, linear, and clustered distribution of the vesicles, ulcers, and scabs in a dermatome supplied by one nerve. Thoracic/lumbar dermatomes are the most frequently involved, followed by the craniofacial area. Lesions heal within 2 to 4 weeks, often with scarring and hypopigmentation. Occasionally, HZI may occur without the appearance of dermatomal lesions (zoster sine eruptione or zoster sine herpete), which makes the diagnosis of this condition challenging; these patients often present with facial palsy. In fact, VZV has been detected in 3% of patients with Bell palsy.[13,15] A On rare occasions and especially in immunocompromised patients, HZI may involve not just the dorsal root ganglion but also the anterior horn cells, leading to myelitis; other rare complications include retinitis and encephalitis.[49]

One of the most important complications of HZI is postherpetic neuralgia, defined as pain that lingers for 120 days[53,55]

after the onset of the acute rash (see Chapter 12). Postherpetic neuralgia affects up to 20% of patients over age 65 and up to 30–50% of patients over age 80; affected individuals have debilitating pain, usually of a sharp, stabbing, burning, or gnawing nature lasting more than 1 month.[51,56] Some unfortunate patients experience pain for years. Predisposing factors include older age (most important), prodromal pain, and more severe clinical disease during the acute rash phase.[57,58]

Oral Manifestations

Primary VZV infection presents as minor acute ulcerations in the mouth that often pale in clinical significance when compared with the skin lesions.

In recurrent VZV infection, the ophthalmic division of the trigeminal (V) nerve is the cranial nerve most often affected (herpes zoster ophthalmicus); corneal involvement may lead to blindness.[51] Involvement of this nerve leads to lesions on the upper eyelid, forehead, and scalp with V_1; midface and upper lip with V_2; and lower face and lower lips with V_3 (Figure 3-9). With involvement of V_2, patients experience a prodrome of pain, burning, and tenderness, usually on the palate on one side. This is followed several days later by the appearance of painful, clustered 1 to 5 mm ulcers (rarely vesicles, which break down quickly) on the hard palatal mucosa or even buccal gingiva, in a distinctive unilateral distribution (Figure 3-10). Ulcers often coalesce to form larger ulcers with a scalloped border similar to those of HSV. These ulcers heal within 10 to 14 days, and postherpetic neuralgia in the oral cavity is uncommon. Involvement of V_3 results in blisters and ulcers on the mandibular gingiva and tongue.

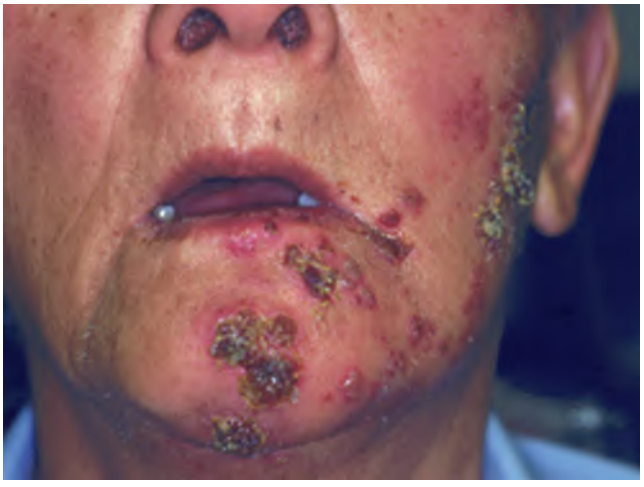

Figure 3-9 Facial lesions of herpes zoster involving the third division of the trigeminal nerve.

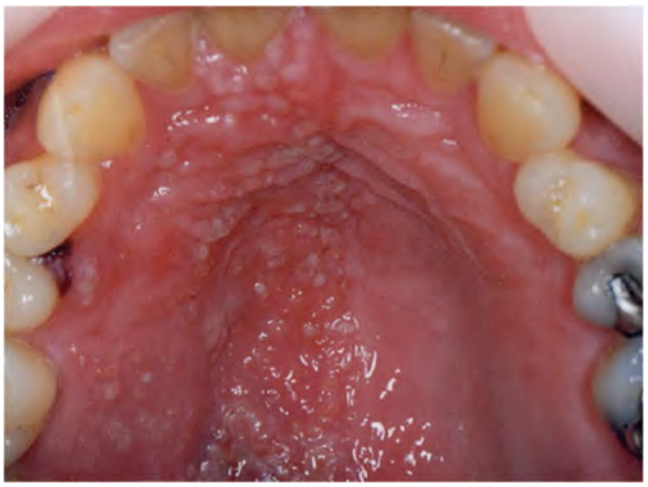

Figure 3-10 Palatal lesions of herpes zoster involving the second division of the trigeminal nerve; note unilateral distribution. *Source:* Courtesy of Dr. Stephen Challacombe.

An uncommon complication of HZI involving the geniculate ganglion is Ramsay Hunt syndrome. Patients develop Bell palsy, vesicles of the external ear, and loss of taste sensation in the anterior two-thirds of the tongue.[52] HZI has been reported to cause resorption and exfoliation of teeth and osteonecrosis of the jawbones, especially in patients with HIV disease.[59–62]

Differential Diagnosis

The pain that is often experienced in the prodrome before the onset of vesicles and ulcers may lead to an incorrect diagnosis of pulpitis, leading to unnecessary dental treatment such as endodontic therapy.

HSV infection appears in a similar fashion and if mild and localized to one side may be mistaken for HZI; laboratory tests differentiate between the two. Other blistering/ulcerative conditions such as pemphigus or pemphigoid are chronic and/or progressive diseases that do not present unilaterally.

In severe cases of localized necrosis of the soft tissues and bone, acute necrotizing ulcerative periodontitis should be considered, particularly in the HIV population. Coinfection with CMV may occur in immunocompromised patients.[63] Medication- (such as bisphosphonate) and radiation-induced osteonecrosis of the jaws will have a history of exposure to bisphosphonate and radiation, respectively, and often is precipitated by dentoalveolar trauma in the absence of clustered ulcers.

In this age of bioterrorism, clinicians should be familiar with the signs of infection with vaccinia (smallpox virus), which presents with characteristic skin blisters and pustules.

Laboratory Findings

As with HSV infection, identification is by viral isolation using cell culture – a traditional method – although VZV is more fastidious and difficult to culture, use of fluorescein-labeled antibody to detect antigen, and use of molecular techniques such as real-time PCR using commercially available kits.[64,65] A simple smear stained with a standard laboratory stain would reveal the presence of multinucleated epithelial cells similar to HSV.

After primary infection, the patient seroconverts and IgG against VZV is detectable in the serum. HZI causes a transient rise in IgM and an increase in levels of IgG, but these are not reliable for diagnostic purposes.[66]

Biopsy is usually not required and is not the diagnostic test of choice since the clinical presentation is usually characteristic. If one should be performed, tissue should always include the intact epithelium adjacent to the ulcer since that is where the cytopathic effect in epithelium is best seen. VZV and HZI are cytopathic to the epithelial cells and result in the formation of multinucleated epithelial cells with viral inclusions, similar to and indistinguishable from HSV infection.

Management

As with HSV infection, management of oral lesions of varicella and HZI is directed toward pain control (particularly the prevention of postherpetic neuralgia), supportive care and hydration (see Table 3-2), and definitive treatment to minimize the risk for dissemination, particularly in immunocompromised patients. Aspirin use, especially in patients with VZV infection or oral viral infections may result in the development of Reye syndrome, which is potentially fatal, and ibuprofen is the preferred analgesic.[67]

Treatment of primary VZV infection and VZI includes the use of acyclovir (800 mg five times a day), valacyclovir (1000 mg three times a day or 1500 mg twice a day), famciclovir (500 mg three times a day), and brivudine (125 mg once a day) for 7 days and these should be started within 72 hours of disease onset.[68,69] This reduces infectivity, the severity of lesions, and hospitalizations for complications. However, acyclovir has poor bioavailability. These drugs also reduce the incidence of pain and postherpetic neuralgia. Combination therapy with 3-weeks of tapering corticosteroid therapy up-front reduces pain, and quickens return to normal activities.[68]

The first line of treatment for postherpetic neuralgia is gabapentin,[70] 5% lidocaine patch,[71] and 0.025–0.8% topical capsaicin, and the second line of treatment is with tricyclic antidepressants and corticosteroids.[55,68] The use of corticosteroids and antiviral therapy together in an attempt to reduce postherpetic neuralgia has not proved effective, although early treatment with famciclovir or valacyclovir may prevent it.[68,72] Case reports suggest that botulinum toxin may provide pain relief.[73]

A vaccine against VZV which contains live, attenuated virus reduces the incidence of varicella outbreaks, but because it establishes latency may be associated with increased zoster incidence.[74] Vaccination of older adults using Zostavax™ (live, attenuated virus), or Shingrix™ (recombinant VZV antigen) reduces incidence of HZI significantly and the latter, post-herpetic neuralgia.[75,76] The use of recombinant virus in a vaccine is more appropriate for use in immunocompromised hosts.

Cytomegalovirus (CMV) Infection

Etiology and Pathogenesis

CMV is a β-herpesvirus, and 50 to 100% of the population world-wide and 50% of the U.S. population has been exposed.[77,78] Risk for exposure increases with age, low socio-economic status, and crowded living conditions. Primary infection may be asymptomatic or cause an infectious mononucleosis-like disease. As with other members of Herpesviridae, CMV establishes latency within the connective tissue cells, such as the endothelium of blood vessels, mononuclear cells, and white blood cells in the connective tissue. Transmission is by direct transfer of infected white blood cells through intimate contact, vertical transmission, blood products, and transplanted organs.[79]

Clinical Findings

Primary CMV infection presents similarly to other viral infections with fever, malaise, and leucopenia and organ-specific findings such as gastroenteritis (most common), pneumonitis, retinitis and hepatitis, and even thromboembolism. Six to 7% of patients with infectious mononucleosis-like symptoms (fever, pharyngitis, and lymphadenopathy) have CMV or HSV infection rather than EBV infection.[80,81]

Manifestations of recrudescent infection and disease are most evident in the immunocompromised population, such as patients who have received organ transplants or those who have AIDS where CMV-related retinitis and gastroenteritis are common. A study on mucocutaneous CMV infection (mostly perianal) in patients with human deficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) revealed that CMV infection of mucocutaneous sites was usually part of a polymicrobial infection with HSV or VZV.[82] The authors suggest that CMV in such cases is not the pathogenic agent for these ulcers since the presence of those two α-herpesviruses alone could account for the ulceration and tissue damage. These authors also noted that CMV was often found in nonlesional skin.

In organ transplant recipients, CMV in the donor organ leads to a high incidence of CMV infection in the recipient.[83] It causes gastrointestinal and pulmonary disease in the first 100 days after allogenic hematopoietic stem cell transplantation.[84] There is growing evidence that CMV infection is associated with Guillain-Barré syndrome especially after renal transplantation, as well as polyradiculopathy and encephalitis in patients with AIDS.[83–85]

Oral Manifestations

CMV infection in the mouth in the immunocompromised patient tends to present as a single large ulcer and less often as multiple ulcers (Figure 3-11). They are usually painful and may have been present for weeks or months. Any site may be involved. Up to one-third of such ulcers are coinfected with other viruses of the herpes family, especially HSV and CMV. [86,87]

There have been occasional reports of mandibular osteomyelitis and tooth exfoliation associated with CMV and VZV infection.[63,88] Both viruses are associated with vasculopathy and thrombosis, which may be the underlying etiopathogenesis.[89,90]

Differential Diagnosis

As indicated earlier, CMV is often seen in association with HSV or VZV infections and, in such situations, may be a bystander rather than pathogenic. Therefore, evaluation for these other two viruses is essential for single or multiple ulcers in the immunocompromised population. In patients with HIV/AIDS, infections with mycobacteria, fungi, and other organisms must be ruled out.

Single ulcers present for weeks or months should be evaluated for squamous cell carcinoma or other malignancies. Since patients who develop such ulcers caused by opportunistic pathogens are often immunocompromised, one should have a high index of suspicion for a malignancy.

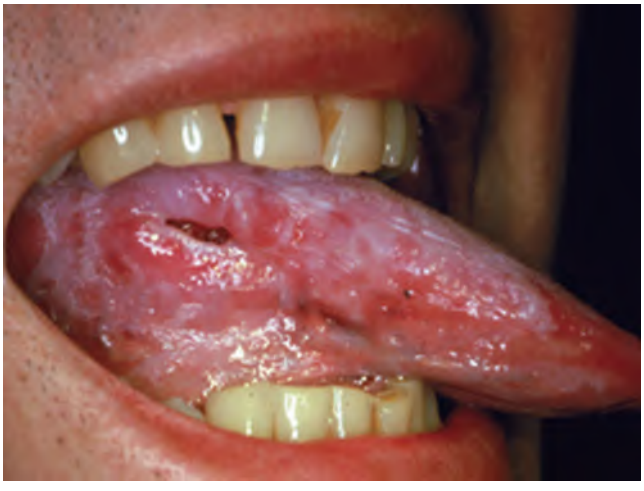

Figure 3-11 Cytomegalovirus ulcer on a background of hairy leukoplakia in a patient with AIDS.

Benign or malignant salivary gland tumors or soft tissue tumors may also become secondarily ulcerated from trauma. Single ulcers on the tongue may also represent traumatic ulcerative granuloma (see below).

Laboratory Tests

CMV infections of the oral cavity presenting as ulcers tend to be deep with viral particles residing in endothelial cells and tissue monocytes. As such, a culture of an ulcer infected by CMV is unlikely to be positive unless there is shedding of CMV from the ulcer surface. Furthermore, CMV may be difficult to grow in shell vial culture so current diagnosis of CMV infection is through real-time PCR viral nuclei acid identification from blood or plasma, and detection of pp65 antigen within leukocytes using a monoclonal antibody.[91] Antibody titers against CMV are unreliable for the diagnosis of active infection.

Biopsy for microscopic examination and/or to obtain tissue for culture is sensitive and specific for identification of CMV in oral ulcers.[88,91] CMV infection produces large intranuclear inclusions within endothelial cells and monocytes in the connective tissue, with an associated nonspecific chronic inflammation. The use of immunohistochemical techniques helps identify CMV if there are only a few infected cells. A biopsy has the advantage of also ruling out any of the other differential diagnoses discussed, such as other viruses or deep fungal infection. It is important to make sure that the biopsy includes normal epithelium because if the ulcer is coinfected with HSV or VZV, these would be identified on the biopsy in the intact epithelium adjacent to the ulcer.

Management

As with all ulcerative lesions, pain is managed with topical anesthetics and systemic analgesics as needed, with appropriate dietary modifications and good hydration (see Table 3-2). CMV infection is treated with ganciclovir 5 mg/kg IV twice daily, valganciclovir (a valine ester and oral prodrug of ganciclovir with approximately 10-fold bioavailability of ganciclovir) 900 mg twice daily, foscarnet, or cidofovir. Newer drugs that include letermovir and vaccines are in development.[92,93]

Epstein-Barr Virus Infection

Epstein-Barr mucocutaneous ulcer is discussed below in the section on solitary lesions.

Coxsackievirus Infection

Coxsackievirus (CV), a ribonucleic acid (RNA) virus, is a member of the genus *Enterovirus* and family Picornaviridae and has features in common with poliovirus. The genus

Enterovirus has several sero-types including enterovirus A, B, C, or D, CV A and CV B virus, poliovirus, and echovirus.[94] More than 90% of infections caused by the nonpolio enteroviruses are either asymptomatic or result in nonspecific febrile illness. The viruses replicate extensively in the lower gastrointestinal tract, and less so in the oropharynx, from where they shed. Transmission is therefore primarily by the fecal–oral route, although some shedding occurs in the upper respiratory tract.

Enterovirus infection is implicated in aseptic meningitis, acute encephalitis, acute paralysis, ocular infections, pleurodynia, myopericarditis, and respiratory illness. Enterovirus (EV) A17 and A6 are associated with more severe disease.[94] EVs, in particular B1, has been implicated in the pathogenesis of type 1 insulin-dependent diabetes mellitus.[95] CV B4 has also been implicated in the pathogenesis of primary Sjögren syndrome in one study, but this was refuted in another study.[96,97]

In the oral cavity, CV infections lead to three disease entities: hand-foot-and-mouth disease, herpangina, and lymphonodular pharyngitis.

Hand-Foot-and-Mouth Disease (HFM)

CVA16 and EV 71 are the most common cause of this vesicular exanthem, although more recently CVA6 has been reported to cause more severe infections. EV71 has been seen in large outbreaks in Southeast Asia. HFM disease, as with many CV infections, including herpangina, tends to be seasonal, occurs in epidemic clusters (such as schools and day care centers), and has high transmission rates.[98,99]

In comparing cases of HFM disease caused by EV71 with those caused by CVA16, EV71 is much more likely to be associated with severe central nervous system disease (such as meningitis and brainstem encephalitis), paralysis, pulmonary edema, and death.[100] In one study of patients with HFM disease and herpangina, 83% of cases were caused by EV71 and only 8% by CVA or CVB.[101] In another study of EV71 infections, 87% of cases manifested with HFM disease and 13% with herpangina.[102]

Clinical Findings

HFM disease usually afflicts children younger than 10 years in summer. Patients have a low-grade fever, emesis, and sore mouth; 75 to 100% of patients have a skin rash, especially on the hands and feet (dorsa, palms, and soles) and 30% on the buttocks.[94] The rash is first red and macular and then becomes vesicular. The incubation period is from 3–7 days and oropharyngeal shedding may last for 4 weeks while gastrointestinal shedding may last 8 weeks to many months.

Oral Manifestations

Patients are febrile and complain of a sore mouth and throat. Lesions begin as erythematous macules that become vesicles and quickly break down to ulcers. Lesions are usually located on the tongue, hard and soft palate, and buccal mucosa but can present on any oral mucosal surface.[94]

Herpangina

The word *herpangina* derives from *herpes*, meaning "vesicular eruption," and *angina*, meaning "inflammation of the throat." CVA (serotypes 1–10 and 22) are the most common viruses isolated from this disease.[94,103,104]

Clinical Findings

As with hand-foot-mouth disease, children under 10 are usually afflicted and outbreaks usually occur in epidemics in summer. Patients develop high fever, headache, and myalgia that usually last only 1 to 3 days.

Oral Manifestations

The first oral symptoms of herpangina are sore throat and pain on swallowing. There may be erythema of the oropharynx, soft palate, and tonsillar pillars. Small vesicles form, but these rapidly break down to 2 to 4 mm ulcers and these persist for 5 to 10 days (Figure 3-12).

Lymphonodular pharyngitis is associated with CVA10 and patients report a sore throat, and develop diffuse small nodules (likely lymphoid hyperplasia) in the oropharynx.[105]

Differential Diagnosis

Lesions of both HFM disease and herpangina may resemble primary herpetic gingivostomatitis. However, lesions on the palms and soles are typical for HFM disease, and ulcers

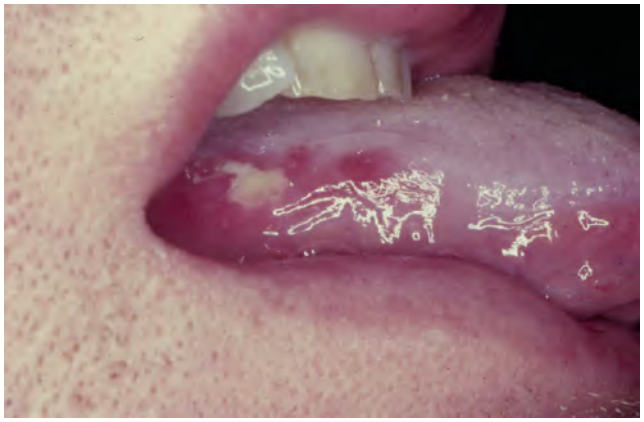

Figure 3-12 A cluster of ulcers on the tongue of a patient with herpangina. The patient also had lesions of the palate and posterior pharyngeal wall.

located only in the posterior oral cavity are typical for herpangina. Bright red and painful gingiva also characterize primary HSV infection, and this is uncommon in CV infections. Chickenpox presents with generalized vesicular skin lesions, but ulcers are not prominent in the oral cavity; patients also appear more ill. Infectious mononucleosis (primary EBV infection) may also present with sore throat and purulent exudates, but serology distinguishes this from CV infections.

Streptococcal infections of the throat generally do not produce vesicles or ulcers seen in HFM disease or herpangina but rather a purulent exudate, although the two may appear similar; cultures distinguish between the two.

Aphthous ulcers are generally not associated with fever or malaise except for the periodic fever syndrome.

Laboratory Tests

Diagnosis is usually made on clinical findings, and culture and biopsies are rarely necessary for diagnosis unless the presentation is atypical or the more virulent subtypes are suspected. CV infections may be diagnosed by culture (usually from the throat or stools), but real-time PCR is now employed for typing.[106]

Management

CV infections are self-limiting (unless complications arise or the patient is immunocompromised), and management is directed toward control of fever and mouth pain, supportive care, and limiting contact with others to prevent spread of the infection. Effective antiviral agents for CV are not available but vaccines are under development.[107]

Necrotizing Ulcerative Gingivitis and Periodontitis

Necrotizing ulcerative gingivitis (NUG), formerly known as acute necrotizing ulcerative gingivitis (ANUG), and its more severe counterpart, necrotizing ulcerative periodontitis (NUP), were reclassified in 2017 by the American Academy of Periodontics under the category of "Necrotizing Periodontal Disease."[108] These are acute ulcerative-inflammatory conditions of the gingiva and periodontium, respectively, that are associated with polymicrobial infection. During World War I, NUG was dubbed "trench mouth" since it was frequent among the soldiers in the trenches. NUG and NUP have strong associations with immune suppression (especially AIDS), debilitation, smoking, stress, poor oral hygiene, local trauma, and contaminated food supply. Diabetes may also be a risk factor.[109] It is unclear if NUG is a forerunner of NUP, but they are often seen in patients with AIDS. Both NUP and noma thrive in communities characterized by a large low socioeconomic class and extreme poverty.[110,111]

Etiology and Pathogenesis

The more important and constant of the microbes involved include *Treponema* species, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Peptostreptococcus species*, *Porphyromonas gingivalis*, *Selenomonas* species, *Aggregatibacter actinomycetemcomitans* and *Campylobacter*.[112,113] In HIV patients, candida and herpesvirus are also commonly present.[114] Since some of these fusospirochetal organisms are common in the periodontal tissues, many believe that it is the permissive environment of an immunocompromised host that allows these microbes to proliferate. The tissue destruction is most probably a result of the production of endotoxins and/or immunologic activation and subsequent destruction of the gingiva and adjacent tissues. In addition, patients show reduced neutrophil chemotaxis and phagocytosis, resulting in poor control of infection. Some have identified herpesviruses within the crevicular fluid,[112] but such viruses shed readily in oral secretions, particularly in areas where there is tissue destruction and therefore maybe nonpathogenic bystanders.

If there is underlying systemic illness, NUG and NUP can spread rapidly from the gingiva to the periodontium and into the soft tissues, giving rise to cancrum oris, noma, or orofacial gangrene.[111] This is particularly devastating in children who are malnourished and live in poverty and is seen not infrequently in Africa. *Fusobacterium necrophorum* is likely to play an important role in the progression of NUP to cancrum oris because this organism produces a dermonecrotic toxin, hemolysin, leukotoxin, and proteolytic enzymes, all leading to extensive tissue destruction.[112] It may also stimulate the growth of *P. intermedia*.

Clinical Findings

NUG and NUP may or may not be associated with fever and malaise, although submandibular lymphadenopathy is usually present. This may be more prominent in patients with an underlying immunodeficiency.

However, noma generally is accompanied by fluctuating fever, marked anemia, high white cell count, general debilitation, and a recent history of some other systemic illness, such as measles.[111]

Oral Manifestations

NUG has a rapid and acute onset. The first symptoms include excessive salivation, a metallic taste, and sensitivity of the gingiva. This rapidly develops into extremely painful and ery-thematous gingiva with scattered punched-out ulcerations, usually on the interdental papillae, although any part of the marginal gingiva may be affected (Figure 3-13). There is accompanying malodor, and there may be gingival bleeding. Because of the pain associated with the gingivitis, there is usually abundant

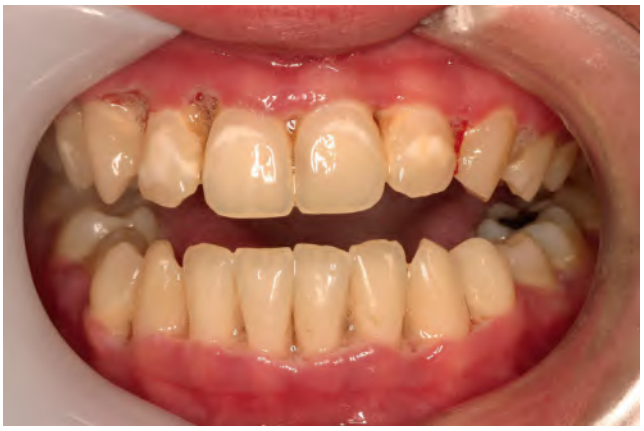

Figure 3-13 Necrotizing ulcerative gingivitis with typical punched out, necrotic, and ulcerated interdental papillae. *Source:* Courtesy of Dr. Hani Mawardi, Boston, MA.

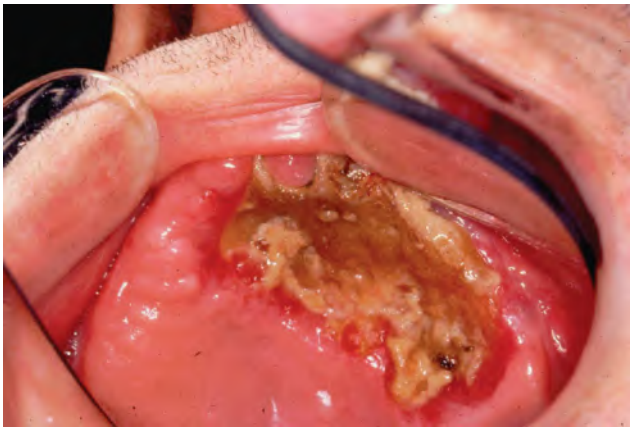

Figure 3-14 Fusospirochetal palatal lesions in a neutropenic patient.

build-up of dental plaque around the teeth because it may be too painful to perform effective oral hygiene.

Patients who are immunocompromised and neutropenic are prone to developing such lesions (Figure 3-14). In patients with AIDS, the prevalence of NUP is strongly predictive of a CD4 count below 200 cell/mm^3.[115] In this population; these areas may lead to osteonecrosis or necrosis of the soft tissues (Figure 3-15).[116]

In patients in whom there is severe immunodeficiency or malnutrition, NUG and NUP may progress to noma (Figure 3-16). The overlying skin becomes discolored, and perforation onto the skin ensues. The orofacial lesions are cone-shaped, with the base of the cone within the oral cavity and the tip at the skin aspect. There is sloughing of the oral mucosa followed by sequestration of the exposed, necrotic bone and teeth. Without treatment, the mortality rate is 70 to 90%.[112]

Differential Diagnosis

The acute onset of erythematous and ulcerated gingiva of NUG may suggest a diagnosis of primary herpetic gingivostomatitis and this is readily ruled out with a culture and by PCR. Desquamative gingivitides (caused by lichen planus, mucous membrane pemphigoid, pemphigus vulgaris, and hypersensitivity reactions) may present primarily on the gingiva, with no skin findings. However, these conditions are not of acute onset but rather chronic and/or progressive over months and years and are characterized by inflammation rather than necrosis.

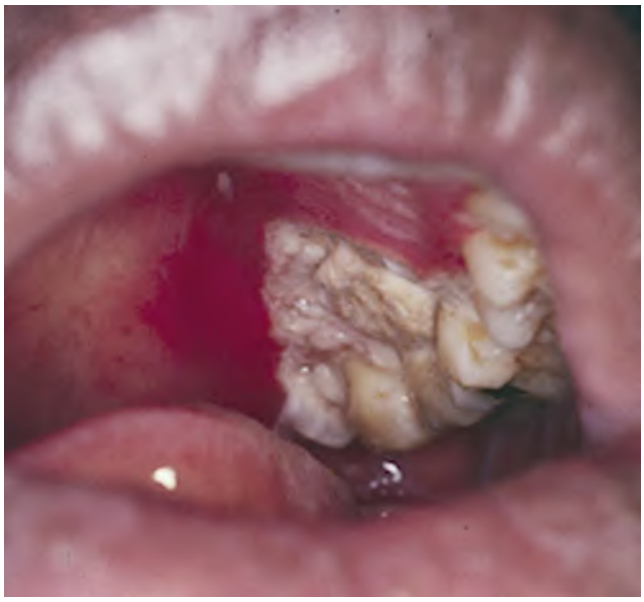

Figure 3-15 Necrotizing ulcerative periodontitis with osteonecrosis in a patient with AIDS.

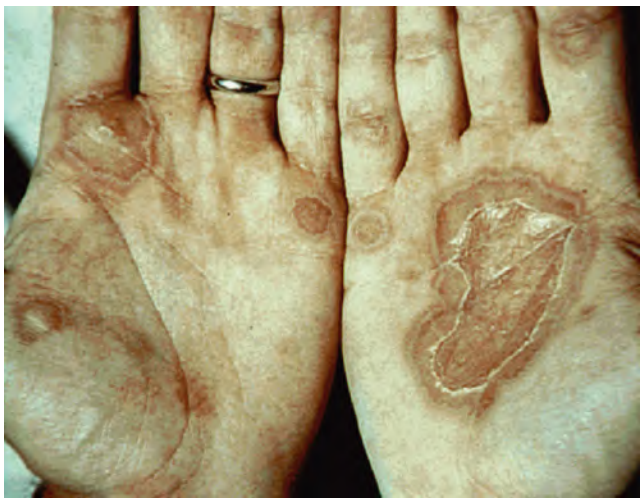

Figure 3-16 Erythema multiforme with target lesions of the skin of the hand.

Neutropenic ulcers in patients on cancer chemotherapy may appear similar, leading to extensive ulceration and necrosis of the marginal gingiva and other mucosal surfaces.

Single large necrotic ulcers of noma suggest deep fungal infections or infections with the herpes family of viruses, especially in immunocompromised patients. Squamous cell carcinoma is also a consideration in this group of patients.

Laboratory Testing

Secretions from the gingival sulcus grow mixed flora but in particular will be positive by culture or PCR for *Treponema* species, *Prevotella intermedia*, *Fusobacterium nucleatum*, and other bacteria as indicated above. Necrotizing gingival lesions may also be caused by microbes other than fusospirochetes, such as *Pseudomonas aeruginosa*.[117]

A biopsy usually is not helpful in making a diagnosis, although biopsies may be performed to rule out some other condition that may have a similar clinical presentation. The lesions demonstrate ulceration, extensive necrosis, leukocytoclasia, and a mixed inflammatory infiltrate. More than half of the cases in patients who were HIV positive were immunoreactive for HIV p24 within focal histiocytes, whereas EBV RNA was identified in 1 (6%) of 17 cases.[118]

Management

This is directed toward supportive care and pain control (see Table 3-2), definitive treatment, and identification of underlying predisposing factors. In patients who are malnourished, nutritional rehabilitation is essential to halt the progress of gingival lesions to noma.

Definitive treatment of NUG and NUP consists of gentle débridement to remove as much of the debris and plaque as possible; this is best accomplished under topical anesthesia during the first few visits. The use of chlorhexidine digluconate mouth rinse led to resolution in >90% of cases.[119] Patients with more extensive disease and/or systemic symptoms may require antibiotics active against gram-negative anaerobes, such as β-lactams.[116] Interestingly, metronidazole, which has little activity against spirochetes, also is effective, suggesting that resolution can occur without treatment of the entire microbial complex.[120]

Once the acutely painful episodes have resolved, scaling and root planing to completely remove all residual plaque and calculus are indicated. Periodontal surgery may be necessary to correct gingival and periodontal defects. It may be appropriate to test the patient for HIV or other immunosuppressive conditions, such as blood dyscrasia.

Cases of noma need aggressive treatment with nutritional supplementation, antibiotics, and tissue débridement. Nevertheless, survivors exhibit significant disfigurement and functional impairment from tissue loss and scarring.[113]

Erythema Multiforme

Erythema multiforme (EM) is an acute, self-limited, inflammatory mucocutaneous disease that manifests on the skin and often oral mucosa, although other mucosal surfaces, such as the genitalia, may also be involved.[121–123] It represents a hypersensitivity reaction to infectious agents (majority of cases) or medications. In general, EM is classified as EM minor if there is less than 10% of skin involvement and there is minimal to no mucous membrane involvement, whereas EM major has more extensive but still characteristic skin involvement, with the oral mucosa and other mucous membranes affected.[122] However, there is likely a subset of EM that affects the oral mucosa only without skin involvement. Historically, fulminant forms of EM were labeled Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis [TEN (Lyell disease)]. However, more recent data suggest that EM is etiopathogenetically distinct from those two latter conditions, and they are discussed separately below.

Etiology and Pathogenesis

EM is a hypersensitivity reaction, and the most common inciting factor is infection, particularly with HSV. Drug reactions to NSAIDS, anticonvulsants, or other drugs play a smaller role.[121] Cases of oral EM precipitated by benzoic acid, a food preservative, have been reported.[123,124]

Some studies show that recurrent EM is associated with HSV infection both by history of HSV infection 1 to 3 weeks before onset of EM, seropositivity for HSV antibodies, and identification of HSV antigens.[125] Using PCR techniques, HSV gene products have been identified in 71 to 81% of cases of recurrent EM.[10,11] It is postulated that HSV antigens incite a T cell-mediated delayed-type hypersensitivity reaction that generates interferon-γ, with the amplified immune system recruiting more T cells to the area. Cytotoxic T cells, natural killer cells, and/or cytokines destroy the epithelial cells. It has been suggested that CD34+ cells, Langerhans cell precursors, carry fragments of HSV DNA to the skin where it incites EM.[126]

A condition reported as mycoplasma-induced rash and mucositis (MIRM) appears similar to EM and also SJS in that patients, almost always pediatric, present with extensive oral and mucosal lesions but usually less prominent skin lesions.[127] However, infection with Chlamydia pneumonia may cause similar lesions.[128] Some have classified such lesions under Mycoplasma-associated SJS but current classification considers it a distinct entity because of the much milder skin presentation.

Clinical Findings

EM generally affects those between ages 20 and 40 years, with 20% occurring in children.[121] Patients with recurrent EM have an average of 6 episodes a year (range 2–24), with a mean duration of 9.5 years; remission occurred in 20% of cases.[125] Episodes usually last several weeks.[121,122] There may be a prodrome of fever, malaise, headache, sore throat, rhinorrhea, and cough. These symptoms suggest a viral (especially respiratory tract) infection, and this is not surprising since infectious agents are known to trigger EM.

Skin lesions appear rapidly over a few days and begin as red macules that become papular, starting primarily in the hands and moving centripetally toward the trunk in a symmetric distribution. The most common sites of involvement are the upper extremities, face, and neck. The skin lesions may take several forms—hence the term *multiforme*. The classic skin lesion consists of a central blister or necrosis with concentric rings of variable color around it called typical "target" or "iris" lesion that is pathognomonic of EM; variants are called "atypical target" lesions (Figure 3-16). The skin may feel itchy and burnt. Postinflammatory hyperpigmentation is common in dark-skinned individuals and may be worsened by sun exposure.

Oral Findings

The oral findings in EM range from mild erythema and erosion to large painful ulcerations (Figures 3-17 and 3-18).[123] When severe, ulcers may be large and confluent, causing difficulty in eating, drinking, and swallowing, and patients with severe EM may drool blood-tinged saliva. Extensive lip involvement with inflammation, ulceration, and crusting is common (Figure 3-19).

Oral lesions are present in 23 to 70% of patients with recurrent EM.[125–130] The most commonly affected sites are the lips (36%), buccal mucosa (31%), tongue (22%), and labial mucosa (19%).[128] Genital and ocular sites are affected in 25 and 17% of cases, respectively.[125]

The concept of pure oral EM is controversial and not universally accepted since some dermatologists believe that the characteristic appearance and distribution of skin lesions are the sine qua non for the diagnosis of EM. Nevertheless, cases of oral EM without skin involvement have been reported.[131] Intraoral lesions are irregular bullae, erosions, or ulcers surrounded by extensive erythema. Crusting and bleeding of the lips are common, but not always present.[124,132]

Differential Diagnosis

Primary HSV gingivostomatitis with its viral prodrome and erosions and ulcerations may resemble oral EM, but these lesions are culture positive for HSV and do not usually present with the typical skin rash. Oral ulcers of HSV are

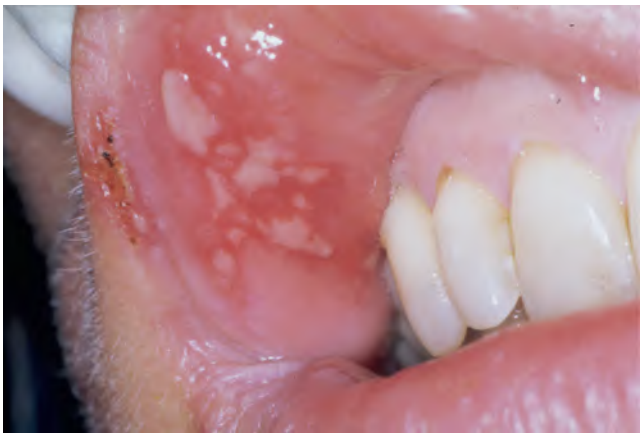

Figure 3-17 Intraoral erythema multiforme with coalescent aphthous-like ulcers and erythema of the buccal mucosa.

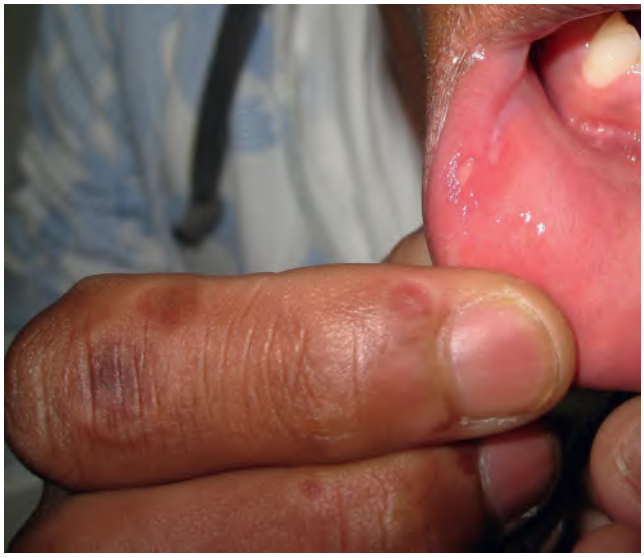

Figure 3-18 Erythema multiforme with target lesions on the skin of the fingers and intraoral ulcers. *Source:* Courtesy of Dr. Adam Lipworth, Boston, MA.

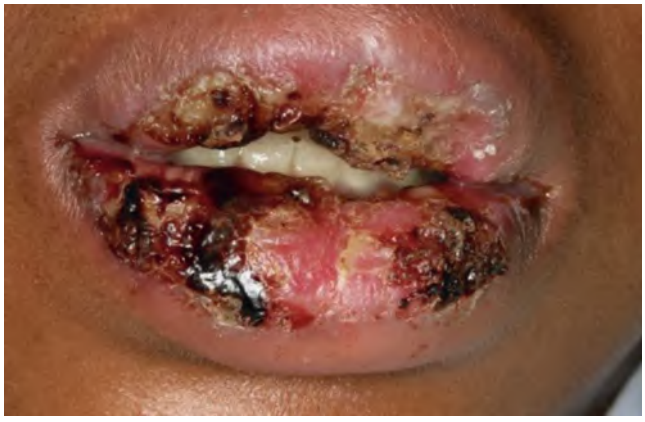

Figure 3-19 Erythema multiforme with hemorrhagic crusts of the lips.

usually smaller, well circumscribed, and clustered, whereas EM lesions are larger and irregular. Autoimmune vesiculobullous disease such as pemphigus and pemphigoid may have oral ulcers and skin lesions, although skin lesions are bullous in nature and not maculopapular, without the centripetal progression seen in EM. They are chronic, slowly progressive diseases that usually persist for months, whereas EM heals within weeks.

Hemorrhagic crusts on the lips are seen in paraneoplastic autoimmune multiorgan syndrome/paraneoplastic pemphigus (associated with malignancies, see below) and Stevens-Johnson syndrome (often drug-induced, see below). The latter may be difficult to distinguish from EM.

Recurrent oral EM in the absence of skin findings may be confused with recurrent aphthous ulcers (see below), but aphthous ulcers present as discrete ovoid or round ulcers, whereas ulcers of EM are more diffuse and irregular with marked erythema.

Laboratory Findings

The diagnosis is made primarily on clinical findings and a recent history of recrudescent HSV infection. IgG and IgM levels are not a reliable test for recrudescence or asymptomatic reactivation although they may be suggestive. A negative IgG level rules out HSV as an etiologic agent.

Early lesions show lymphocytes and histiocytes in the superficial dermis around superficial dermal vessels. This is followed by hydropic degeneration of basal cells, keratinocyte apoptosis and necrosis, subepithelial bulla formation, and a lymphocytic infiltrate.[133] Leukocyte exocytosis is also usually noted.

Management

Mild oral EM can be managed with systemic or topical analgesics for pain and supportive care since the disease is self-limiting and resolves within a few weeks. More severe cases are usually managed with systemic corticosteroids although patients often worsen on discontinuation of steroid therapy. Topical steroids may also help resolve lesions. Cases suspected of being HSV-associated should be treated with antiviral medications, and prophylaxis may prevent recurrences. Treatment with acyclovir at the first sign of disease in recurrent EM controls disease in approximately half of patients.[125] Other treatment modalities include dapsone, hydroxychloroquin, mycophenolate mofetil, azathioprine, colchicines, methotrexate, and intravenous immunoglobulin. [134]

Continuous acyclovir at 400 mg twice a day prevents development of EM in most patients with HSV-associated recurrent disease, whereas EM not related to HSV responded well to azathioprine (100–150 mg/d).[127] Other studies have also shown good suppression of recurrent HSV-associated EM using 500 mg of valacyclovir twice a day or 250 mg of famciclovir twice daily.[44,135] Dapsone (100–150 mg/d) and antimalarials are partially successful in suppressing recurrent outbreaks but may be associated with significant side effects.[127]

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TENs)

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both rare severe necrolytic mucocutaneous disorders resulting from hypersensitivity to medications and are clinically and etiopathogenetically distinct from EM. A diagnosis of SJS is made if there is less than 10% of body surface involvement, SJS-TEN overlap syndrome if 10–30% of body surface is involved and TEN if >30% is involved.[136,137] The mortality rate of SJS and TEN are 1–5% and 25–35% respectively. SJS and TEN start with a prodrome of fever and malaise and the development of generalized eruption of macules, papules, atypical target lesions, vesicles, and bullae. The more common inciting drugs include allopurinol (most common), anticonvulsants, antibiotics, and NSAIDs.[137] In Han Chinese, development of SJS/TEN to the aromatic anticonvulsants—such as carbamazepine, phenytoin, and lamotrigine—is highly associated with HLA-B*1502[138] while HLA-B*5801 is strongly associated with allopurinol associated SJS/TEN universally.[139]

The mucosal surfaces of the eye, genitalia, and mouth are almost always severely affected by SJS/TEN, always with skin involvement. The typical oral manifestation is hemorrhagic crusts on the vermilion and extensive ulcerations and erythema on the oral and other mucosal surfaces (Figures 3-20, 3-21). These lesions resemble oral lesions of paraneoplastic autoimmune multiorgan syndrome/paraneoplastic pemphigus, which are long-standing and associated with malignancy (see below) as well as EM.

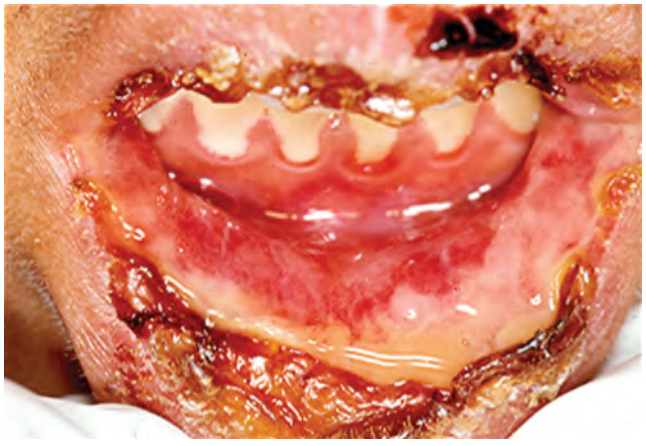

Figure 3-20 Stevens-Johnson syndrome. Lips and labial mucosa (*A*), skin (*B*), and penile (*C*) lesions in a 17-year-old male with Stevens-Johnson syndrome.

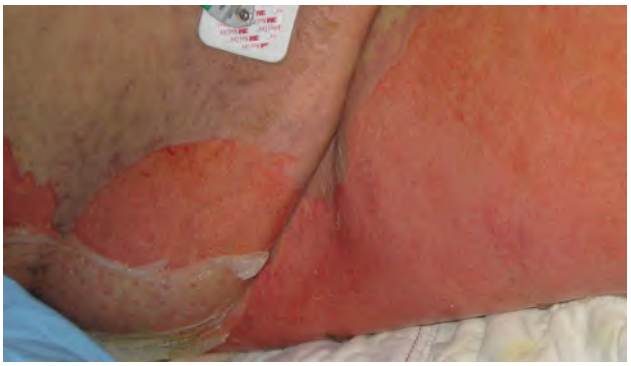

Figure 3-21 Toxic epidermal necrolysis with necrolysis or peeling of the epidermis. *Source:* Courtesy of Dr. Adam Lipworth, Boston, MA.

Histopathologically, most of the disease is localized in the epidermis, presumably this being the site where the drug or its metabolite is bound, with less inflammation in the dermis as is usually seen in EM.

Because of the severity of this condition, treatment is generally with intensive supportive care because of loss of skin barrier, intravenous immunoglobulin, systemic steroids, cyclosporine, plasmapheresis, cyclosporine, and tumor necrosis factor alpha-inhibitor.[140,141] Because of the strong genetic associations with HLA haplotypes, in the future, some of such severe cutaneous adverse reactions may be substantially reduced by pharmacogenetic screening.[142]

Plasma Cell Stomatitis and Oral Hypersensitivity Reactions

Etiology and Pathogenesis

This is a group of conditions that have protean manifestations. Oral hypersensitivity reactions may take the following forms:

1) Acute onset of ulcers such as in oral EM (discussed above).
2) Red and white reticulated lesions of a lichenoid hypersensitivity reaction (discussed in Chapter 4, "Red and White Lesions of the Oral Mucosa").
3) Fixed drug eruption.
4) Marked erosion and erythema especially on the gingiva with or without ulceration called plasma cell stomatitis (PCS).
5) Swelling of the lips/angioedema (see Chapter 19, "Immunologic Diseases").
6) Oral allergy syndrome that presents mainly with symptoms of itching with or without swelling of the oral structures and oropharynx.

This discussion concentrates on lesions of PCS. PCS generally causes erythema and less often ulcers, but is included here for completeness.

PCS is a hypersensitivity reaction that was first described in the late 1960s and early 1970s and was likely a contact stomatitis to a component of chewing gum.[143] Since then, sporadic cases have continued to be reported, and these are all likely caused by a sensitizing contactant, whether or not the contactant is identified. These include khat (*Catha edulis*),[144] components of toothpaste,[144,145] mint candies,[146] and household cleaners.[147] Sometimes, the terms *mucous membrane plasmacytosis* and *plasma cell orificial mucositis* are used because there may be involvement of the upper respiratory tract.[148] Because of the intense plasma cell infiltration, it is believed that this is a B cell-mediated disorder, with T cells augmenting the response. Some believe that this is caused by components of plaque bacteria, although this is not a universally accepted concept.[149]

Clinical Findings

PCS occurs within days of exposure to the contactant, with most signs and symptoms limited to the oral cavity. Some lesions may affect the periorificial tissues or the oropharynx, leading to upper airway symptoms of hoarseness, dysphagia, and mild airway obstruction.[148] Endoscopy may reveal erythematous and thickened mucosa, often with a cobblestoning pattern from the edema. An obvious allergen/contactant is not always identified.[148,150]

Oral Manifestations

PCS occurs within a few days of exposure. It presents as brightly erythematous macular areas of the oral cavity, almost always involving the marginal and attached gingiva or alveolar mucosa and often involving other soft tissues, such as the maxillary and mandibular sulcus, tongue, or buccal mucosa (Figure 3-22). Ulcers may be present, and there may be epithelial sloughing and desquamation. The gingiva may also be swollen and edematous. Patients may

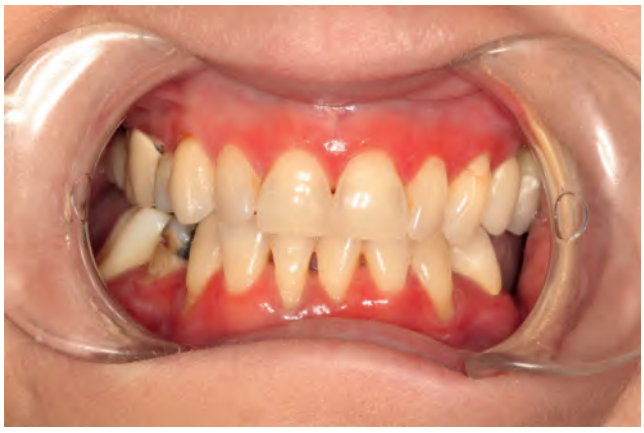

Figure 3-22 Plasma cell gingivitis presenting as desquamative gingivitis.

complain of pain and sensitivity and bleeding of the gingiva on brushing. Angular cheilitis with fissuring and dry, atrophic lips have been reported.[143,151]

Some cases reported as PCS consisted of a very localized area of erythematous gingiva, usually around a single tooth and measuring usually < 1 cm.[149] Interestingly, two adults in this series also demonstrated plasma cell balanitis. It is unclear if this represented classic PCS since most cases of PCS tend to be diffuse.

Differential Diagnosis

The differential diagnosis for PCS includes any of the desquamative gingivitides, such as erythematous/erosive lichen planus, and the autoimmune vesiculobullous disorders, such as mucous membrane pemphigoid and pemphigus vulgaris. The lesions will become chronic if the patient continues to be exposed to an undetected allergen. A biopsy for both routine histology and direct immunofluorescence studies to rule out mucous membrane pemphigoid and pemphigus vulgaris is necessary to make the diagnosis.

Another condition that PCS can mimic is pubertal or pregnancy-induced gingivitis and plaque-associated gingivitis. The difference in the histopathology is in the density of plasma cells since nonspecific gingivitis generally also is associated with a plasma cell infiltrate. The clinical appearance of diffuse red gingiva with a history of recent exposure to a new topical agent helps make the diagnosis, especially if discontinuation of the agent leads to resolution. Some previous cases reported as PCS may constitute such plaque-associated and pubertal gingivitis.[149] Chronic granulomatous gingivitis caused by components of polishing agents such as pumice also often present with sensitive or painful erythematous gingiva. A biopsy will show the presence of particulate matter in the gingival connective tissue.

Mouth-breathers often present with erythematous and sometimes edematous gingiva, usually around the upper anterior teeth. A good history and correlation with the histopathologic findings help differentiate this from PCS.

Erythematous candidiasis may present with marked gingival erythema (often linear) without the usual white curdy papules of "thrush" or pseudomembranous candidiasis and will resolve with anti-fungal therapy. *Candida* may also secondarily infect an area of PCS.

Fixed drug eruptions are rare in the oral cavity and present as areas of ulceration or erosion that recur at the same site whenever exposed to a certain medication.[152]

PCS should not be confused with a direct contact irritation of the tissues such as from strongly flavored foods and dentifrices.[153] This would occur in any individual and does not represent a hypersensitivity reaction because ulcers are caused by the noxious and caustic nature of the chemical causing a mucosal burn.

Laboratory Findings

A biopsy is the most useful diagnostic test for this condition, followed by patch testing to identify the allergen.

A biopsy of the gingiva in PCS shows parakeratosis, epithelial hyperplasia, neutrophilic exocytosis, and numerous spongiotic pustules in the absence of *Candida*.[143,154] The most significant finding is dense sheets of plasma cells in the lamina propria; many dilated capillaries lie close to the surface, accounting for the marked erythema. Eosinophils are not seen usually.[148] Immunoperoxidase stains will invariably show the plasma cell infiltrate to be polyclonal, typical for a reactive/inflammatory process, and not monoclonal, which typifies neoplastic lesions.[73]

Management

PCS is self-limiting and will generally, but not always, regress if the contactant is identified and removed. Nevertheless, pain control and anti-inflammatory agents may be helpful during the healing process. Topical steroids may help reduce inflammation and speed healing.[155] Some lesions have resolved with intralesional triamcinolone injections, although the gingiva is a particularly difficult location for such injections.[156] Cases have also responded well to prednisone.[150] Gingivectomies may be needed to recontour lesions that are long-standing and more fibrotic. One case showed improvement with 2% fusidic acid.[157]

THE PATIENT WITH RECURRING ORAL ULCERS

Recurring oral ulcers are among the most common problems seen by clinicians who manage diseases of the oral mucosa. There are several diseases that should be included in the differential diagnosis of a patient who presents with a history of recurring ulcers of the mouth, including recurrent aphthous stomatitis, Behçet syndrome, recrudescent HSV infection, and recurrent oral EM. HSV infection and EM were discussed earlier in this chapter.

Recurrent Aphthous Stomatitis (RAS)

RAS is a disorder characterized by recurring ulcers confined to the oral mucosa in patients with no other signs of disease. RAS is considered a diagnosis of exclusion since hematologic deficiencies, immune disorders, and connective tissue diseases may cause oral aphthous-like ulcers clinically similar to RAS.

RAS affects approximately 20% of the general population, but when specific ethnic or socioeconomic groups are studied, the incidence ranges from 5% to 50%.[158] RAS is classified according to clinical characteristics: minor ulcers, major

ulcers (Sutton disease, periadenitis mucosa necrotica recurrens), and herpetiform ulcers (Table 3-3). There are cases in which a clear distinction between minor and major ulcers is blurred, particularly in patients who experience severe discomfort from continuous or frequent episodes of multiple ulcers. These lesions have been referred to as "severe" minor ulcers or complex aphthosis.

Etiology and Pathogenesis

It was once assumed that RAS was a form of recurrent HSV infection, and there are still clinicians who mistakenly call RAS "herpes." Many studies done during the past 50 years have confirmed that RAS is not caused by HSV.[159] This distinction is particularly important at a time when there is specific effective antiviral therapy available for HSV that is ineffective for RAS. "Herpes" is an anxiety-producing word, suggesting a sexually transmitted disease among many laypersons, and its use should be avoided when it does not apply. There have been theories suggesting a link between RAS and a number of other microbial agents, including oral streptococci, *Helicobacter pylori*, VZV, CMV, and human herpesvirus (HHV)-6 and HHV-7, but there are presently no conclusive data linking RAS to a specific microorganism.[160]

The major factors presently linked to RAS include genetic factors, hematologic or immunologic abnormalities, and local factors, such as trauma and smoking. There is increasing evidence linking local immune dysfunction to RAS, although the specific defect remains unknown. During the past 30 years, research has suggested a relationship between RAS and various immune abnormalities including: lymphocytotoxicity, antibody-dependent cell-mediated cytotoxicity, defects in lymphocyte cell sub-populations, an alteration in the CD4 to CD8 lymphocyte ratio,[161] and dysfunction of the mucosal cytokine network, resulting in an exaggerated cell-mediated immune response.[162]

The best-documented factor is heredity. A study of 1303 children from 530 families demonstrated an increased susceptibility to RAS among children of RAS-positive parents. Another study demonstrated that patients with RAS-positive parents had a 90% chance of developing RAS, whereas patients with no RAS-positive parents had a 20% chance of developing the lesions.[163] Further evidence for the inherited nature of this disorder results from studies in which genetically specific human leukocyte antigens (HLAs) have been identified in patients with RAS, particularly in certain ethnic groups.[164] There have been studies linking minor RAS to genetic factors associated with immune function, particularly genes controlling release of the proinflammatory cytokines. A unified model of etiology postulates that triggers such as stress, or hormonal changes trigger a cascade of proinflammatory cytokines directed against oral mucosa.[165]

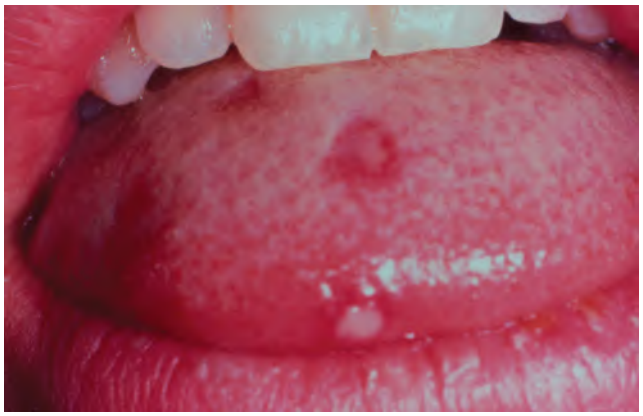

Figure 3-23 Iron deficiency anemia with ulcers on tongue.

Hematologic deficiency, particularly of serum iron, folate, or vitamin B12, appears to be an etiologic factor in 5%–10% patients with aphthous-like ulcers although these lesions more often occur on keratinized mucosa (Figure 3-23). Studies of RAS populations from the United Kingdom show a higher level of nutritional deficiency than studies performed in the United States.[166]

Aphthous-like ulcers may also be seen in celiac disease, an autoimmune disease caused by intolerance to gluten and childhood periodic fever syndromes such as periodic fever, aphthosis, pharyngitis and adenopathy (PFAPA) syndrome[167] (see Chapter 25 Pediatric Oral Medicine).

It was initially reported in the 1960s that there was a negative correlation between RAS and a history of smoking, and many clinicians have reported that RAS is exacerbated when patients stop smoking. A study measuring a nicotine metabolite present in the blood of smokers confirmed that the incidence of RAS is significantly lower among smokers. The nicotine metabolites are believed to decrease levels of proinflammatory cytokines and increase anti-inflammatory cytokines.[159,168]

Other factors that have been reported associated with RAS include anxiety, periods of psychological stress, localized trauma to the mucosa, menstruation, upper respiratory infections, and food allergy.

Oral Findings

The first episodes of RAS most frequently begin during the second decade of life. The lesions are confined to the oral mucosa and begin with prodromal burning from 2 to 48 hours before an ulcer appears. During this initial period, a localized area of erythema develops. Within hours, a small white papule forms, ulcerates, and gradually enlarges over the next 48–72 hours. The individual lesions are round-to-ovoid, symmetric, and shallow (similar to viral ulcers), but no tissue tags are present from ruptured vesicles, which helps distinguish RAS from diseases that start as vesicles, such as pemphigus, and pemphigoid. Multiple lesions are

often present, but the number, size, and frequency vary considerably (Figures 3-24 through 3-27). The buccal and labial mucosae are most commonly involved. Lesions rarely occur on the heavily keratinized palatal mucosa or gingiva. In mild RAS, the lesions reach a size of 0.3–1.0 cm and begin healing within a week. Healing without scarring is usually complete in 10–14 days.

Most patients with RAS have between two and six lesions at each episode and experience several episodes a year. The disease is an annoyance for the majority of patients with mild RAS, but it can be painfully disabling for patients with multiple minor RAS or major RAS. Patients with major ulcers develop deep lesions that are larger than 1 cm in diameter and last for weeks to months (Figure 3-25). In the most severe cases, large portions of the oral mucosa may be covered with large deep ulcers that can become confluent, and are extremely painful, interfering with speech and eating. These patients may occasionally require hospitalization for intravenous feeding and treatment with systemic corticosteroids. The lesions may last for months and sometimes be misdiagnosed as squamous cell carcinoma, granulomatous disease, or a blistering disease such as pemphigus. The lesions heal slowly and leave scars that may result in decreased mobility of the uvula and tongue.

The least common variant of RAS is the herpetiform type, which tends to occur in adults. The patient presents with more than 10 small punctate ulcers, measuring <5 mm, scattered over large portions of the oral mucosa.

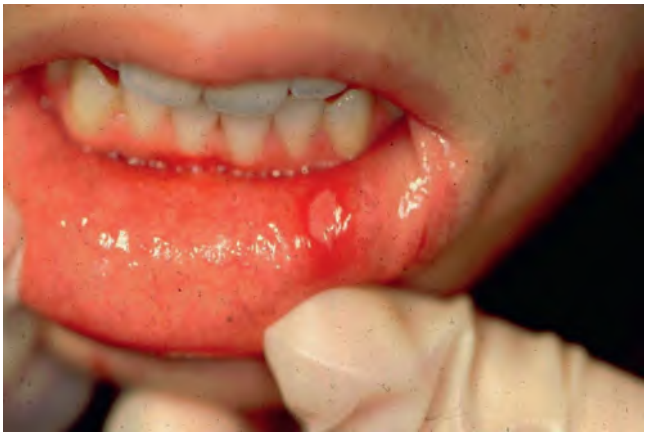

Figure 3-24 Recurrent aphthous ulcer of the labial mucosa.

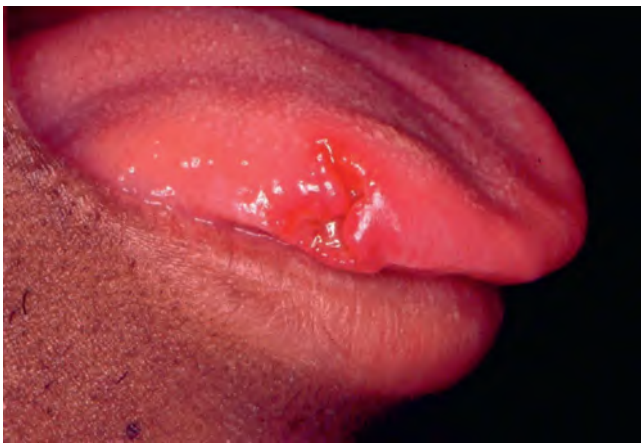

Figure 3-25 Major recurrent aphthous ulcer involving the tongue of a patient with HIV disease.

Differential Diagnosis

RAS is the most common cause of recurring oral ulcers and is essentially diagnosed by exclusion of other diseases. A detailed history, examination, and when necessary laboratory testing by a knowledgeable clinician should distinguish RAS from primary acute lesions such as viral stomatitis or erythema multiforme or from chronic multiple lesions such as pemphigus or pemphigoid, as well as from other conditions associated with recurring ulcers, such as RIH, connective tissue diseases, drug reactions, and other dermatologic disorders. The history should include obtaining symptoms, which may suggest oral ulcers from HIV, connective tissue disease such as lupus erythematosus, gastrointestinal complaints suggestive of inflammatory bowel disease, and associated skin, eye, genital, or rectal lesions.

Laboratory Findings

Laboratory tests should be ordered when patients do not follow the usual pattern of RAS; for example, when episodes of RAS become more severe, begin past the age of 25, or are accompanied by other signs and symptoms. Biopsies are only indicated when it is necessary to exclude other diseases, particularly granulomatous diseases such as Crohn disease, sarcoidosis, or blistering diseases such as pemphigus or pemphigoid (Figure 3-26).

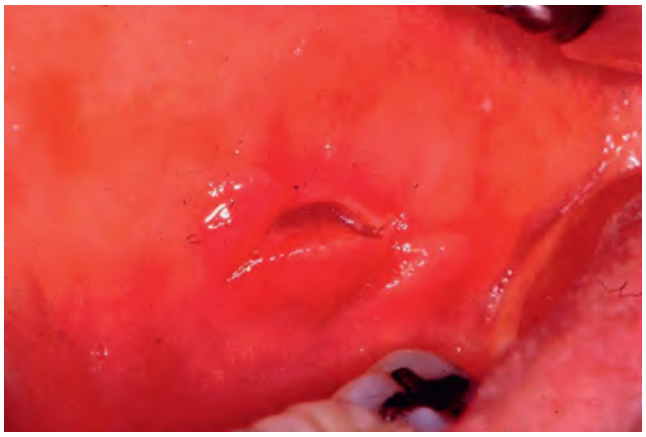

Figure 3-26 Oral ulcer involving the buccal mucosa of a patient with Crohn's disease.

Patients with severe minor aphthae or major aphthous ulcers should have known associated factors investigated, including connective tissue diseases and hematologic abnormalities, such as reduced levels of serum iron, folate, vitamin B12, and ferritin. Patients with abnormalities in these values should be referred to an internist for further management. HIV-infected patients, particularly those with CD4 counts below 100/mm^3, may develop major aphthous ulcers, and, occasionally, such oral ulcers are the presenting sign of AIDS.

Biopsies reveal only a superficial ulcer covered by a fibrinous exudate with granulation tissue at the base and a mixed acute and chronic inflammatory infiltrate. Studies of early lesions of RAS demonstrate an infiltration of large granular lymphocytes and helper-induced CD4 lymphocytes with focal degeneration of basal cells and the formation of small intraepithelial vesicles. The appearance of the ulcer is associated with the appearance of cytotoxic suppressor lymphocytes.[169]

Management

Management is tailored to the severity of the disease. In mild cases with two or three small lesions, use of a protective emollient such as Orabase™ often alleviates pain and facilitates healing. Pain relief of minor lesions can be effected with a topical anesthetic agent such as benzocaine or lidocaine. In more severe cases, the use of a high-potency topical steroid preparation, such as fluocinonide, betamethasone, or clobetasol, placed directly on the lesion, shortens healing time and reduces the size of the ulcers. The effectiveness of the topical steroid is partially based on good instruction and patient compliance regarding proper use. The steroid gel can be carefully applied directly to the lesion after meals and at bedtime two to three times a day or mixed with an adhesive such as Orabase prior to application. Larger lesions can be treated by placing a gauze sponge containing the topical steroid on the ulcer and leaving it in place for 15–30 minutes to allow for longer contact of the medication. Other topical preparations that have shown promise in decreasing the healing time of RAS lesions include use of chlorhexadine or a topical tetracycline such as doxycycline, which can be used either as a mouthrinse or applied as a paste directly to the lesions.[170] Intralesional steroid injections can be used to treat large indolent major RAS lesions. It should be emphasized that no available topical therapy reduces the frequency of new lesions. Use of lasers had been studied as a method of pain relief for patients with large ulcers.

When patients with major aphthae or severe cases of multiple minor aphthae do not improve sufficiently with topical therapy, use of systemic therapy should be considered. Drugs that have been reported to reduce the number of ulcers in selected cases of major aphthae include colchicine, pentoxifylline, dapsone, short bursts of systemic steroids, and thalidomide.[169,171] Each of these drugs has the potential for side effects, and the clinician must weigh the potential benefits versus the risks.[171]

Thalidomide, a drug originally marketed as a nonaddicting hypnotic in the 1950s, was withdrawn from the market in the early 1960s due to its association with severe, deforming, and life-threatening birth defects. Further investigation demonstrated that thalidomide has significant anti-inflammatory and immunomodulatory properties and is useful in treating a number of diseases, including erythema nodosum leprosum, discoid lupus erythematosus, graft-vs-host disease, multiple myeloma, and Behçet syndrome. The drug has also been shown to reduce both the incidence and severity of major RAS in both HIV-positive and HIV-negative patients.[172] The use of thalidomide for RAS should be reserved for management of severe major RAS where other less toxic therapies, including high-potency topical steroids, colchicine, and pentoxifylline, have failed to control the disease.[173] Thalidomide must be used with extreme caution in women during childbearing years owing to the potential for severe life-threatening and deforming birth defects. All clinicians prescribing thalidomide in the United States must be registered in the REMS (Risk Evaluation Mitigation Strategy) program for thalidomide and patients receiving the drug must be thoroughly counseled regarding effective birth control methods that must be used whenever thalidomide is prescribed. For example, two methods of birth control must be used, and the patient must have a pregnancy test monthly. Other side effects of thalidomide include peripheral neuropathy, gastrointestinal complaints, and drowsiness. Monitoring patients taking long-term thalidomide for the development of peripheral neuropathy with periodic nerve conduction studies is recommended.

Behçet's Disease (Behçet Syndrome)

Behçet's disease (BD) was initially described by the Turkish dermatologist Hulusi Behçet as a triad of symptoms including recurring oral ulcers, recurring genital ulcers, and eye involvement. BD is now understood to be a multisystem disorder with many possible manifestations. The highest incidence of BD has been reported in eastern Asia, the Middle East, and the eastern Mediterranean, particularly Turkey and Japan, where BD is a leading cause of blindness in young males; however, cases have been reported worldwide, including Europe and North America.[174]

Etiology and Pathogenesis

BD is a systemic perivasculitis characterized by hyperactivity of neutrophils with enhanced chemotaxis and elevated proinflammatory cytokine IL-8, IL-17, and TNF-α playing a

major role in the pathogenesis.[175] The HLA-B51 genotype is most frequently linked to BD, especially in patients with severe forms of the disease in Asia.[176]

Clinical Manifestations

The highest incidence of BD is in young adults between the ages of 25 and 40, with the oral mucosa as the most common site of involvement. The genital area is the second most common site of involvement and presents as ulcers of the scrotum and penis in males and ulcers of the labia in females. The eye lesions consist of uveitis, retinal vasculitis, vascular occlusion, optic atrophy, and conjunctivitis. Blindness is a possible complication of the disease, and periodic evaluation by an ophthalmologist is necessary.

Systemic involvement occurs in over half of patients with BD. Skin lesions resembling erythema nodosum or large pustular lesions occur in over 50% of patients with BD. These lesions may be precipitated by trauma, and it is common for patients with BD to have a cutaneous hyperreactivity to intracutaneous injection or a needlestick (pathergy). Arthritis occurs in greater than 40% of patients and most frequently affects the knees, ankles, wrists, and elbows. The affected joint may be red and swollen, as in rheumatoid arthritis, but involvement of small joints of the hand does not occur, and permanent disability does not result.[174]

In some patients, central nervous system involvement is the most distressing component of the disease. This may include brainstem syndrome, involvement of the cranial nerves, or neurologic degeneration resembling multiple sclerosis that can be visualized by magnetic resonance imaging of the brain.[177] Other reported signs of BD include thrombophlebitis, intestinal ulceration, venous thrombosis, and renal, cardiac, and pulmonary disease. Both pulmonary involvement and cardiac involvement are believed to be secondary to vasculitis, which may involve all layers of large blood vessels Involvement of large vessels is life threatening because of the risk of arterial occlusion or aneurysms.

BD in children, which most frequently presents between the ages of 9 and 10 years, has similar manifestations to the adult form of the disease, but oral ulcers are a more common presenting sign in children, whereas uveitis is less common. Oral lesions are the presenting symptom in more than 95% of children with BD. A variant of BD, MAGIC syndrome, has been described. It is characterized by mouth and genital ulcers with inflamed cartilage.[178]

Oral Findings

The most common site of involvement of BD is the oral mucosa. Recurring oral ulcers appear in more than 90% of patients; these lesions cannot be distinguished either clinically or histologically from RAS (Figure 3-27). Some patients experience mild recurring oral lesions; others have deep, large, scarring lesions characteristic of major RAS. These lesions may appear anywhere on the oral or pharyngeal mucosa.

Differential Diagnosis

Because the signs and symptoms of BD overlap with those of several other diseases, particularly the connective tissue diseases, it has been difficult to develop criteria that meet with universal agreement. A collaborative study developed the following diagnostic criteria based on a point system where 4 or more points is strongly associated with BD: oral, ocular, and genital lesions score 2 points each, while skin lesions, and neurologic and vascular manifestations score 1 point each (Figure 3-28). Positive pathergy test is an optional test but also scores 1 if positive.[179]

Laboratory Findings

BD is a clinical diagnosis based up the criteria described above. Laboratory tests are used to rule out other diseases,

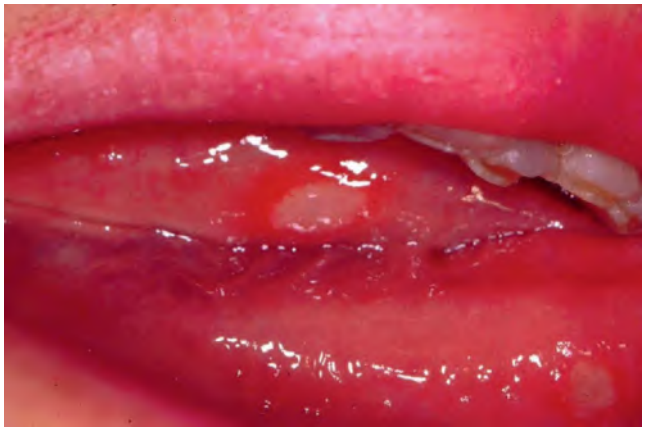

Figure 3-27 Ulcer of the tongue of a patient with Behçet's disease.

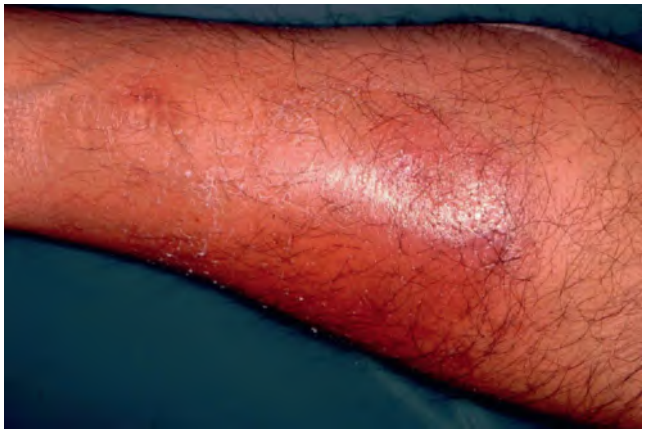

Figure 3-28 Early skin lesion of pemphigus vulgaris.

such as connective tissue (e.g., lupus erythematosus) and hematologic diseases causing severe neutropenia.

Management

The management of BD depends on the severity and the sites of involvement. Patients with sight-threatening uveitis, vascular, GI, or central nervous system lesions require aggressive therapy with systemic steroids, immunosuppressive drugs, interferon alpha, or anti-TNF biologics.[180] Pentoxifylline, which has fewer side effects than immunosuppressive drugs or systemic steroids, has also been reported to be effective in decreasing disease activity, particularly of oral and genital lesions.[181] Dapsone, colchicine, and thalidomide have also been used effectively to treat mucosal lesions of BD.[182] Apremilast, a biologic which decreases proinflammatory cytokines, was shown in a placebo controlled clinical trial to decrease the incidence and severity of oral and genital ulcers in a majority of patients[183] and is taken orally.

THE PATIENT WITH CHRONIC MULTIPLE LESIONS

Patients with chronic multiple persistent oral ulcerative lesions often have a delayed diagnosis as the clinical presentation may be confused with other recurrent ulcerative disorders including EM or RAS. The clinician can avoid misdiagnosis by carefully questioning the patient on the initial visit regarding the natural history of the lesions. In recurring disorders such as severe RAS or EM, the patient may experience continual new episodes of ulceration of the oral mucosa, but individual lesions heal and new ones form. In the category of disease described in this section, the same lesions are present for weeks to months often expanding in size. The major diseases in this group that can affect the oral mucosa are pemphigus vulgaris (PV), paraneoplastic pemphigus (PNP), bullous pemphigoid (BP), mucous membrane pemphigoid (MMP), linear IgA disease (LAD), epidermolysis bullosa acquisita (EBA), and erosive lichen planus. Lichen planus is discussed in Chapter 4.

Pemphigus

Pemphigus includes a group of autoimmune, potentially life-threatening diseases that cause blisters, peeling or erosions of the skin and/or mucous membranes, characterized by intraepidermal or epithelial acantholysis. The predisposition to develop the autoantibodies that cause pemphigus is genetically determined, but the triggering mechanism that initiates the immune response is unknown, though occasionally drugs may be implicated.

The major variants of pemphigus are pemphigus vulgaris (PV), pemphigus foliaceus, and paraneoplastic pemphigus (PNP). Pemphigus vegetans is a variant of pemphigus vulgaris, and pemphigus erythematosus is a variant of pemphigus foliaceus. Pemphigus vulgaris and paraneoplastic pemphigus frequently present with oral lesions and will be discussed in detail below. Pemphigus foliaceus (PF) is much less common than PV and only affects the skin. The increased number of pemphigus foliaceus cases in South America (Brazil and neighboring countries) and North Africa (Tunisia and neighboring countries) is the result of an endemic form of the disease in these areas, where it affects mostly young adults. In fogo selvagem, the endemic form of pemphigus foliaceus in Brazil, an initial immune response against the sand fly salivary antigen LJM11 is speculated to cause a cross-reaction with the PF antigen desmoglein 1.

Pemphigus Vulgaris (PV)

PV is the most common form of pemphigus, accounting for over 80% of cases.

Etiology and Pathogenesis

Both genetic and environmental factors are associated with the onset of pemphigus. Pemphigus is a polygenic disease with an increased prevalence of low titers of disease-associated autoantibodies in healthy first-degree relatives of patients. A strong association with pemphigus vulgaris has been observed for HLA-DRB1*0402 (which is predominant in Ashkenazi Jews), HLA-DRB1*1401, HLA-DRB1*1404 and HLA-DQB1*0503 (which are both prevalent in non-Jewish patients of European and Asian descent).[184]

Environmental factors under consideration include viruses (such as herpes simplex), dietary factors, and physiological and psychological stressors. Several drugs have been implicated in the induction of pemphigus and though uncommon, the diagnosis is challenging as the clinical presentation is indistinguishable and the latency period may be several months. There are three groups of chemical structures that have been suggested to cause drug-induced pemphigus: thiol drugs (e.g., captopril, carbimazole, and penicillin), phenol drugs (e.g., rifampicin, levodopa, and aspirin) and nonthiol, nonphenol drugs (e.g., calcium channel blockers, ACE-inhibitors and nonsteroidal antiinflammatory drugs). PF is the most common pattern observed in up to 70% of thiol-induced cases while nonthiol drugs tend to trigger a PV phenotype. Initial management is to stop the offending drug and, if needed, additional conventional treatment. The disease may continue in 50% in spite of drug withdrawal while others recover completely. Recovery following drug withdrawal is more likely in thiol-triggered cases.[185]

The underlying mechanism responsible for lesions in PV is the binding of IgG and sometimes IgA autoantibodies to transmembrane glycoprotein adhesion molecules present on desmosomes called desmogleins.[186,187] Desmoglein 1 (Dsg1) is the dominant glycoprotein expressed in the skin and though also present throughout the epithelia in mucous membranes, the dominant molecule in mucosal desmosomes is desmoglein 3 (Dsg3). Individuals genetically susceptible to pemphigus harbor desmoglein reactive B and T cells.[188] Patients with PV mainly involving the mucous membranes have antibodies primarily against Dsg3, but patients with PV involving both the skin and mucosa will have antibodies against both Dsg3 and Dsg1.[189] Evidence for the relationship of the IgG autoantibodies to PV lesion formatio, includes studies demonstrating the formation of blisters on the skin of mice after passive transfer of IgG from patients with PV.[190] The precise mechanism of the acantholysis after pemphigus IgG binds to Dsg 3 on the cell surface is unknown. There is, however, evidence to support signaling molecules and metabolic pathways in the development of acantholysis, involving, for example, p38 mitogen-activated protein kinase (MAPK) and its downstream effectors ultimately leading to a reduction in the number of desmosomes. It has been shown that activation of autoreactive T cells responsive to Dsg 1 and 3 in the context of HLA-DRB1*04:02 leads to the induction of IgG autoantibodies and loss of epidermal adhesion.[191] This concept has been developed into a potential therapeutic strategy. Using a chimeric autoantibody receptor (CAAR) on T cells in this case Dsg, adapted T cells specifically kill anti-Dsg3 B cells in a PV mouse model.[192,193]

Epidemiology

The incidence of pemphigus depends upon geographical location. In Central Europe and the United States, it is estimated to be between 1 and 7 patients/million/year. It occurs more frequently in the fifth to sixth decades of life, although rare cases have been reported in children. Although universally encountered, there is a racial predisposition noted among Ashkenazi Jews and Asian subgroups including those originating from Gujurat in India. Generally, PV is more common than pemphigus foliaceus (PF), with ratios ranging from 4:1 to 9:1.

Clinical Manifestations

General

The classic lesion of PV is a thin-walled bulla arising on otherwise normal skin or mucosa. The blister or bulla rapidly breaks but may continue to extend peripherally, eventually leaving larger areas denuded of skin (Figures 3-28 and 3-29). A characteristic sign of the disease, the Nikolsky sign, may be elicited by application of gentle lateral pressure to an erosion or blister. It is not however recommended as it is painful and while typically seen in PV may also be seen in other blistering conditions.

There are three broad clinical subgroups of PV: mucosal-dominant type (limited cutaneous involvement) associated with blisters in the deep layers of the oral mucosa owing to anti-Dsg 3 IgG autoantibodies; mucocutaneous type (both mucosal and cutaneous involvement) with blisters in the deep layers of the oral mucosa and epidermis, owing to anti-Dsg 3 and anti-Dsg 1 IgG autoantibodies, respectively; and cutaneous type (cutaneous involvement alone) with predominantly anti-Dsg 1 IgG autoantibodies.

The majority of patients will present with oral lesions and thus the dental profession will often encounter these patients first. Skin lesions when present may involve any surface including the scalp, anogenital skin, and periungual areas with an average lag period of 4 months. Lesions on the scalp may result in a chronic, thickened hyperkeratotic areas that can become secondarily infected. In flexural sites the skin can appear thickened or "vegetating" and may be referred to as pemphigus vegetans.

In severe cases of PV, the conjunctival, nasopharyngeal, laryngeal, esophageal, or anogenital mucosae may be involved and patients may become cachexic and dehydrated. Endoscopic examination, particularly where esophageal symptoms are present, should be performed to determine the severity of the lesions. Mucocutaneous PV tends to be a more severe disease, proving slower to respond to treatment and less likely to achieve remission off-treatment than purely mucosal PV. Rarely patients with pemphigus develop acute fulminating disease, but, in most cases, the disease develops more slowly, usually taking months to develop to its fullest extent. Since the advent of corticosteroids most patients will improve relatively quickly. However, there is significant morbidity and occasionally a mortality rate in elderly patients and

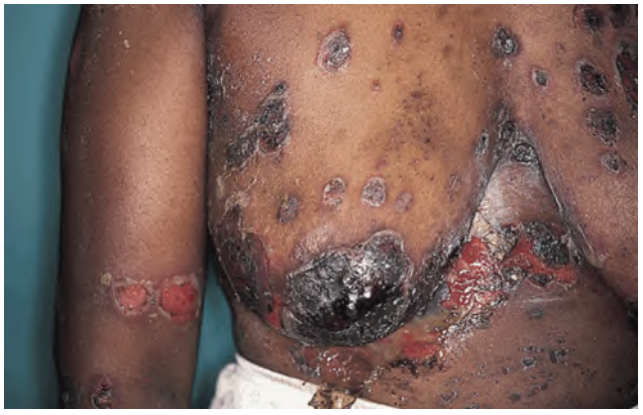

Figure 3-29 Extensive involvement of the skin in a patient with pemphigus vulgaris.

in patients requiring high doses of corticosteroids who develop infections and bacterial septicemia.

Oral Findings

Eighty to 90% of patients with PV develop oral lesions sometime during the course of the disease, and in 60% of cases, oral lesions are the first sign. It is common for the oral lesions to be present for weeks to months before the skin lesions appear. In a subgroup of patients, PV may affect the oral mucosa as the sole site. Thus, dental specialists and primary care physicians need to recognize the oral clinical signs. There is evidence to suggest that early treatment leads to be more rapid disease control, however the delay in diagnosis may be several months.

Intraorally, while transient blisters may be reported by the patient and are occasionally seen, more typically, PV presents with multiple shallow irregular erosions. These correspond to the loss of a thin irregular layer of epithelium leaving a denuded erythematous base. As the ulcers are not full thickness, that is, penetrating the corium, there is not a yellow sloughy base (Figures 3-30 and 3-31). The edges of the lesion particularly may continue to extend peripherally over a period of weeks until they involve larger areas of the oral mucosa. Most commonly, lesions start on the buccal mucosa, often in areas of trauma along the occlusal plane. The palatal mucosa, tongue, and gingiva are other common sites of involvement. As lesions start to heal, they form a more defined margin and eventually develop a white appearance before resolving completely. When ulcers are present on the dorsum of the tongue, these may be longstanding and may eventually heal with loss of the papillae. Elsewhere in the mouth, long-term damage or scarring is not a feature of this condition.

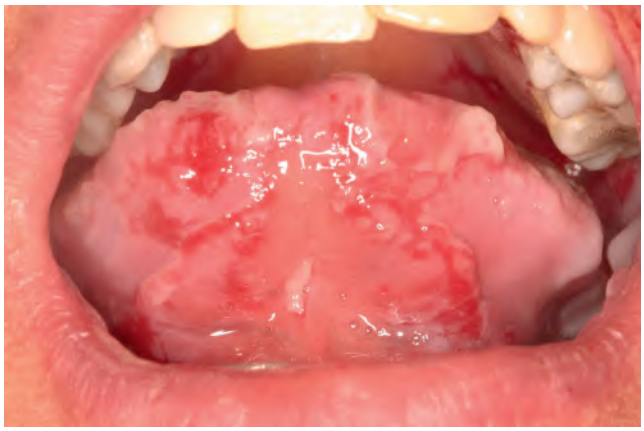

Figure 3-30 Pemphigus vulgaris presenting as shallow, irregular red erosions of the ventral tongue with ulcers and tissue tags.

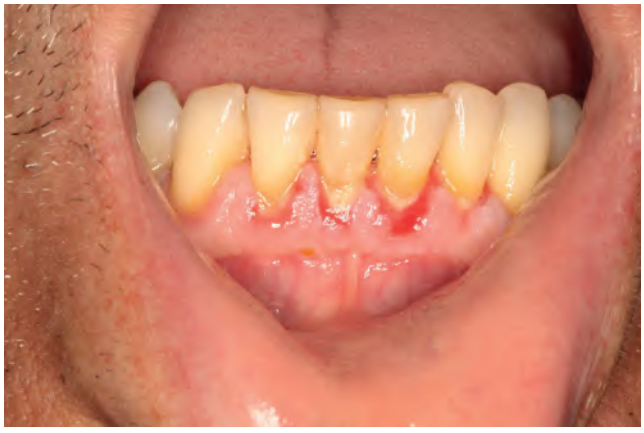

Figure 3-31 Pemphigus vulgaris presenting as ragged erosions of the gingival margin.

Differential Diagnosis

If an accurate history and examination is performed, the clinician should be able to distinguish the lesions of pemphigus from those caused by acute viral infections, such as primary herpetic stomatitis or recurrent EM, as these are generally transient and spontaneously remitting. While recurrent EM can rarely give rise to almost persistent ulceration, individual lesions will heal over 2 to 3 weeks. It is also important for the clinician to distinguish pemphigus lesions from RAS. While RAS lesions may be severe, individual lesions heal and recur often in a different site. The Stevens-Johnson–Toxic epidermal necrolysis (SJS-TEN) spectrum must also be considered in patients with an abrupt onset of mucocutaneous lesions, but this is usually in the context of a new medication and patients are generally very unwell. In pemphigus, the same lesions continue to extend peripherally over a period of weeks to months. Lesions of PV are not round and symmetric like RAS lesions but are erythematous, shallow, and irregular and often have detached epithelium at the periphery. In some cases, the lesions may start on the gingiva as desquamative gingivitis. It should be remembered that desquamative gingivitis is not a diagnosis in itself; these lesions must be biopsied to distinguish PV from subepithelial blistering diseases such as mucous membrane pemphigoid or lichen planus.

Laboratory Findings

PV is diagnosed by biopsy and this can be taken from either oral mucosa or skin. Two samples are taken, one for histology and a second for direct immunofluorescence (DIF). The latter is the gold standard test for diagnosis. In blistering skin or oral diseases, the ideal sample includes a new intact vesicle less than 24 hours old for histopathology. However, because intact blisters are rarely seen, the biopsy specimen should be taken from the advancing edge of the lesion, where areas of characteristic suprabasilar acantholysis may

be observed by the pathologist. Specimens taken from the center of a denuded area are nonspecific histologically as well as clinically. Occasionally more than one set of biopsies is necessary before the correct diagnosis can be made.

The separation of cells, called acantholysis, takes place in the lower layers of the stratum spinosum (Figure 3-32).

A second biopsy for direct immunofluorescence (DIF) should be performed whenever PV is included in the differential diagnosis. This study is best performed on a biopsy specimen taken from clinically normal-appearing perilesional mucosa or skin, and placed in Michel's transport medium. In the laboratory, fluorescein-labeled antihuman immunoglobulins are placed over the patient's tissue specimen. In cases of PV, the technique will detect IgG bound to the surface of the keratinocytes (Figure 3-33). It distinguishes PV from the subepidermal immunobullous diseases.

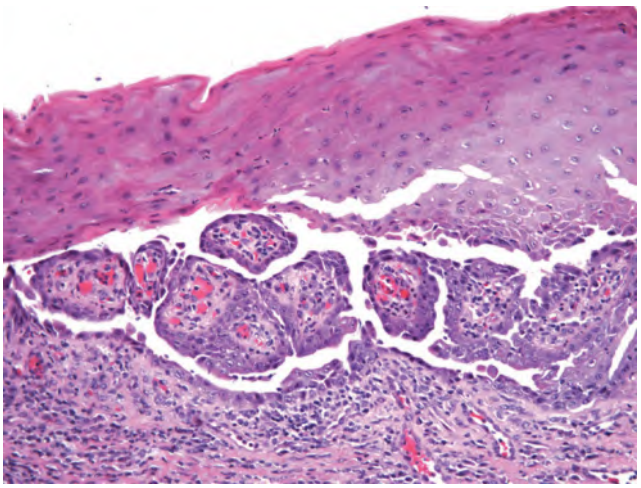

Figure 3-32 Photomicrograph of pemphigus vulgaris showing suprabasilar bulla with acantholysis.

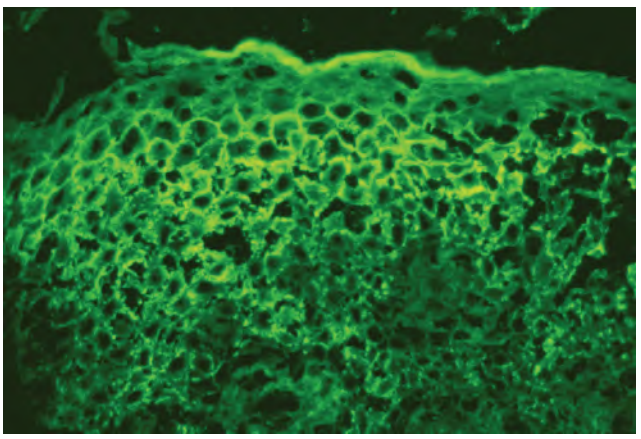

Figure 3-33 Direct immunofluorescence study of pemphigus vulgaris showing intercellular deposition of IgG.

In PV, if the adjacent "normal" tissue is sampled, the result is positive in 100% samples.[194]

Indirect immunofluorescent (IIF) antibody tests performed on a patient's serum are helpful in distinguishing PV from pemphigoid and other chronic oral lesions and in following the progress of patients during treatment. In this technique, serum from a patient with a bullous disease is placed over a prepared slide of a mucosal structure (usually monkey esophagus), or salt-split human skin and autoantibodies present in the serum will bind to the target antigens. The slide is then overlaid with fluorescein-tagged antihuman immunoglobulin. Patients with PV have circulating anti-DSG antibodies that bind to the keratinocyte surfaces and are detected using the fluorescent microscope. The titer of the antibody has been related to the level of clinical disease and may be repeated periodically during treatment to determine disease activity.[195] The association, however, is not always present with some patients having active disease and negative IIF and vice versa. An enzyme-linked immunosorbent assay (ELISA) is more sensitive than IIF and can distinguish anti-DSG1 antibodies from anti-DSG3 in serum samples.[196] The ELISA can distinguish PV from pemphigus foliaceous and may be helpful in determining disease activity and prognosis.[197] Recent work has shown that saliva is potentially a useful alternative to serum for ELISA with desmoglein 3 IgG detectable in saliva by ELISA with a similar sensitivity to serum (61% saliva vs. 74% serum).[198]

Management

Optimal patient management begins with achieving an early diagnosis, when lower doses of medication can be used for shorter periods of time to control the disease. Thereafter it is dependent upon several factors including the severity and activity of the disease and patient comorbidities. Clinical and patient reported outcome measures have been devised and validated for use in PV. These clinical tools combined with ELISA results enable clinicians to have a more objective way to assess response to treatment and ultimately determine disease remission. For combined oral and skin disease, the Pemphigus Disease Activity Index (PDAI) [199] and the Autoimmune Bullous Skin Disease Intensity Score (ABSIS)[200] have been validated.[201] In a comparative validation study for oral PV, the most sensitive tool was the Oral Disease Severity Score (ODSS)[202] which has the benefit of being applicable to all oral AIBD and Oral LP. Patient reported outcome measures in use include the Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire and the Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) questionnaire.[203,204]

Following initial assessment, patient management may be divided into two phases as agreed by the international pemphigus committee: induction of remission and remission

maintenance.[205] In remission induction, the initial aim of treatment is to induce disease control, defined as new lesions ceasing to form and established lesions beginning to heal (median 3 weeks). During a consolidation period, which varies in length, the aim is for 80% of mucosal and skin lesions to have healed with no new lesions for at least 2 weeks. Oral lesions are often the most resistant and careful oral disease severity assessment is paramount.The mainstay of treatment for this phase is high doses of systemic corticosteroids, usually given in dosages of 1 to 2 mg/kg/d in severe disease and 0.5–1 mg/kg/d in milder cases. The second phase of management is remission maintenance. During this phase, the ultimate goal of treatment should be to maintain remission on prednisolone 10 mg daily or less, with 10 mg being the dose designated arbitrarily as "minimal therapy" by international consensus with adjuvant drugs facilitating remission. The UK consensus guidelines group recommend the daily dose be reduced by 5–10 mg every 2 weeks down to 20 mg daily, then by 2–5 mg every 2–4 weeks down to 10 mg daily, and thereafter reduce slowly in increments of 1 mg.[206]

When substantial doses of steroids are required for weeks or months, adjuvant therapy is usually recommended, to maintain remission and to reduce the total steroid dose as well as the associated serious complications. The most commonly used adjuvants are the immunosuppressive drugs mycophenolate mofetil and azathioprine. Other agents used include cyclophosphamide, IVIG and methotrexate and alternative interventions include immunoadsorption, plasmapheresis, or plasma exchange. There is weak evidence only to support the use of dapsone and more studies are required. Overall, the evidence for benefit of adjuvants in PV has been variable. A systematic review and meta-analysis, which included 10 trials and pooled adjuncts together, concluded that they were not beneficial for achieving remission but collectively decreased risk of relapse by 29%.[207]

In 2017, the first RCT to conclusively demonstrate the benefit of an adjuvant drug was published, showing that rituximab (a monoclonal antibody against the CD20 molecule of B lymphocytes) combined with short-term prednisolone had superior efficacy to prednisolone alone, with rates of complete remission of PV, off all treatment, of 89% compared with 34% at 2 years.[208] Prednisolone could be stopped in around 70% patients initially treated with rituximab leading to a two-fold decrease in the number of severe treatment side effects. The FDA have since approved rituximab as a first line agent in moderate and severe PV. This approach is revolutionizing the management of PV and the long-term complications of treatment will become much less significant.

As many patients with oral PV will fit the category of moderate PV, the above systemic options including rituximab will be necessary. However, for those with mild oral disease, a combination of topical corticosteroids and low dose oral prednisone may suffice alongside optimal oral hygiene.

Paraneoplastic Pemphigus (PNP)

PNP is a rare, severe blistering disease first reported in five patients in 1990.[209] It is a multiorgan disease associated with an underlying neoplasm, which may precede the onset, co-present, or follow on. The underlying tumor is most frequently a non-Hodgkin lymphoma followed by chronic lymphocytic leukemia, thymoma or Castleman disease. PNP is also referred to as paraneoplastic autoimmune multiorgan syndrome (PAMS) because of the involvement of other systems, such as the lungs in particular, and the variable skin findings namely pemphigus, pemphigoid, EM-like, graft-vs.-host disease-like and lichen planus-like lesions.

Etiology and Pathogenesis

Patients with PNP develop IgG autoantibodies against multiple antigens, including desmoglein 3, desmoglein 1, and various proteins of the plakin family. Antidesmoglein antibodies, -desmocollin, and -A2ML1, may all contribute to the induction of acantholysis, whereas the relevance of the anti-plakin autoantibodies is not yet understood. T cell-mediated cytotoxicity is involved in the pathogenesis and induces more severe and refractory oral lichenoid stomatitis or mucositis, as well as polymorphic lichenoid skin eruptions.

Epidemiology

Paraneoplastic pemphigus mostly occurs in patients 45–70 years of age, with equal prevalence in both sexes.

Clinical Findings

General

Patients with PNP develop severe blistering and erosions of the mucous membranes and skin. The onset of the disease is often rapid, and oral and conjunctival lesions are both common and often severe. Skin lesions may resemble the inflammatory lesions of a drug reaction, lichen planus, or EM, as well as the blisters seen in pemphigus (Figure 3-34). Lesions of the palms and soles are suggestive of PNP. The scalp is usually spared.[210] In severe cases, the lesions may mimic TEN and often also involve the respiratory epithelium. Unlike EM or TEN, the lesions of PNP continue to progress over weeks to months. Death usually results from severe infection due to the immunosuppressive therapy, associated malignancy, and progressive pulmonary involvement (bronchiolitis obliterans).[211]

Oral Findings

Oral ulcers and erythema are the most common manifestation of PNP, and the oral disease is frequently extensive (a panstomatitis) and painful. The lesions are frequently

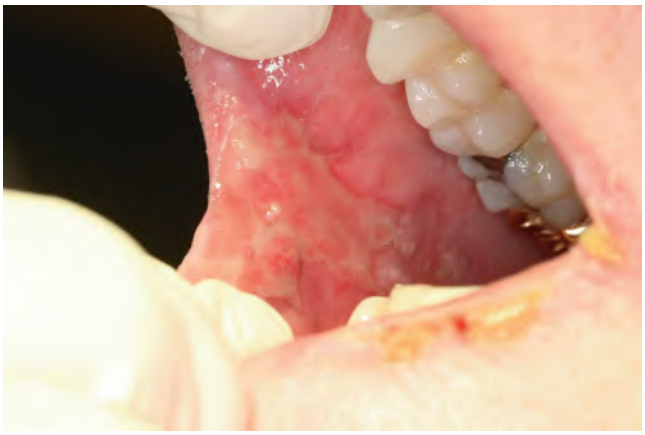

Figure 3-34 Extensive lesions of the tongue in a patient with paraneoplastic pemphigus.

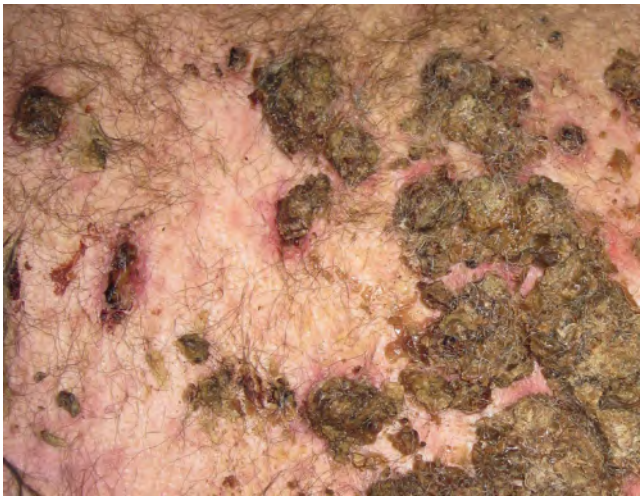

Figure 3-35 Pemphigus vegetans with vegetative lesions of the skin. Courtesy of Dr. Adam Lipworth, Boston, MA.

inflamed and necrotic, with large erosions covering the lips, tongue, and soft palate (Figure 3-35). Hemorrhagic crusts on the lips are characteristic.

Differential Diagnosis

The differential diagnosis is usually pemphigus vulgaris but includes other dermatological disorders including severe mucocutaneous LP or the subepidermal blistering diseases.

Laboratory Findings

Histopathology of lesions of PNP includes changes suggestive of EM, lichen planus, pemphigoid, and pemphigus. There is inflammation at the dermal–epidermal junction and keratinocyte necrosis in addition to the characteristic acantholysis seen in PV. DIF studies show deposition of IgG along the basement membrane similar to pemphigoid, as well as on the keratinocyte surface, forming a lattice pattern similar to PV. IIF demonstrates antibodies that not only bind to epithelium but to liver, heart, and bladder tissue as well.[212] Rat bladder is considered a useful substrate for differentiating PNP from PV as it does not contain desmogleins and therefore in the right clinical setting is specific for desmoplakin antibodies detected in PNP. Negative rat bladder IIF, however, does not preclude the diagnosis of PNP. Immunoblotting with epidermal extract is considered the gold standard for diagnosis; the 210 kDa envoplakin and 190 kDa periplakin being highly sensitive and specific for PNP.[213] ELISAs have also now been developed for these antigens.

Management

Patients with PNP secondary to localized tumors such as Castleman disease improve with the surgical removal of the tumor. Patients with PNP resulting from lymphoma, however, have a poor prognosis and usually die within 2 years from a combination of the underlying disease, respiratory failure, and extensive mucocutaneous involvement.

Use of a combination of prednisone and immunosuppressive drug therapy may help to control the severity of the skin lesions, but the oral, conjunctival, and pulmonary disease is frequently resistant to treatment. Rituximab and intravenous immunoglobulins can be helpful in these cases. High potency topical steroid therapy, topical tacrolimus, and intralesional steroid injection can be helpful in reducing the severity of oral mucosal lesions.

Subepithelial Bullous Disorders

The subepithelial bullous dermatoses are a group of mucocutaneous blistering diseases characterized by the development of autoantibodies to autoantigens in the basement membrane zone. This is a complex zone containing several interlinking macromolecules that connect the basal keratinocyte of the epithelium to the underlying corium or in the skin the epidermis to the dermis.

The diseases in this group include bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease, and epidermolysis bullosa aquisita. There is significant overlap among these diseases, and the diagnosis is based upon clinical manifestations combined with routine histopathology and immunopathological tests identifying autoantibody reactivity with specific target antigens. When one of these diseases is included in the differential diagnosis, a biopsy for DIF should be obtained.

Bullous Pemphigoid (BP)

BP is the most common autoimmune subepidermal blistering skin disease. It occurs mainly in adults over the age of 60 years and may last from a few months to several years

with a variable course. There are several subtypes but the most frequent is the classical BP presentation with intact blisters on an erythematous base. Oral lesions are infrequent but where encountered are usually in this variant. They are typically transient, often mild, and are seen in those with more severe skin disease. It is important to remember that the majority of patients seen in oral medicine departments with a history of skin lesions and a presumptive diagnosis of BP will in fact have mucous membrane pemphigoid.

Etiology and Pathogenesis

BP has both genetic and environmental associations. It is associated with the class II allele DQB1*03:01 and has been reported in conjunction with other diseases as would be expected in an elderly population. However, the association is significantly higher than might be expected in neurological disorders such as Parkinson's disease, dementia, and multiple sclerosis; thromboembolic disorders, such as strokes, or certain drug therapies, such as antibiotics, antihypertensive, loop diuretics and dipeptidyl peptidase-IV inhibitors, and checkpoint inhibitors.

BP is an autoimmune disease caused by the binding of autoantibodies to specific antigens found in the lamina lucida region of the basement membrane on the hemidesmosomes of epithelial basal cells. These antigens are glycoproteins referred to as bullous pemphigoid antigens, BP 180 and BP 230.[214] Binding of antibody to antigen activates both leukocytes and complement, causing localized damage to the basement membrane, resulting in vesicle formation in the subepithelial region. Studies have shown a correlation between disease activity and serum titers of IgG antibodies against the immunodominant domain of BP180, the NC16a domain, and other epitopes on BP180. Once anti-NC16A autoantibodies bind to BP180, several pathways are activated, including complement activation and deposition, neutrophilic chemotaxis with release of proteases, and elastases that promote the disruption of the BMZ leading to blister formation. [215]

Epidemiology

Bullous pemphigoid (BP) is the most frequent AIBD in Central Europe. Its incidence reaches around 20/million/year but is much higher in the very elderly.

Clinical Manifestations

General

The characteristic skin lesion of BP is a tense blister on an inflamed base accompanied by urticarial plaques that chiefly involve the scalp, abdomen, extremities, axilla, and groin (Figure 3-36). Pruritis is a common feature of the skin lesions. Patients with BP may experience one episode or recurrent bouts of lesions with a wide spectrum of disease severity. A recent systematic review and meta-analysis included 25 studies and demonstrated a 1-year combined mortality rate of 23.5%. Higher mortality rates were obtained in Europe (26.7%) followed by Asia (20.5%) and the US (15.1%), possibly related to an increased number of comorbidities and older age in European patients in comparison to Americans and Asians, respectively.[216]

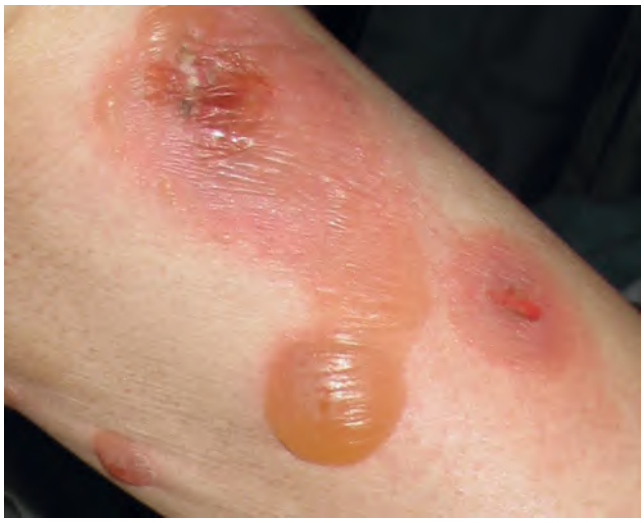

Figure 3-36 Bullous pemphigoid resulting in tense skin blisters. *Source:* Courtesy of Dr. Adam Lipworth, Boston, MA.

Oral Findings

Oral involvement occurs in 10% to 20% of BP patients.[217] The oral lesions of BP are smaller, form more slowly, and are less painful than those seen in PV. The oral lesions are clinically and histologically indistinguishable from oral lesions of mucous membrane pemphigoid, but early remission of oral lesions in BP is typical. Desquamative gingivitis if present is more suggestive that the patient has MMP. It is recognized that a small subgroup of MMP patients do present with a BP-like cutaneous eruption, but the skin resolves with treatment while the oral mucosal lesions persist.

Differential Diagnosis

Oral diseases that appear clinically similar to BP include mucous membrane pemphigoid (MMP), ulcerative LP, PV, and the other subepithelial bullous dermatoses. The ulcerative form of LP frequently has the characteristic white lacy lesions or Wickham striae and may have a violaceous hue if the lips are affected (see Chapter 4). PV usually has more extensive ragged erosions involving several oral mucosal surfaces. The other subepithelial bullous dermatoses (described below) appear clinically similar to MMP and can only be distinguished by immunofluorescent, ELISA, or molecular techniques.

Laboratory Findings

Routine histology of a biopsy specimen demonstrates separation of the epithelium from the connective tissue at the

basement membrane zone and an inflammatory infiltrate that is usually rich in eosinophils, particularly in skin biopsies.

DIF study of a biopsy specimen taken from perilesional-inflamed tissue demonstrates deposition of IgG and C3 bound in a linear band to the basement membrane. IIF study of serum obtained from patients with BP demonstrates IgG antibodies bound to the epidermal aspect using the salt-split skin technique (see below). The salt-split skin test is particularly useful in distinguishing BP from EBA, the latter producing IgG antibodies localized to the dermal side of the salt-split skin (floor of the blister). It has been shown that epidermal binding sera, if examined carefully at high magnification, shows an n-serrated fluorescent pattern to distinguish it from dermal binding sera, which give a u-serrated pattern.[218] Circulating autoantibodies against pemphigoid antigens BP 180, specifically the NC16A domain which is the main target antigen, and BP 230, can be detected in serum samples using ELISA and are useful in both diagnosis and monitoring of disease activity.[219]

Management

Patients with localized oral lesions of BP may be treated with high-potency topical steroids, such as clobetasol or betamethasone, whereas patients with more extensive disease require use of systemic corticosteroids alone or combined with immunosuppressive drugs such as azathioprine, cyclophosphamide, mycophenolate, or rituximab.[220] Patients with moderate levels of disease may minimize use of systemic steroids by use of dapsone, or tetracycline, doxycycline, or minocycline, which may be combined with niacinamide.[221]

Mucous Membrane Pemphigoid [MMP]

MMP is a rare chronic autoimmune subepithelial blistering disease that primarily affects the squamous epithelia; that is, the mouth, conjunctivae, upper airways, anogenital sites, and skin. It results in mucosal blistering, ulceration, and subsequent scarring in sites of predilection. Historically it has sometimes been referred to as cicatricial pemphigoid, but this term has now been superseded by MMP as it does not always scar. A multidisciplinary approach including dermatologists, ENT surgeons, ophthalmologists, and others as indicated is paramount in these patients.

Etiology and Pathogenesis

The primary lesion of MMP occurs when IgG and/or IgA autoantibodies directed against basement membrane zone (BMZ) antigens, lead to an inflammatory response with subepithelial separation and vesicle formation. The main antigens involved in disease pathogensis include epitopes on BP180 (the membrane proximal NC16a domain as in BP), as well as epitopes on the C-terminal domain) and laminin 332. Other proposed autoantigens include BP230, a6b4 integrin, and type 7 collagen. Subsets of MMP have been identified by the technique of immunofluorescent staining of skin that has been split at the basement membrane zone with the use of 1M sodium chloride prior to DIF (the "salt-split skin" technique).[222] The majority of cases of MMP demonstrate IgG directed against antigens on the epidermal side of the salt-split skin, which have been identified as BP Ag2 (BP180) or BP230. However, cases of MMP have also been identified where the antigen is present on the dermal side of the split. This latter antigen has been identified as laminin-332 (previously referred to as epiligrin or laminin 5, an adhesion molecule that is a component of the anchoring filaments of the basement membrane.[222–224] MMP associated with laminin-332 has been reported to carry a higher risk of association with an underlying malignancy, but the evidence for this is not yet conclusive.[225] Further research is required regarding the possible association with malignancy, and clinicians should consider a possible underlying malignancy in newly diagnosed dermal binding MMP patients.[226] HLA DQB*0301 is significantly associated with MMP[227] and is associated with T cell recognition of BMZ antigens. Drugs have rarely been associated also with the onset of MMP; for example, the gliptin antidiabetic agents.

Epidemiology

Mucous membrane pemphigoid has an annual incidence of 1.3–2.0 per million inhabitants in France and Germany. The mean age at onset varies in studies between 55–65 years and it is approximately twice as common in females. It is seen predominantly in Caucasian patients, though it is universal.

Clinical Manifestations

General

Lesions of MMP may involve any mucosal surface, but the oral mucosa is the most frequently reported site. Ahmed and Hombal amalgamated 16 case series of 457 cases and Setterfield studied 140 cases of patients drawn from a full range of clinics.[228,229] Their data has shown that the oral mucosa was affected in 85–87% patients and the conjunctiva in 64–5%. While the oral mucosa is relatively protected from scarring in the eye, MMP can lead to scarring and adhesions developing between the bulbar and palpebral conjunctiva called symblepharon (Figure 3-37). Subsequent corneal damage is common, and progressive scarring may lead to blindness in some patients. Ulceration and scarring may also affect the nasopaharynx (15–28%), genital mucosa (17–26%), esophagus (4–10%), and larynx (4–8%). In all sites, it causes pain and stricture formation and in the larynx may be life threatening leading to hoarseness, difficulty in breathing, and asphyxiation. Esophageal involvement may cause

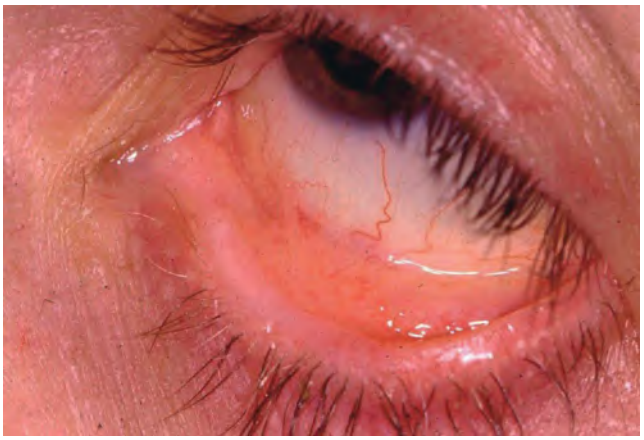

Figure 3-37 Mucous membrane pemphigoid of the conjunctiva with symblepharon formation.

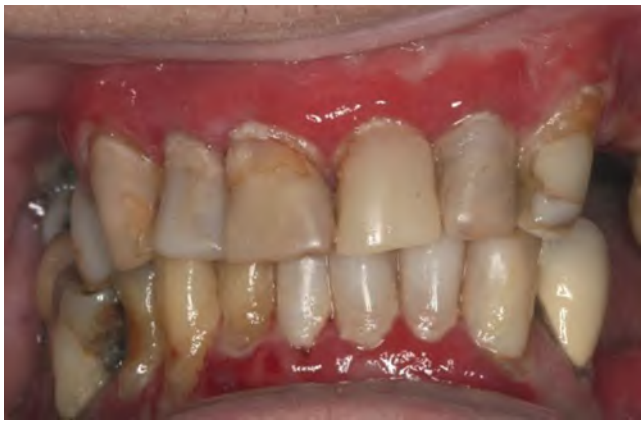

Figure 3-38 Moderately severe desquamative gingivitis of mucous membrane pemphigoid.

dysphagia, leading to debilitation and frequent dilatations. Skin lesions, present in 24–39%, often affect the head and neck but may be generalized and often scar.[228,229]

Oral Findings

Oral lesions occur in 85% of patients with MMP. Intraoral sites include the gingiva

(80%), buccal mucosa (58%), palate (26%), alveolar ridge (16%), tongue (15%), and lower lip (7%).[230,229] Desquamative gingivitis may occur alone or in addition to other intraoral sites. It typically manifests as erythema of the attached gingiva with or without blistering and ulceration. It may be localized or generalized (Figures 3-38 and 3-39). Lesions elsewhere may present as patches of erythema, intact blisters, or ulcers with a yellow base and well-defined margin (Figure 3-40). Scarring, while unusual in the oral mucosa, may be seen as a loss of sulcal depth, scarring of the buccal mucosa or soft palate. Broadly, three oral phenotypes are recognized: pure gingival lesions, extragingival lesions, or both.

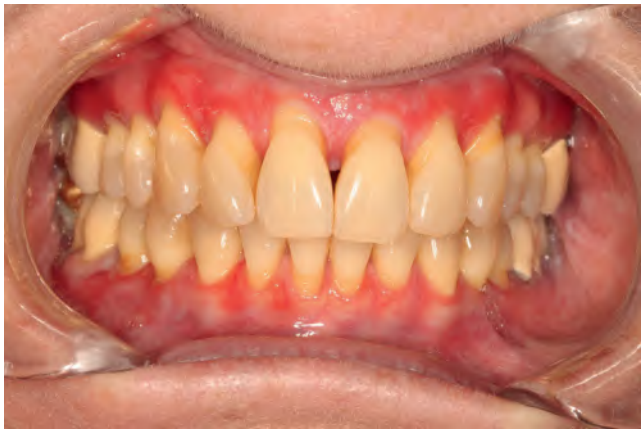

Figure 3-39 Moderate desquamative gingivitis of mucous membrane pemphigoid.

Differential Diagnosis

In the oral mucosa the differential diagnosis includes the autoimmune blistering diseases and lichen planus. Desquamative lesions resemble the lesions of erosive lichen planus and PV and in all cases of desquamative gingivitis, biopsy should include both routine histology and DIF for definitive diagnosis.

Laboratory Findings

Patients with suspected MMP should have biopsy specimens taken from a perilesional site for routine histology and from an adjacent normal site for DIF studies.[231] A large retrospective study has shown a 94% positivity for linear IgG, IgA, and/or C3 at the BMZ from perilesional biopsies and 90% positivity from a separate normal buccal punch.

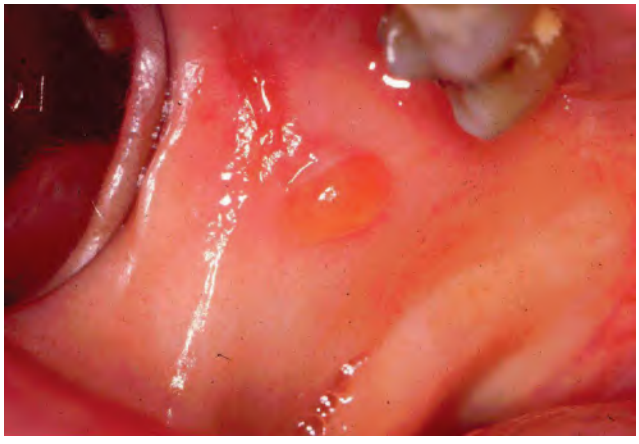

Figure 3-40 Intact vesicle of buccal mucosa in a patient with mucous membrane pemphigoid.

Where patients had pure desquamative gingivitis, a sample taken from the adjacent reflected alveolar mucosa was positive in 100% patients. The failure rate for DIF is usually due to mechanical problems largely due to loss of epithelium. Histopathology reveals subepithelial clefting with preservation of basal cells and a mixed inflammatory cell infiltrate (Figure 3-41 and Figure 3-42). IIF using salt-split skin detects the presence and titer of anti-BMZ IgG and IgA antibodies and localizes the binding to the roof or base. The presence of both IgG and IgA is associated with a more severe disease and the IgG antibody titer is related to disease severity.[232,233] ELISA tests commercially available can identify BP180 NC16a antibodies (in both serum and saliva),[234] BP230, and collagen type 7 (see section Epidermolysis bullosa acquisita below). An important aspect of diagnosis is the detection of laminin 332 antibodies.[235] At present there is no commercially available ELISA and sera need to be sent to national referral centers for molecular testing if dermal binding.

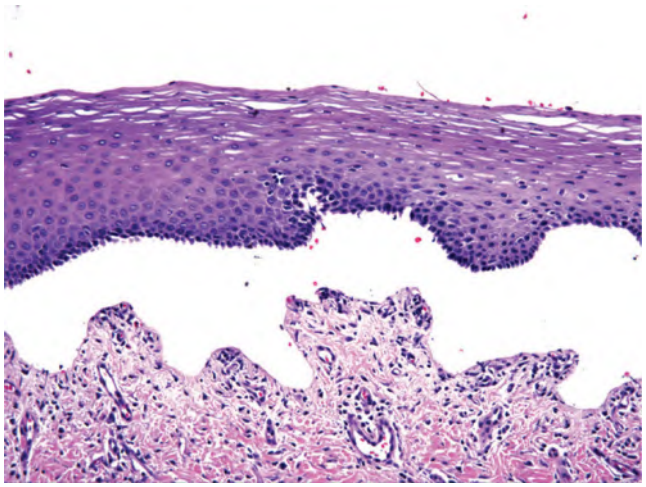

Figure 3-41 Photomicrograph of mucous membrane pemphigoid showing intact basal cells and subepithelial bulla.

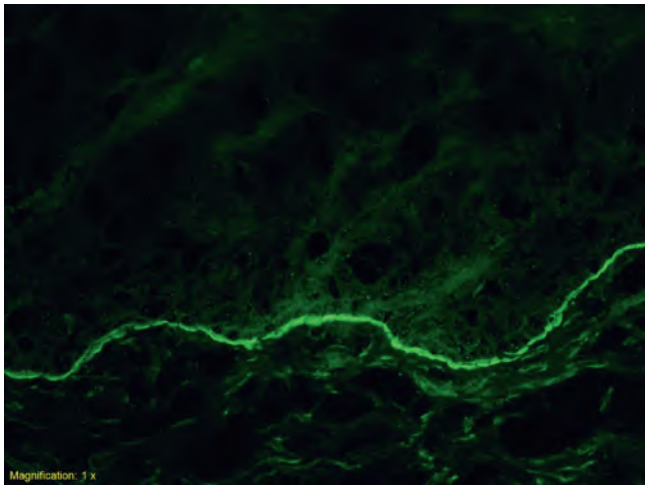

Figure 3-42 Direct immunofluorescence study of mucous membrane pemphigoid showing linear IgG deposition in the basement membrane zone.

Management

Management of MMP depends on the severity of symptoms and sites of involvement. A multidisciplinary approach is necessary for optimal patient care. The degree of morbidity varies but for the majority of patients presenting to oral medicine, it is a mild to moderately severe condition that may last for many years necessitating long-term treatment. To date there is limited good evidence upon which to base treatment. Studies are largely limited to retrospective case series. However, there are recommended approaches based upon the evidence available.[226,236] Fundamental to assessing disease severity and response to treatment is the use of a clinical outcome score. The ODSS has now been validated for use in MMP and has been shown to have the optimal sensitivity when compared to other methods proposed at present.[237]

For mild oral disease, optimizing oral hygiene and use of topical corticosteroids either directly in a paste, such as clobetasol and Orabase (a custom made tray can be used) or as a mouthwash, such as betamethasone sodium phosphate 0.5 mg or fluticasone propionate 400 lg in10 mL of water as a 3-min rinse can be helpful. (Figure 3-43). Intralesional triacinolone to localized ulcers may be effective. For mild to moderate disease, doxycycline can be tried or if ineffective dapsone (always check for glucose-6-phosphate deficiency) or sulfapyridine.[238,239] Dapsone always causes a degree of hemolysis and occasionally methemoglobinemia, and thus careful monitoring is necessary. Another rare side effect of dapsone is hypersensitivity syndrome, characterized by fever, lymphadenopathy, skin eruptions, and occasional liver involvement. For more severe oral lesions or where there is multisite involvement, often immunosuppressive treatment is needed, including low dose systemic steroids,

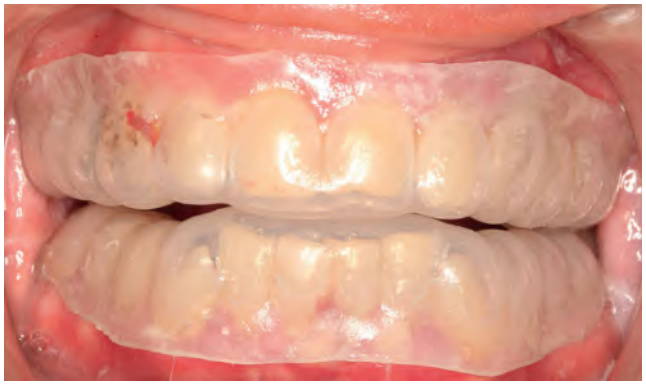

Figure 3-43 Soft custom-made trays may be used to hold topical steroids to treat desquamative gingivitis.

immunosuppressive drug therapy such as azathioprine, mycopheolate mofetil or methotrexate, or rituxumab. Pulsed intravenous (IV) cyclophosphamide, IV immunoglobulin, and rituximab are reserved for recalcitrant disease.[240,241]

An important aspect of management at present is how to investigate patients with confirmed laminin 332 autoantibodies. There is a body of evidence to suggest that this subgroup of patients may have an increased risk of developing an underlying malignancy. However, this remains an area for ongoing work. A thorough history and examination must be undertaken in patients with MMP and dermal binding sera and all routine age appropriate routine cancer screening undertaken. The neoplasms reported are usually adenocarcinomas though hematological malignancies have rarely been described. At present the extent of investigation to be recommended is unclear.

Linear IgA Disease (LAD)

LAD is a rare acquired subepithelial autoimmune blistering disease characterized by the deposition of predominantly IgA rather than IgG in the basement membrane. LAD occurs in children below the age of 10 (historically referred to as chronic bullous disease of childhood) and adults older than 60. While rare, it is the most common cause of autoimmune blistering in childhood. The clinical manifestations may resemble MMP, BP, and EBA. It is important to note that the majority of adults with linear IgA and a predominantly mucosal disease must be considered to have MMP.[226]

Etiology and Pathogenesis

The cause of the majority of cases is unknown, but some reported cases have been drug-induced (e.g., vancomycin, amiodarone and nonsteroidal anti-inflammatory agents) or are associated with systemic diseases, including hematologic malignancies, ulcerative colitis, or connective tissue diseases, such as dermatomyositis.[242,243] The target antigens associated with a majority of cases of LAD are the shed ectodomain of BP180, a 120, or 97kDa antigen detected on immunoblotting. It is associated with HLA-B8, HLA-CW7, and HLA DR3. In the older group, the disease has a more benign course and where associated, withdrawal of the offending drug results in remission

Epidemiology

It has an incidence of 25–1.0/million population in Europe.

Clinical Manifestations

General

The skin lesions of LAD are characterized by annular pruritic papules and blisters, giving a "cluster of jewels" appearance. In children, the skin of the lower abdomen, genitalia, and perineum are involved while in adults, the disease affects the face, extensor surfaces, hands, and feet. Ocular involvement may be seen in adults and children.

Oral Findings

Oral lesions are common in LAD and may be seen in up to 70% of patients. These lesions are clinically indistinguishable from the oral lesions of MMP, with blisters and erosions of the mucosa frequently accompanied by desquamative gingivitis.[244–246]

Laboratory Findings

Routine histology demonstrates subepithelial separation similar to MMP, but DIF study will show deposition of IgA and, occasionally, IgG and C3. Neutrophils are a prominent feature within the blister. IIF is usually negative, but when positive, will demonstrate circulating IgA antibodies against a basement membrane antigen.[247]

Management

The majority of patients will have a disease triggered by a drug and therefore identification is key. As in MMP, topical corticosteroids may be helpful. Dapsone and sulfapyridine are often effective when topical steroids alone are insufficient. More severe cases may require a combination of systemic corticosteroids and immunosuppressive drug therapy such as mycophenolate mofetil

Epidermolysis Bullosa Acquisita (EBA)

EBA is a very rare chronic mucocutaneous immunobullous disease with two predominant subtypes: the classic form, which is characteristically associated with prominent scarring, and the inflammatory form that resembles BP.

Etiology and Pathogenesis

IgG and occasionally IgA antibodies target the NC1 or occasionally the NC2 domain of type VII collagen, which forms the anchoring fibrils in the lower basement membrane. Damage and loss results in sub-basilar bullae.[248]

Epidemiology

EBA is a rare autoimmune blistering disease with an annual incidence of less than 0.5/million. It may occur at any age in adulthood and is associated with HLA-DR2 in African-Americans and HLA-DRB1*15:03 in African descent patients in France. It may be associated with Crohn's disease and systemic lupus erythematosus

Clinical Manifestations

Both subtypes of EBA may present with oral mucosal lesions. The classic type associated with mechanobullous lesions on

trauma prone sites such as the elbows and knees is typically more severe in the mucous membranes and scarring is prominent. Extensive oral ulceration may affect any site in the mouth but typically involves the tongue and may lead to ankyloglossia and microstomia. Other mucosal sites such as the esophagus, conjunctivae, and larynx may be involved. In the inflammatory type with more widespread skin lesions, the oral mucosa may also be affected with ulceration and mild gingival inflammation.

Differential Diagnosis

MMP but tongue and lip involvement is more typical in EBA and much less frequent in typical MMP.

Laboratory Findings

An oral biopsy typically shows a subepithelial split often with minimal inflammation. DIF typically shows linear BMZ IgG and C3 which in an area of blistering is localized to the base of the split. The pattern is u-serrated in contrast to MMP and BP which is n-serrated.[218] IIF is positive in approximately 50% sera; IgG specificity can be confirmed with an ELISA.

Management

The treatment is as described for MMP and LAD, with therapy depending upon the extent and severity of the clinical lesions. EBA can be very recalcitrant to treatment; however, dapsone is often a useful drug and may be combined with colchicine. Systemic corticosteroids, immunosuppressive drugs, rituximab, or intravenous immunoglobulin may be required to control the lesions in severe widespread EBA.

THE PATIENT WITH SINGLE ULCERS

The most common cause of single ulcers on the oral mucosa is trauma. The diagnosis is usually based on the history and physical findings. However, squamous cell carcinoma is always in the differential diagnosis for a nonhealing ulcer. As such, all ulcers present for 2 to 4 weeks without evidence of healing should be biopsied to rule out squamous cell carcinoma or other pathology, and in the immunocompromised patients, deep fungal or viral infection. Oral cancer is discussed in detail in Chapter 7.

Infections that may cause a chronic oral ulcer include CMV ulcers (see above); mycobacterial infections (including atypical mycobacterial infections); the endemic mycoses such as histoplasmosis, blastomycosis, and coccidioidomycosis; nonendemic invasive fungal infections such as mucormycosis, aspergillosis, and cryptococcosis; syphilis; and parasitic infections such as leishmaniasis. These infectious oral ulcers are described detail in Chapter 21, "Infectious Diseases."

Traumatic Injuries Causing Solitary Ulcerations

Etiology and Pathogenesis

Single mucosal ulcers may be caused by direct physical mechanical, thermal, or chemical trauma to the mucosa or even vascular compromise, causing tissue damage and ulceration. Acute bite injuries, an example of direct physical/mechanical trauma, occur often on the oral mucosa and may be particularly severe if this occurs when the mucosa is numb after local anesthesia has been given for dental procedures. Traumatic injuries may also result from malocclusion, ill-fitting dental prostheses, overzealous toothbrushing and flossing, self-injurious habits, and oral piercings.[249,250]

Thermal injuries including electrical burns are sometimes seen in children who inadvertently chew on electrical wiring. More commonly, thermal burns occur on the palatal mucosa from ingesting hot foods and beverages (such as hot pizza or coffee). The use of a microwave oven to reheat foods often results in differential heating so that cheese and pastry fillings may be overheated compared with other parts of the food, leading to burns.[251] An iatrogenic cause of thermal injury is from a heated dental instrument inadvertently contacting the mucosa. The burn is usually more serious if the mucosa has been anesthetized and there is prolonged contact.[252]

Chemical trauma is caused by patients or dentists placing noxious and caustic substances directly on the mucosa either as a therapeutic measure or unintentionally. Sucking on, chewing, or hours-long contact of medications formulated to be swallowed (such aspirin or oral bisphosphonates) may also lead to severe oral ulcers.[253] Mouthwashes or other over-the-counter oral care products with high alcoholic content, hydrogen peroxide, or phenols used too frequently or undiluted can cause mucosal ulcerations.[254]

Some over-the-counter medications for treating aphthous ulcers contain high concentrations of silver nitrate, phenols, or sulfuric acid and should be used with caution. Ulcers have also resulted in the use of denture cleansers as an oral rinse.[255] Prolonged contact of methacrylate monomer on the mucosa may also lead to necrosis of the mucosa. Necrosis of the bone and mucosa has been reported from chemicals used in endodontics if these are pushed past the apices of teeth.[256]

Vascular compromise leads to oral ulcers and two main patterns are identified. One is a condition known as necrotizing sialometaplasia where there is local infarction of the salivary gland tissue leading to overlying ulceration, exfoliation of the necrotic tissue, and healing. Many etiologies have been identified including vasoconstrictors, sustained pressure, and bulimia and the most common location for this condition is the hard palatal mucosa although any location

that contains salivary glands may be affected.[257] Another is systemic vasculitis, where inflammation of vessels leads to thrombosis and infarction. Tongue necrosis is a particularly well documented aspect of giant cell (temporal) arteritis.[258]

Oral Findings

These present as acute ulcerations and necrosis of the mucosa with a clear antecedent history of injury (Figure 3-44). The extent of the ulceration depends on the agent involved and the site depends on the activity involved.

Electrical burns in particular are caused by high heat, are generally fairly extensive, involve the lips, and are generally seen in young children and toddlers. The initial lesions are charred and dry appearing. However, after a few days, this charred crust sloughs, and there may be excessive bleeding when the underlying vital structures are exposed.

Burns from hot foods and beverages are generally small and localized to the hard palatal mucosa or lips and are usually seen in teenagers and adults (Figure 3-45). The area usually presents as an area of tenderness and erythema that develops into ulcers within hours of the injury. It may take several days to heal depending on the extent of the injury.

Ulcers from vascular compromise such as necrotizing sialometaplasia and vasculitic lesions last for weeks and months.

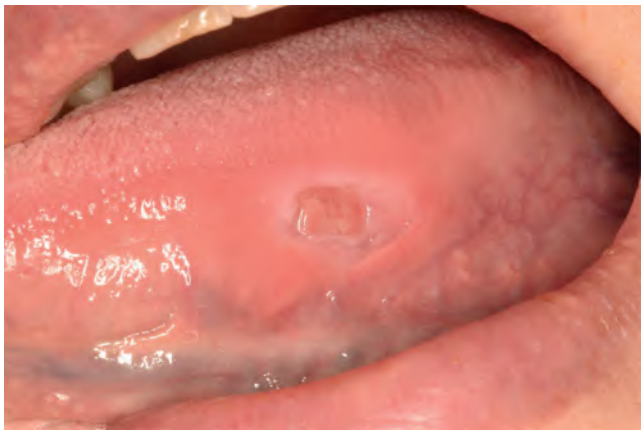

Figure 3-44 Traumatic ulcer of the lateral tongue, healing.

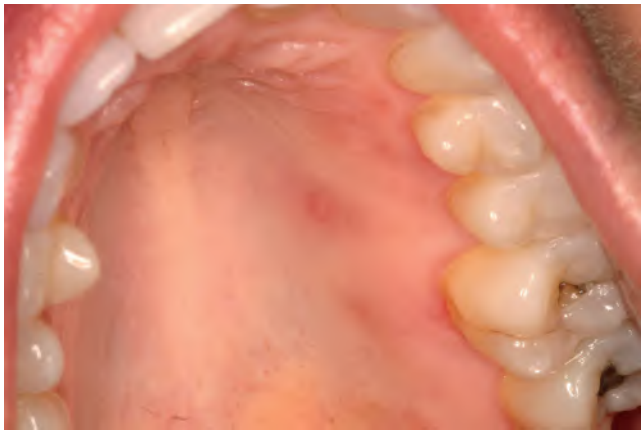

Figure 3-45 Ulcer from hot pizza burn on the palatal mucosa.

Differential Diagnosis

Careful history taking and identification of the causative agent clinch the diagnosis. However, in all cases, patients should be carefully monitored for healing to ensure that a secondary infection does not develop or that another cause of an oral ulcer, such as oral cancer, was mistakenly overlooked.

Laboratory Testing

None is required if there is a clear history of injury to the site. Culture may be needed if the areas do not heal well or if suppuration develops, suggesting a secondary bacterial infection. A biopsy should be performed if the ulcer does not heal within a few weeks. If leakage of an endodontic filler is suspected, periapical films should be taken.

Biopsy is not necessary if the etiology is obvious. However, if a biopsy is done, the mucosa will show ulceration with acute and chronic inflammation. The epithelium adjacent to the ulcer shows varying degrees of coagulation and necrosis. Care must be taken to rule out the presence of infectious agents that may secondarily infect the site (such as HSV on the hard palatal mucosa).

Biopsies of necrotizing sialometaplasia show distinct stages of infarction of mucous glands to metaplasia of ducts to healing. For a diagnosis of giant cell arteritis, patients must fulfill three of the five criteria as set out by the American College of Rheumatology: age over 50, recent onset of localized headache, temporal artery tenderness or decreased temporal artery pulse, raised erythrocyte sedimentation rate greater than or equal to 50 mm/h, and positive temporal artery biopsy.[259]

Management

Smaller lesions caused by less severe thermal or chemical injury heal on their own once the irritant is removed. Pain control can be achieved with topical anesthetics (such as viscous lidocaine). Topical steroids or intralesional steroid injections may be useful. Avoidance of re-injury is also important, and this may be effected by counseling patients regarding the avoidance of use of caustic substances and the correct use of medications. Dentists also should be careful to take protective measures when using caustic substances or heated instruments.

Electrical burns are generally deep and more extensive, and healing often results in scarring and contracture. If the corners of the mouth are involved, microstomia may result. Children benefit from the use of microstomia prevention devices during this healing period, although surgical correction may still be

required to restore function and esthetics. Antibiotics may be necessary to prevent a secondary infection since these burns often take several weeks to heal.[260] Necrotizing sialometaplasia heals on its own while ulcers of vasculitic origin will generally require treatment with systemic corticosteroids.[261]

Traumatic Ulcerative Granuloma (Eosinophilic Ulcer of Tongue)

Etiology and Pathogenesis

This ulcerative condition of the oral cavity is considered traumatic in nature, although less than 50% of patients recall a history of injury. These lesions have been experimentally induced in animals by inflicting crush injury on the tongue, the most common site of these lesions.[262] It is likely that the penetrating nature of the inflammation results in myositis that leads to chronicity. However, other acute or chronic ulcerative conditions left untreated may become deep and penetrating. Similar lesions are seen on the ventral tongue in infants caused by the tongue rasping against newly erupted primary incisors, a condition known as Riga-Fede disease. Patients with familial dysautonomia and other conditions, such as Riley–Day syndrome and Lesch–Nyhan syndrome, who have congenital incapacity to sense pain, often also develop similar ulcerative and necrotic ulcers because they are unaware of the self-inflicted injury.[263]

Clinical Manifestations

There is a bimodal age distribution with one group in the first two years of life, where lesions are associated with erupting primary dentition.[264] The second group is in adults in the fifth and sixth decades.[265]

Oral Findings

In children, the ulcers involve the anterior ventral or dorsal tongue associated with erupting mandibular or maxillary incisors, respectively. The tongue is the site of involvement in approximately 60% of adult cases, usually on the posterior and lateral aspects.[266]

An ulcer develops that may not be painful in two-thirds of cases and may persist for months. A history of trauma is elicited in only 20–50% of cases. The ulcer generally appears cleanly punched out, with surrounding erythema and keratosis if present for weeks or months (Figures 3-46 and 3-47). They range from 0.5 cm to several centimeters in size. The surrounding tissue is usually indurated and long-standing lesions are often depressed. Other sites that may be involved include the buccal mucosa and labial mucosa, floor of the mouth, and vestibule, all sites where there is abundant underlying skeletal muscle. Five percent are multifocal, and recurrences are not uncommon. In some cases, the lesions present as an ulcerated, mushroom-shaped, polypoid mass on the lateral tongue.[267]

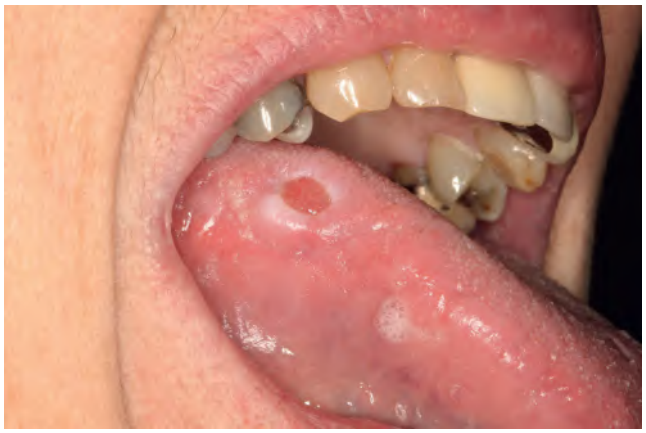

Figure 3-46 Traumatic ulcerative granuloma of the tongue, a typical site; note the surrounding keratosis.

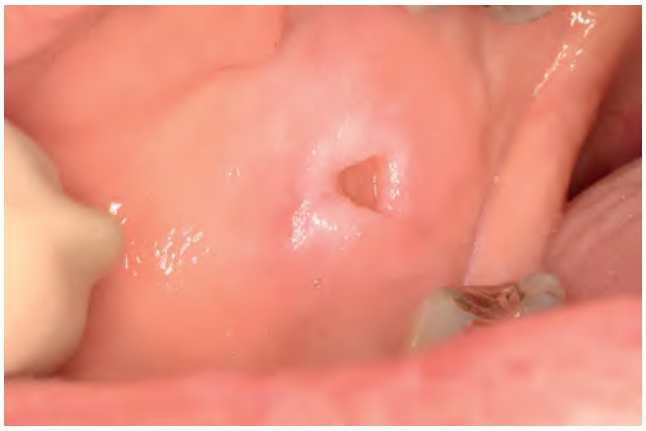

Figure 3-47 Traumatic ulcerative granuloma of the buccal mucosa; note the depressed appearance of the ulcer and surrounding keratosis.

Differential Diagnosis

In children, the diagnosis is usually obvious because of the presence of newly erupted dentition and the location of the ulcers.

The long duration of these lesions, presence of induration, lack of pain, and lack of surrounding erythema readily distinguish them from RAS, although major aphthous ulcers are often associated with scarring and induration and may develop into traumatic ulcerative granuloma. The presence of a single, chronic, painless ulcer with induration raises the suspicion for squamous cell carcinoma (especially if it is on the tongue), salivary gland malignancy, or lymphoma. Rare cases that had been diagnosed as traumatic ulcerative granuloma have subsequently been shown to represent CD30+ T-cell lymphomas.[268] An infectious etiology should also be considered, especially deep fungal or CMV infection, particularly in immunocompromised hosts. Another entity, EBV-associated mucocutaneous ulcers, may

appear similar and also contain CD30+ cells; these have been reported in immunocompromised and immunosenescent (elderly) patients.[269]

Laboratory Findings

A biopsy is almost always required to confirm the clinical diagnosis and to rule out a malignancy or other conditions. Excision of the lesion often results in complete resolution of the ulcer.

The mucosa is ulcerated, but unlike an aphthous ulcer, the inflammation is deeply penetrating, with chronic inflammatory cells infiltrating the underlying skeletal fibers. There is muscle degeneration associated with variable numbers of eosinophils and mononuclear histiocyte-like histiocytes/macrophages. Immunoperoxidase staining is important to rule out a lymphoma, especially the CD30+ type.[270]

Management

A careful history is important to rule out continued trauma to the site, although this is sometimes difficult to elicit and then prevent, especially if trauma occurs during sleep. Intralesional steroid injections performed over a few weeks will often resolve these lesions. Wound debridement also often leads to complete resolution, although up to one-third of cases recur. The use of a nightguard on the lower teeth may help reduce nighttime trauma from parafunctional habits.

SUGGESTED READING

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4

Red and White Lesions of the Oral Mucosa

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RED AND WHITE TISSUE REACTIONS

One challenging aspect of oral medicine is that many lesions of different conditions look alike. The same diagnosis may also manifest in various ways. Thus, in order to become a successful clinician in differential diagnosis, appreciation of the very versatile appearances of the same disease requires considerable clinical acumen and experience. It is also important to appreciate that the oral mucosa in some patients may appear to be different from what we perceive as normal-looking mucosa.

There are different ways of classifying oral mucosal lesions. One is in accordance with the most prominent colors in which they can manifest. The difference that we (or our patient) see often is the change of color. Observing those changes is important as they guide us in establishing the diagnosis.[1] Although many shades of different colors may appear in the mouth indicating pathologic changes, two of the most striking ones are red and white. Following this rather rough and nonspecific truncation, we need to refine the features to obtain the correct diagnosis.

"White lesion" stands for any mucosal area that appears whiter than its adjacent tissue. It does not represent a specific etiologic or microstructural group of mucosal conditions. Its surface is usually also of a different texture, or may be raised from its surroundings. When considering red and white

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

lesions, we are assuming that the epithelial integrity is still preserved, as otherwise we would have ulceration. Indeed, within the time course of a single oral condition, we can see different stages and intensities. Its current red and/or white appearance can progress toward an ulcerative stage (e.g., in lichen planus), which may appear whitish or yellowish due to fibrinous exudate and pseudomembranes. Therefore, there is a temporal component to the clinical appearance of the condition with a tendency to change over time. Thus, classifying those oral conditions exclusively according to their red or white appearance cannot be fully feasible. All red and white lesions may present in combinations of all of the above.

White lesions of oral mucosa are white as a consequence of several possible structural occurrences:[2]

1) Increased thickness of the corneal layer (in keratinized epithelium).
2) Keratinization of epithelium that does not normally contain a corneal layer (nonkeratinized epithelium). Both (1) and (2) manifest as hyperkeratosis (Figures 4-1 and 4-2).
3) Formation of abnormal keratin.
4) Epithelial edema: intra- and extracellular accumulation of fluid in the epithelium may also result in clinical whitening (Figure 4-3).
5) Abnormal keratinization occurring prematurely within individual cells or groups below the stratum granulosum (dyskeratosis often also contains hyperkeratosis).

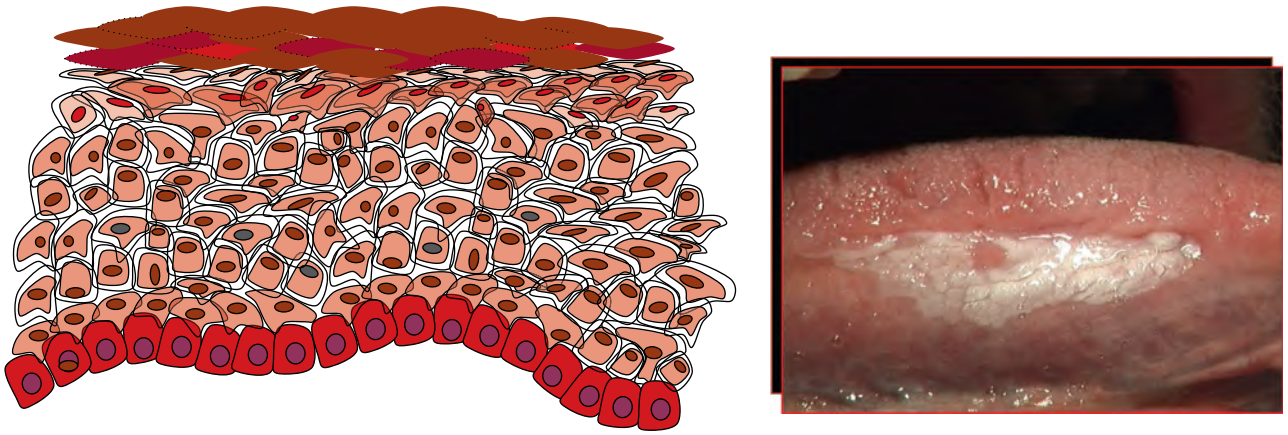

Figure 4-1 Mechanisms leading to a white appearance of the oral mucosa due to an increased production of keratin (hyperkeratosis).

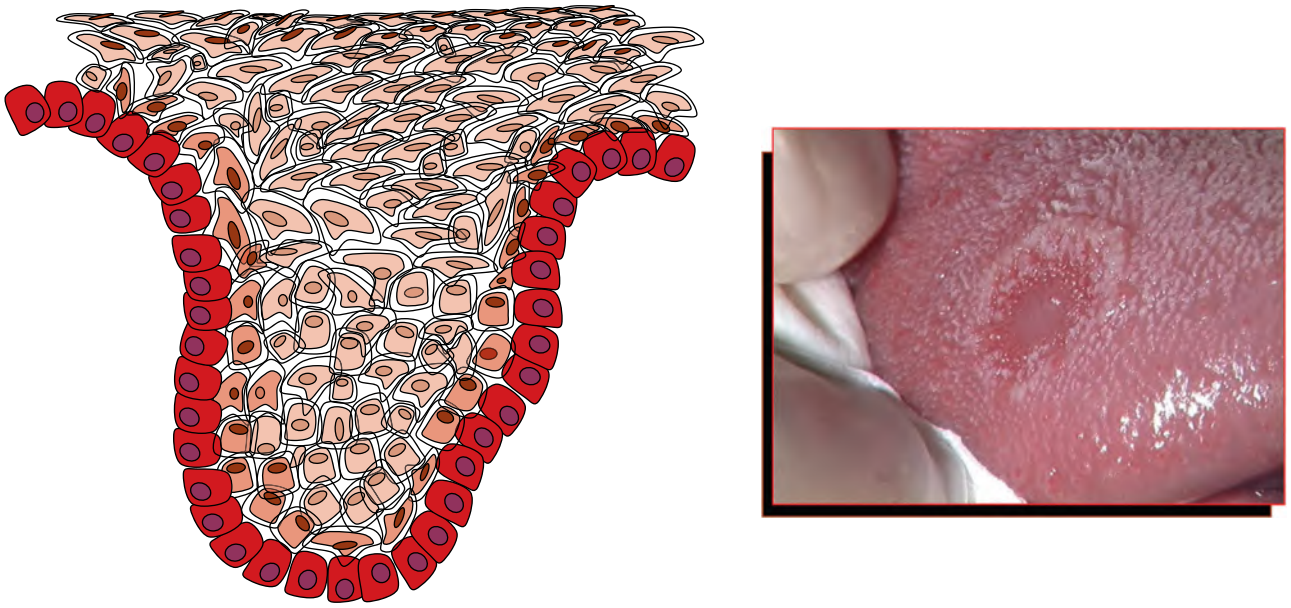

Figure 4-2 Mechanisms leading to a white appearance of the oral mucosa due to an abnormal but benign thickening of stratum spinosum (acanthosis).

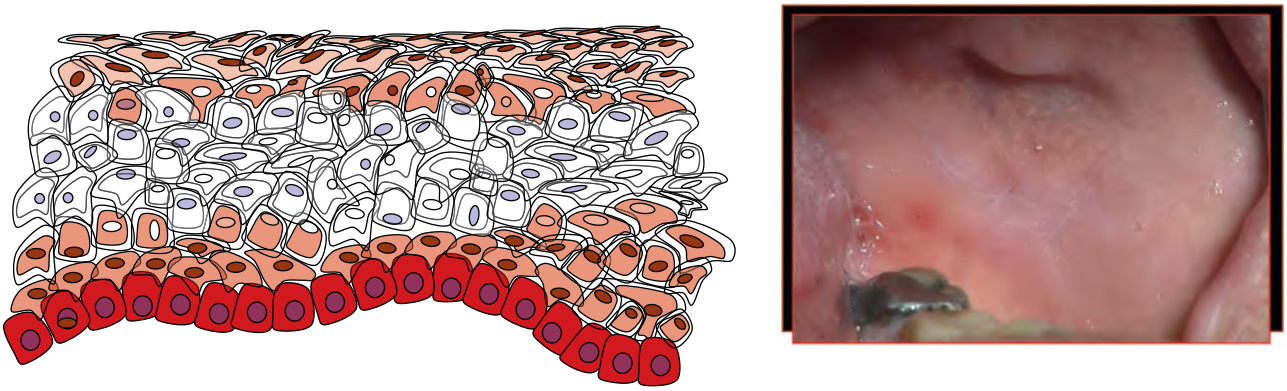

Figure 4-3 Mechanisms leading to a transparent white appearance of the oral mucosa due to intra- and extracellular accumulation of fluid in the epithelium (leukodema).

6) Subepithelial superficial fibrosis, which with its decreased vascularity network causes a diffuse whitish appearance; Any overall epithelial thickening (acanthosis) itself does not seem to cause whiteness.

Keratins are a family of fibrous scleroproteins, which form intermediate filaments necessary for maintaining the structural integrity of keratinocytes and thus for epithelial protection and support. Keratin present in the white oral lesion is likely to be different from keratin normally occurring in oral mucosa (e.g., that produced on the hard palate or attached gingiva). This type of keratin resembles the keratin on the skin, and absorbs water when overly hydrated by oral fluids, resulting in swelling and a white appearance similar to that of skin immersed in water for a prolonged time. Any of those also changes the refractive index as well as causes different reflection and dispersion of light waves, which we see as white.

Apart from structural epithelial changes, a white or "whitish" appearance may result from exogenous deposits, such as microbial colonies (e.g., candidal mycelium) and their effects on the host surface (exudate, necrotic cellular debris, and metabolic products). Fungi can, thus, produce whitish pseudomembranes consisting of sloughed epithelial cells, fungal mycelium, and neutrophils, which are loosely attached to the oral mucosa (Figure 4-4).

Clinicians should be aware of the possibility of being misled by the color of fibrin pseudomembranes. There are many shades of grayish and whitish fibrin pseudomembranes that to the unskilled eye can resemble the white appearance of hyperkeratosis, whereas it is fibrin covering an ulcerated area. Sometimes a fibrin pseudomembrane can present a yellowish appearance and one should not mistake it for purulent matter or infection.

The pink appearance of oral mucosa results from tissue translucency, allowing the light to pass through the epithelium into the lamina propria and reflect the blood vessels containing hemoglobin.

A red lesion of the oral mucosa may develop as the result of atrophic epithelium (Figure 4-5), characterized by a reduction in the number of epithelial cells. It may also be the result of loss of the superficial cell layers (superficial erosion, Figure 4-6) or increased vascularization due to proliferation of vessels. Redness or erythema may further be caused by dilatation of vessels associated with inflammation of the oral mucosa, reduced epithelial keratinization, and, importantly, cellular proliferation signifying a possible malignancy.

Oral mucosal lesions also present with different tissue surface consistency, and white lesions may appear as reticular, plaque-like, papular, or pseudomembranous, which affect the clinical appearance of the lesions. Most red, and particularly most white, lesions are benign. Red lesions may also display a change of surface texture, which may become granular, velvety, and rough. It is important to note those features, as they are suggestive of neoplasia. Palpation of white and red lesions is necessary in addition to inspection, as indurated lesions should draw additional suspicion for possible malignancy.[3]

Our clinical approach to differential diagnosis should appreciate many other features of the lesion (Table 4-1). These include presence of *pain*, *single* versus *multiple* lesions, *distribution* in specific areas, the *borders* toward the unaffected tissue (clear or hazy, straight or crooked), *onset*, *duration*, *change in shape* and *size*, whether it is *raised* in comparison to surrounding mucosa, its *relapsing* nature, and reasons for *improvement* or *exacerbation*.

In addition to more detailed assessment of oral condition, we also need to obtain a closer and better understanding of the whole patient. A patient's specific systemic condition and associated medications are potentially very closely related to oral disease, so knowing and understanding them may be very relevant to the oral condition. However, there are cases in which patients are unaware of their systemic conditions. Thus, by recognizing oral lesions,

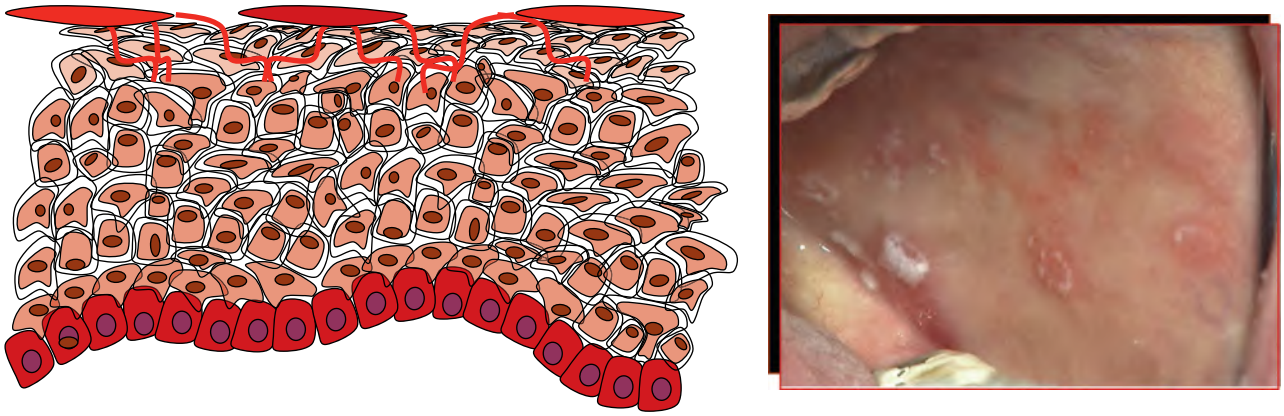

Figure 4-4 Mechanisms of a white appearance of the oral mucosa due to microbes, particularly fungi, which can produce whitish pseudomembranes consisting of sloughed epithelial cells, fungal mycelium, and neutrophils, which are loosely attached to the oral mucosa (plaques).

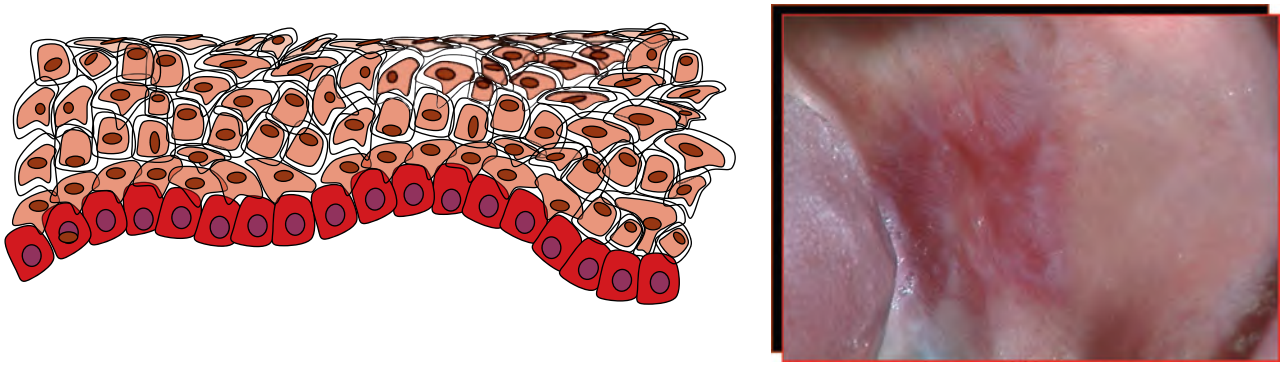

Figure 4-5 Mechanisms leading to a red appearance of the oral mucosa; a red lesion of the oral mucosa may develop as the result of an atrophic epithelium (atrophy).

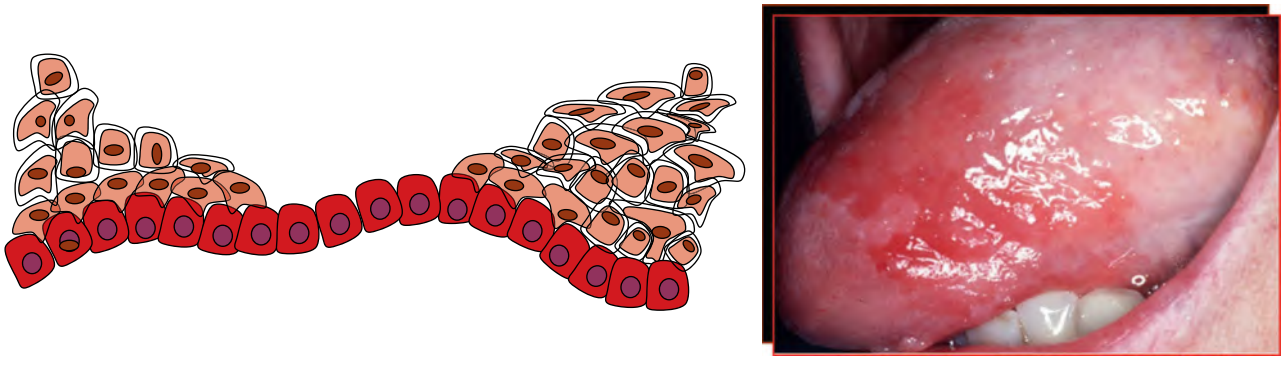

Figure 4-6 Mechanisms leading to a red appearance of the oral mucosa characterized by a reduction in the number of epithelial cells or increased vascularization; that is, dilatation of vessels and/or proliferation of vessels.

we sometimes note the initial indication of possibly undiagnosed systemic disease. Age can also be a significant factor in differentiating between similarly presenting conditions, which is perhaps more important for some other instances than most of those described in this chapter, such as the relevance of enlarged neck lymph nodes in children (frequent reactive lymphadenitis) and adults aged 65 years or older (more likely to represent malignancy), as well as in cases of mouth ulcers in young and old patients (discussed elsewhere).

Table 4-1 Main clinical characteristics of red or white lesions.

Is pain present?
Are lesions single or multiple?
Are lesions bilateral or unilateral?
Is the distribution of lesions linked to mucosal type?
Are lesion borders defined or indistinct?
Date of onset
Are lesions associated with changes of the skin?
Duration of lesion
Any changes in shape, size, or texture with time?
Any previous response to therapy?
What makes the pain or the lesions worse?
Have lesions healed and recurred?

INFECTIOUS DISEASES

Oral Candidiasis

Oral candidiasis is the most prevalent opportunistic infection affecting the oral mucosa. It is common, but often wrongly considered by the unskilled as a culprit for many oral conditions or white lesions. In the vast majority of cases, oral candidiasis is caused by *Candida albicans*. *C. albicans* is one of the components of normal oral microflora and more than 60% of people carry this organism. Rate of carriage increases with age of the patient and *C. albicans* can be found in over 60% of dentate patients over the age of 60 years. Most candidal infections only affect mucosal linings, and vaginal candidiasis is said to affect 50% of the female population of the planet at one time or another. There are many different additional *Candida* species that can be seen in the oral cavity, including C. *glabrata*, *C. guillermondii*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, *C. pseudotropicalis*, and *C. stellatoidea*. Candidiasis is often referred to as a disease of the diseased and is associated with underlying hematologic or immunologic deficiencies and a huge increase in the numbers of oral candida, as well as the conversion from the commensal yeast form (saprophytic stage) to the infecting pathogenic (parasitic) form. Thus it is incumbent on clinicians to determine the reasons for oral candidiasis, not just prescribe antifungals.

Candidiasis is said to affect in particular the very young, the very old, the very dry, and the very sick. Every candidiasis starts after local or systemic factors enable commensal *Candida* to become pathogenic. Those local factors include lack of saliva (medications causing dry mouth, autoimmune diseases, head and neck radiotherapy), denture wearing, topical steroid use, use of antibiotics or immunosuppressive drugs, systemic conditions including diabetes, anemia, or HIV, as described in detail in this chapter. Rare systemic manifestations of candidal infections may have a fatal course and are major causes of morbidity and mortality, causing a variety of diseases from mucosal infections to deep tissue disease, which may lead toward candidemia and organ involvement. Systemic candidal infections are mostly limited to hospital patients who are immunocompromised or with other severe comorbidities.[4]

Oral medicine largely deals with oral mucosal candidal infections, but also considers local or systemic disturbances that may predispose to fungi becoming invasive instead of remaining commensal. Candidal infections encountered in an oral medicine setting usually do not result in serious consequences for overall health, but can produce discomfort (inflammation may cause tenderness) or may change a person's appearance (e.g., angular cheilitis). Successful treatment depends on identifying and eliminating predisposing factors. On rare occasions, a longstanding intractable candidal infection in individuals with disturbed immune responses may produce granulomatous reactions.

Classification

There have been a number of classifications, but the most useful is that which combines chronicity with clinical presentation, as seen in Table 4-2. Pseudomembranous lesions present with removable small white plaques (see later), while erythematous lesions present essentially as red lesions with no white plaques.[5] These are both superficial forms of candidiasis, whereas all chronic hyperplastic forms are associated with hyphae driving down within the epithelium (Table 4-2). Oral forms may also be associated with candidiasis affecting extraoral sites, usually in conditions or genetic diseases where normal innate or adaptive host responses are compromised (Table 4-3).

Etiology and Pathogenesis

C. albicans, *C. tropicalis*, and *C. glabrata* comprise together over 80% of the species isolated from human mucosal candidal infections. To invade the mucosal lining, the microorganisms must adhere to the epithelial surface, therefore candidal strains with better adhesion potential are more virulent than strains with poorer adhesion ability.[6] Penetration of the epithelial cells by yeasts is facilitated by their production of lipases and proteinases, and for the yeasts to remain within the epithelium, they must overcome constant desquamation of surface epithelial cells.[7]

There is an association between oral candidiasis and the influence of local and general predisposing factors. The local predisposing factors (Table 4-4) are able to promote growth of the yeast or to affect the immune response of the oral mucosa. General predisposing factors are often related to an individual's immune and endocrine status (Table 4-4). Drugs

Table 4-2 Classification of oral candidiasis.

Type	Examples
Pseudomembranous—acute	Thrush
Pseudomembranous—chronic	With inhalers
Erythematous—acute atrophic	After antibiotic therapy
Erythematous—chronic atrophic	Denture stomatitis; in HIV
Chronic hyperplastic (nodular and plaque-like subtypes)	Candidal leukoplakia, median rhomboid glossitis
Candida-associated lesions	Denture stomatitis; angular cheilitis

Table 4-3 Candidiasis affecting extraoral sites and conditions predisposing to candidiasis.

Familial chronic mucocutaneous candidiasis
Diffuse chronic mucocutaneous candidiasis
Erythematous candidiasis endocrinopathy syndrome
Chronic severe combined immunodeficiency
DiGeorge syndrome
Chronic granulomatous disease
HIV disease

Table 4-4 Predisposing factors for oral candidiasis.

Local Predisposing Factors for Oral Candidiasis and *Candida*-Associated Lesions	General Predisposing Factors for Oral Candidiasis
Denture wearing	Immunosuppressive diseases
Smoking	Immunosuppressive drugs
Inhalation steroids	Chemotherapy
Topical steroids	Endocrine disorders, e.g., diabetes
Hyperkeratosis	Hematinic deficiencies
Quality and quantity of saliva	Systemic antibiotics
Atopic constitution	Impaired health status
Imbalance of the oral microflora	

as well as diseases that suppress the adaptive and innate immune systems can affect the susceptibility of the mucosal lining. Pseudomembranous candidiasis is also associated with fungal infections in young children, who have neither a fully developed immune system nor a fully developed oral microflora.

Denture stomatitis and angular cheilitis are referred to as *Candida*-associated infections, as they are always associated with raised counts of intraoral *Candida* and also since bacteria may cause these infections.

Epidemiology

The prevalence of candidal strains as part of the commensal oral flora shows large geographic variations, often also related to the method of culture, but an average figure of 50% is generally accepted. Candidal strains are more frequently isolated from women and the vaginal carriage is similar. Hospitalized patients have a higher prevalence, presumably related to comorbidities. In complete denture wearers, the prevalence of *Candida* associated with denture stomatitis has been reported as nearly 70%. There is a view that candidiasis is frequently over-reported in those without experience of the normal anatomy of the oral cavity. Thus, even slight elongation of the filiform papillae on the dorsum of the tongue may be erroneously diagnosed as candidiasis, as may be almost any white patch in the oral cavity. This misconception is found not only among lay people, but also among many medical and dental professionals.

Clinical Findings

Pseudomembranous Candidiasis

The acute form of pseudomembranous candidiasis (thrush; see Table 4-2) is recognized as the classic candidal infection (Figure 4-7). The infection predominantly affects patients taking antibiotics, immunosuppressant drugs, or having a disease that suppresses the immune system.

The infection typically presents with loosely attached membranes comprising fungal organisms and cellular debris (desquamated epithelial cells and polymorphonuclear lymphocytes), which leaves an inflamed, sometimes bleeding area if the pseudomembrane is removed. Less pronounced infections sometimes have clinical features that are difficult to discriminate from food debris like egg and yoghurt. There is also a chronic form of pseudomembranous candidiasis, often associated with immunodeficiency. The clinical presentations of acute and chronic

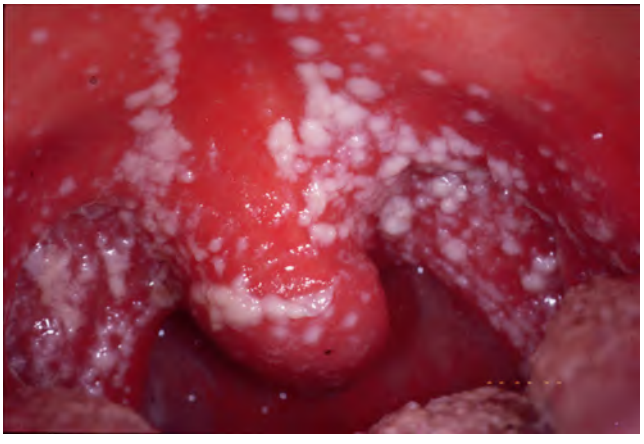

Figure 4-7 Pseudomembranous candidiasis at the soft palate, uvula, and palatoglossal arches during the immunosuppressive phase following heart transplantation.

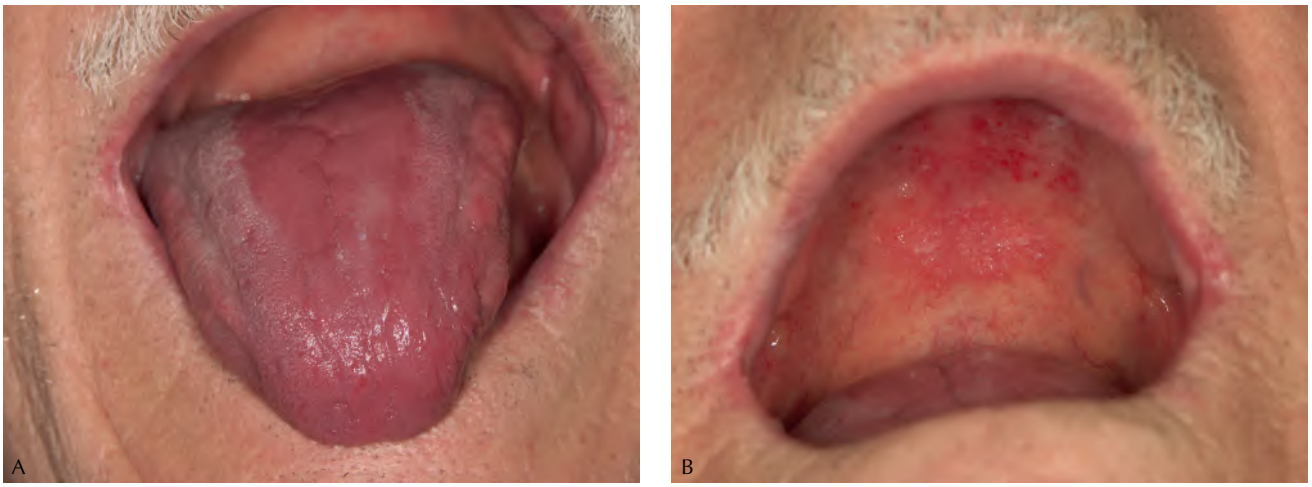

Figure 4-8 Erythematous candidiasis caused by inhalation steroids (A) on the dorsum of the tongue and (B) the associated contact (kissing) lesion on the hard palate.

pseudomembranous candidiasis are indistinguishable. The chronic form may emerge as the result of HIV infection, as patients with this disease may be affected by a pseudomembranous candidal infection for a long period of time. Patients treated with steroid inhalers may also show pseudomembranous lesions of a chronic nature. Patients infrequently report symptoms from their lesions, although some discomfort may be experienced from the presence of the pseudomembranes.

Erythematous Candidiasis

The erythematous form of candidiasis was previously referred to as atrophic oral candidiasis. However, an erythematous surface may not just reflect atrophy but can also be explained by increased vascularization. In addition, the erythematous form seen on the tongue in HIV infection is associated with loss of lingual papillae and a contact lesion on the hard palate. Lesions of erythematous candidiasis have a diffuse border (Figure 4-8), which helps distinguish them from erythroplakia, which usually has a sharper demarcation and often appears as a slightly submerged lesion. Quantitative analysis of *Candida* counts in saliva will reveal raised counts in all forms of candidiasis. The infection is also seen in the palate and the dorsum of the tongue of patients who are using inhalation steroids. Other predisposing factors that can cause erythematous candidiasis are smoking and treatment with broad-spectrum antibiotics. The acute and chronic forms present with identical clinical features.

Chronic Hyperplastic Candidiasis (Chronic Plaque Type and Nodular Candidiasis)

The chronic plaque type of oral candidiasis is synonymous with the older term *candidal leukoplakia*. A white irremovable plaque characterizes the typical clinical presentation, which may be indistinguishable from oral leukoplakia (Figure 4-9). A histologic feature (see later) is the penetration of candidal hyphae through the epithelial cells and the associated subepithelial chronic inflammatory response (Figure 4-10). This often results in mild to moderate dysplasia, especially in the chronic plaque type and the nodular type of oral hyperplastic candidiasis (Figure 4-11). This is considered reversible with treatment, but very rarely cases go on to malignant transformation. It has been hypothesized that *Candida* species may induce this transformation through their capacity to catalyze nitrosamine production, which is carcinogenic.[8]

Median Rhomboid Glossitis

Median rhomboid glossitis is clinically characterized by an erythematous lesion in the center of the posterior part of the dorsum of the tongue (Figure 4-12). As the name indicates, the lesion has an oval configuration. This area of erythema results from atrophy of the filiform papillae and the surface may be lobulated. The etiology is not fully clarified, but biopsies yield candidal hyphae in more than 85% of the lesions.[9] Smokers and denture wearers have an increased risk of developing median rhomboid glossitis, as well as patients using inhalation steroids. Sometimes a concurrent erythematous lesion may be observed in the palatal mucosa (contact lesion). Median rhomboid glossitis is asymptomatic, and management is restricted to a reduction of predisposing factors and systemic antifungals.

Although it may cause concern for patients who either discover the lesion themselves (e.g., while self-examining in search for symptoms, such as in burning mouth syndrome) or via health professionals, the lesion does not entail any increased risk for malignant transformation. Unlike the lateral and ventral tongue, cancer is very rare on the dorsal

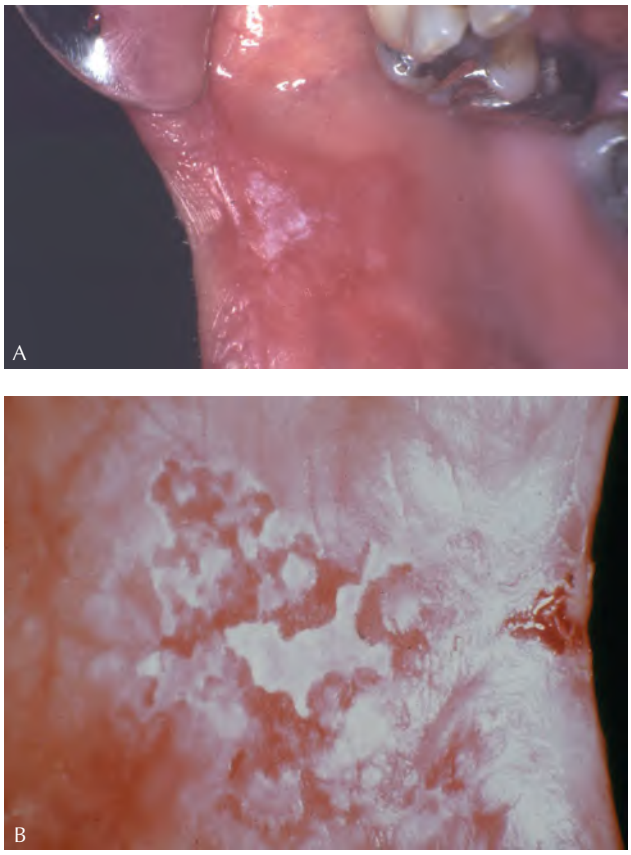

Figure 4-9 (A) Chronic hyperplastic candidiasis inside the right commissure. This white plaque is not removable, was bilateral, and histology (Figure 4-10) showed hyphae penetrating through epithelial cells. (B) Plaque type chronic candidiasis in the right buccal mucosa.

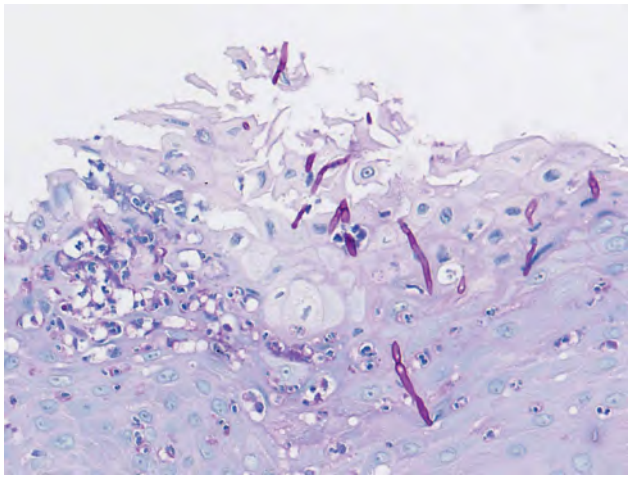

Figure 4-10 Periodic acid–Schiff (PAS) staining of a biopsy from chronic hyperplastic candidiasis (Figure 4-9A) showing invading hyphae drilling through oral epithelial cells.

tongue and virtually nonexistent right in its center. If a biopsy of median rhomboid glossitis is taken, one should be aware that it can easily be misinterpreted by pathologists as being malignant.[10] Although it is a benign lesion, histologically it

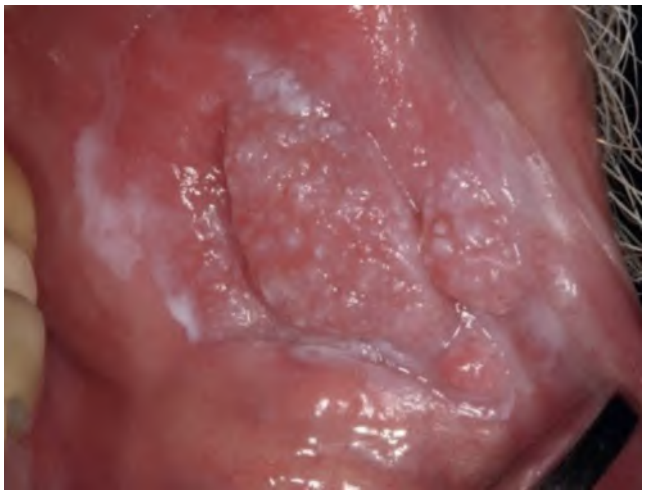

Figure 4-11 Chronic nodular candidiasis in the left retrocommissural area.

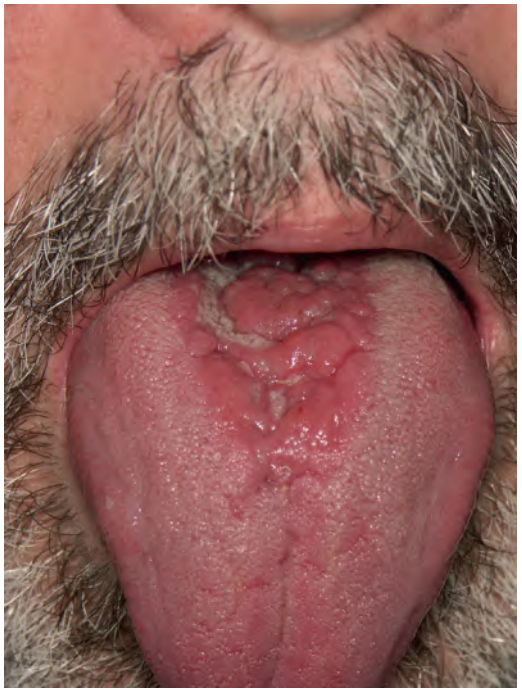

Figure 4-12 Median rhomboid glossitis apparently arising from the junction of the posterior third and anterior two-thirds of the tongue. Histology confirmed chronic hyperplastic candidiasis.

simulates cancer, which is why it has been styled "pseudoepitheliomatous hyperplasia" (epithelioma is a historical term for cancer). Elongated rete pegs resemble nests of cancer cells. Histopathology findings of deeper layers show muscular fibrosis and hyalinization (which are increased by excision). Therefore, neither biopsy nor surgical intervention is recommended in cases of median rhomboid glossitis.

Denture Stomatitis

The most prevalent site for denture stomatitis is the denture-bearing palatal mucosa (Figure 4-13), whether acrylic or

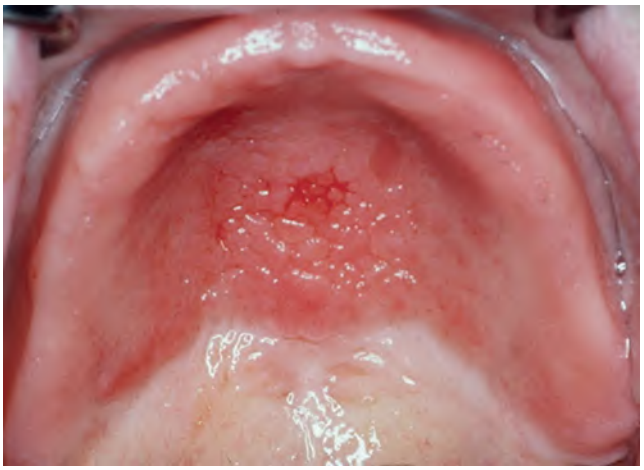

Figure 4-13 Chronic atrophic candidiasis (denture stomatitis) type III with a granular mucosa in the central part of the palate.

chrome cobalt. It is unusual for the mandibular mucosa to be involved. *Candida* resides on the denture surface, and the erythema appears to be a mucosal reaction to *Candida* and other microorganisms.

Denture stomatitis is classified into three different types:

- Type I is limited to erythematous sites caused by trauma from the denture.
- Type II affects a major part of the denture-covered mucosa.
- Type III has a granular mucosa (reactive proliferation of underlying fibrous tissue) in addition to the features of type II. The denture serves as a vehicle that accumulates sloughed epithelial cells and protects the microorganisms from physical influences such as salivary flow.

The microflora is complex and may, in addition to *C. albicans*, contain bacteria from several genera, such as *Streptococcus*, *Veillonella*, *Lactobacillus*, *Prevotella* (formerly *Bacteroides*), and *Actinomyces* strains. It is not known to what extent these bacteria participate in the pathogenesis of denture stomatitis. Nearly every patient with denture stomatitis will report wearing dentures overnight. Thus, denture stomatitis is the consequence of continuous irritation, both microbial and mechanical from the upper denture, on the underlying mucosal surface. The term "denture sore mouth" is a misnomer, as it normally does not produce any symptoms and is usually diagnosed by the dentist, since patients are frequently unaware. Oral medicine specialists still get referrals with a misdiagnosis of allergy to the denture.

Angular Cheilitis

Angular cheilitis presents as infected fissures of the commissures of the mouth, often surrounded by erythema (Figure 4-14). The lesions are frequently co-infected with both *Candida albicans* and *Staphylococcus aureus*. Atopy, vitamin B_{12} deficiency, iron deficiencies, and loss of vertical dimension are all associated with this disorder. The reservoir for *Candida* in the cheilitis is intraoral, so treatment must not be limited to the commissures. Many patients with angular cheilitis will also have denture stomatitis.

Oral Candidiasis Associated with HIV

More than 90% of AIDS patients have had oral candidiasis during the course of their HIV infection, and the infection is considered a portent of AIDS development (Figure 4-15). Oropharyngeal candidiasis is related to the degree of immunosuppression and is most often observed in patients with CD4 counts <200 cells/mL. The most common types of oral candidiasis in conjunction with HIV are chronic pseudomembranous candidiasis, erythematous candidiasis of the middle of the tongue and palate, and angular cheilitis. As a result of antiretroviral therapy (ART), the prevalence of

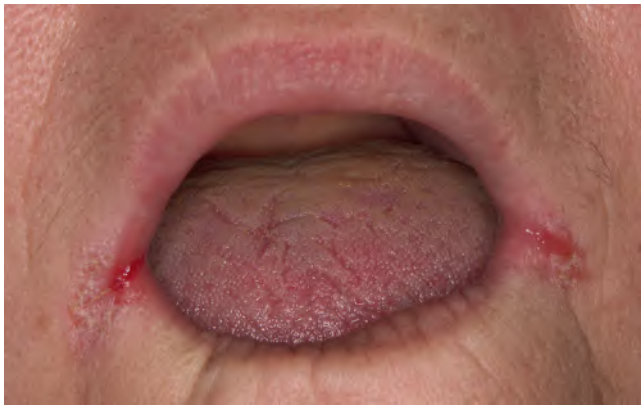

Figure 4-14 *Candida*-induced bilateral angular cheilitis. Treatment must include the intraoral *Candida* reservoir.

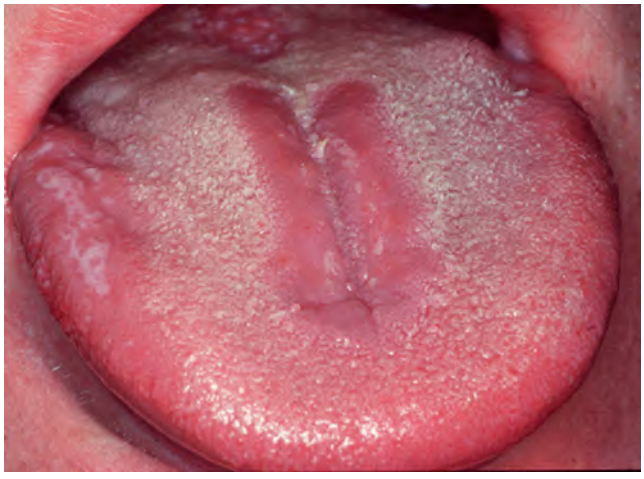

Figure 4-15 Erythematous candidiasis of the central part of the tongue in an AIDS patient. Hairy leukoplakia can be seen at the right lateral border.

oral candidiasis has decreased substantially. Oral candidiasis associated with HIV infection is presented in more detail in Chapter 21, "Infectious Diseases."

Clinical Manifestations of Mucocutaneous Candidiasis

More widespread candidiasis (see Table 4-3), besides oral involvement, is accompanied by systemic mucocutaneous candidiasis and other immune deficiencies. Chronic mucocutaneous candidiasis (CMC) embraces a heterogeneous group of disorders, but is characterized by recurrent or persistent infections affecting the nails, skin, and oral and genital mucosae caused by *Candida* species (Figure 4-16A).[11] The face and scalp may be involved, and granulomatous masses can be seen at these sites. Approximately 90% of patients with CMC also present with oral candidiasis. The oral manifestations may involve the tongue (Figure 4-16B) and white plaque-like lesions are seen in conjunction with fissures. CMC can occur as part of endocrine disorders, including hyperparathyroidism and Addison's disease. Recent studies revealed that an impairment of interleukin-17 (IL-17) immunity underlies the development of CMC. Th17 cells produce IL-17 and play an important role in host mucosal immunity to *Candida*. Impaired phagocytic function by neutrophilic granulocytes and macrophages caused by myeloperoxidase deficiency have also been associated with CMC.

Chédiak–Higashi syndrome, an inherited disease with a reduced and impaired number of neutrophilic granulocytes, lends further support to the role of the phagocytic system in candidal infections, as these patients frequently develop candidiasis. Severe combined immunodeficiency (SCID) syndrome is characterized by a defect in the function of the cell-mediated arm of the immune system. Patients with this disorder frequently contract disseminated candidal infections. Thymoma is a neoplasm of thymic epithelial cells that also is associated with systemic candidiasis. Thus, both the innate and adaptive immune systems are critical to prevent the development of systemic mucocutaneous candidiasis.

Diagnosis and Laboratory Findings

The presence of candidal microorganisms as a member of the commensal flora complicates the discrimination of the normal state from infection. *Candida* cells can be found in 60% of people in numbers of up to 500 cfu/mL as normal commensals. However, in infection, these numbers may increase to over 10,000 cfu/mL and any increase to over 1000 cfu/mL may be seen in candidal infections. It is imperative that both clinical findings and laboratory data (Table 4-5) are balanced in order to arrive at a correct diagnosis. Sometimes antifungal treatment has to be initiated to assist in the diagnostic process, with a good clinical response indicating a retrospective diagnosis. Smears (cytology) are useful for indicating hyphae, and salivary culture for indicating numerically raised counts. Swabs indicate neither hyphae nor counts, but can confirm the presence of raised amounts of *Candida*.

Smears from the infected area comprise epithelial cells, debris, and *Candida*. The material is fixed in isopropyl alcohol and air-dried before staining with periodic acid–Schiff (PAS). The detection of several yeast organisms in the form of hyphae- or pseudohyphae-like structures is usually considered a sign of infection, although these structures can occasionally be found in normal oral mucosa. This technique is particularly useful when pseudomembranous oral candidiasis and angular cheilitis are suspected (Table 4-6). Cultivation of saliva, oral washings, or swabs are performed on Sabouraud agar and in the case of saliva or washings the cfu/mL can be determined (Table 4-7). To discriminate between different candidal species, an additional examination can be performed on chromogenic agar (e.g., Pagano–Levin agar). Imprint culture technique can also be used

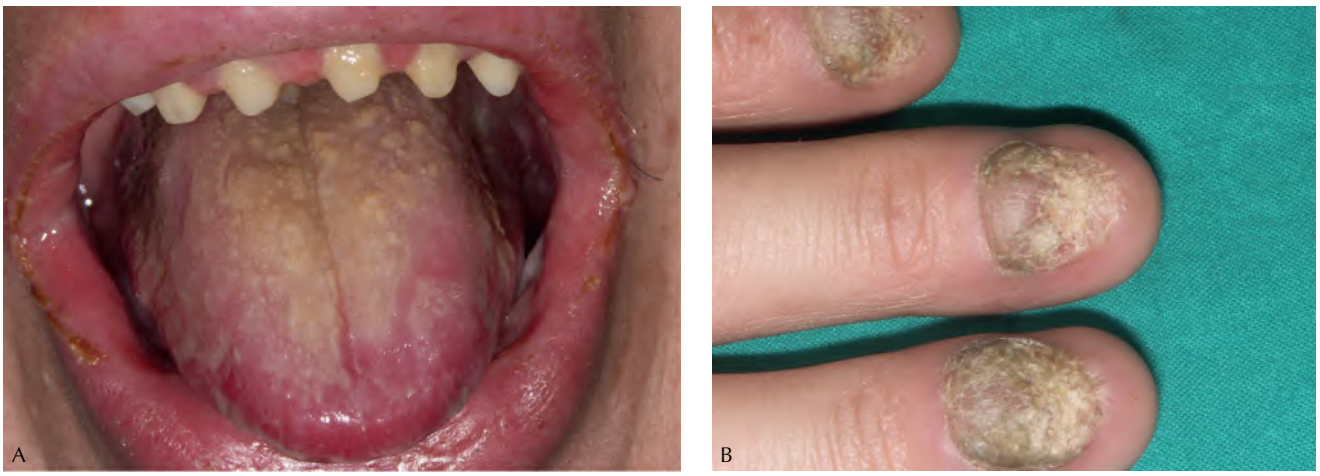

Figure 4-16 Chronic candidiasis of (A) dorsum of tongue and (B) fingernails of a patient with chronic mucocutaneous candidiasis.

Table 4-5 Routine tests for patients with suspected oral candidiasis.

Smears (cytology)
Swabs
Culture of saliva (or saline rinses) for cfu/mL
Biopsies
Hematology
Full blood picture, liver function tests
Hematinics (iron/ferritin, folate, vitamin B_{12})
Immunology, endocrinology

Table 4-6 Summary of laboratory tests in relation to different types of oral candidiasis.

	Smear	Swab	Saliva cfu/mL	Biopsy
PC	+	±	+	–
EC	+	±	+	–
CAC	±	+	+	–
AC	+	+	±	–
CHC	+	±	+	+
AAC	±	+	+	–
MRG	+	±	+	+*

AAC, acute atrophic candidiasis; AC, angular cheilitis; CAC, chronic atrophic candidiasis; CHC, chronic hyperplasic candidiasis; EC, erythematous candidiasis; MRG, median rhomboid glossitis; PC, pseudomembranous candidiasis.
+ = useful; ± = sometimes useful; – = not useful; * = not usually necessary since MRG is diagnosed on clinical grounds.

where sterile plastic foam pads (2.5 × 2.5 cm) are moistened in Sabouraud broth and placed on the infected mucosal or denture surface for 60 seconds. The pad is then firmly pressed onto Sabouraud agar, which will be cultivated at 37 °C. The result is expressed as colony forming units per cubic milliliter (cfu/mL[2]). This method is a valuable adjunct in the diagnostic process of erythematous candidiasis and in denture stomatitis, where high counts will be found on the denture but not on the palate.

In chronic plaque type and nodular candidiasis, cultivation techniques have to be supplemented by a biopsy and histopathologic examination (Table 4-6). This examination is primarily performed to identify the presence of any epithelial dysplasia and to identify invading candidal hyphae by PAS staining (Figure 4-10).

If clinical signs of *Candida* infection are not evident, then undertaking laboratory investigations may not be appropriate, and sometimes the clinical signs are so obvious (e.g., pseudomembranous candidiasis) that laboratory tests may not be needed and antifungal therapy may be initiated without confirmatory tests. Tests may also be helpful if the expected response to treatment does not materialize. These may include speciation and testing for antifungal sensitivity, especially for the azoles. Some species (e.g., *C. krusei*, *C. glabrata*) have natural resistance to azoles, and others may become resistant after previous exposure.

Management

Treatment for fungal infections, which usually includes antifungal regimens, will not always be successful unless the clinician addresses predisposing factors that may cause recurrence. Local factors are often easy to identify but sometimes not possible to reduce or eradicate. Antifungal drugs have a primary role in such cases. In smokers, cessation of the habit may result in disappearance of the infection even without antifungal treatment (Figure 4-17). Superficial mucosal infections are often best treated with topical antifungals, whereas chronic hyperplasic types will respond best to systemic therapy. The most commonly used antifungal drugs belong to the groups of polyenes or azoles (Table 4-8).

Polyenes such as nystatin and amphotericin are usually the first choices in treatment of primary oral candidiasis and are both well tolerated. Polyenes are not absorbed from the gastrointestinal tract and are not associated with development of resistance. They exert the action through a negative effect on the production of ergosterol, which is critical for the yeast's cell membrane integrity. Polyenes can also affect the adherence of the fungi to epithelial cells.

Whenever possible, elimination or reduction of predisposing factors should always be the first goal for treatment of denture stomatitis as well as other opportunistic infections. This involves improved denture hygiene and a recommendation not to use the denture while sleeping. The denture hygiene is important to remove nutrients, including desquamated epithelial cells, which may serve as a source of nitrogen, which is essential for the growth of the yeasts. Denture cleaning also disturbs the maturity of a microbial environment established under the denture. As porosities in the denture can harbor microorganisms, which may not be removed by physical cleaning, the denture should be stored in antimicrobial solution during the night. Different solutions, including alkaline peroxides, alkaline hypochlorites, acids, and disinfectants, have been suggested. Chlorhexidine may also be used, but can discolor the denture and also counteracts the effect of nystatin.[12]

Surgical excision of type III denture stomatitis is sometimes advised in an attempt to eradicate microorganisms present in the deeper fissures of the granular tissue. However, this is neither sensible nor necessary, and it should not even be considered. Improved hygiene, better-fitting dentures, and not wearing them overnight should clear the inflammation and edema sufficiently.

Table 4-7 *Candida* Isolation in the clinic and quantification from oral samples.

Method	Main Steps	Advantages	Disadvantages
Smear	Scraping, smearing directly onto slide	Simple and quick	Low sensitivity
Salivary culture	Patient expectorates 2 mL saliva into sterile container; vibration; culture on Sabouraud agar by spiral plating; counting	Quantifies actual counts against normal range Useful to monitor response to therapy	Longer chairside time; not useful for xerostomics Does not identify site of infection
Oral rinse	Subject rinses for 60 s with phosphate-buffered saline at pH 7.2, and returns it to the original container; cultured and counted as in previous methods	Simple method Sensitive Normal ranges available	Recommended in hyposalivation Does not identify site of infection
Impression culture	Maxillary and mandibular alginate impressions; casting in agar fortified with Sabouraud broth; incubation	Useful to determine relative distributions of yeasts on oral surfaces	Useful mostly as a research tool
Imprint culture	Sterile plastic foam pads moistened with Sabouraud broth, placed on lesion for 60 s; pad pressed on Sabouraud agar plate and incubated; colony counter used	Sensitive and reliable; can discriminate between infected and noninfected sites	Reading above 50 CFU/cm^2 can be inaccurate Useful mostly as a research tool

Source: Adapted from Sitheeque MA, Samaranayake LP. Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia). *Crit Rev Oral Biol Med*. 2003;14(4):253–267.

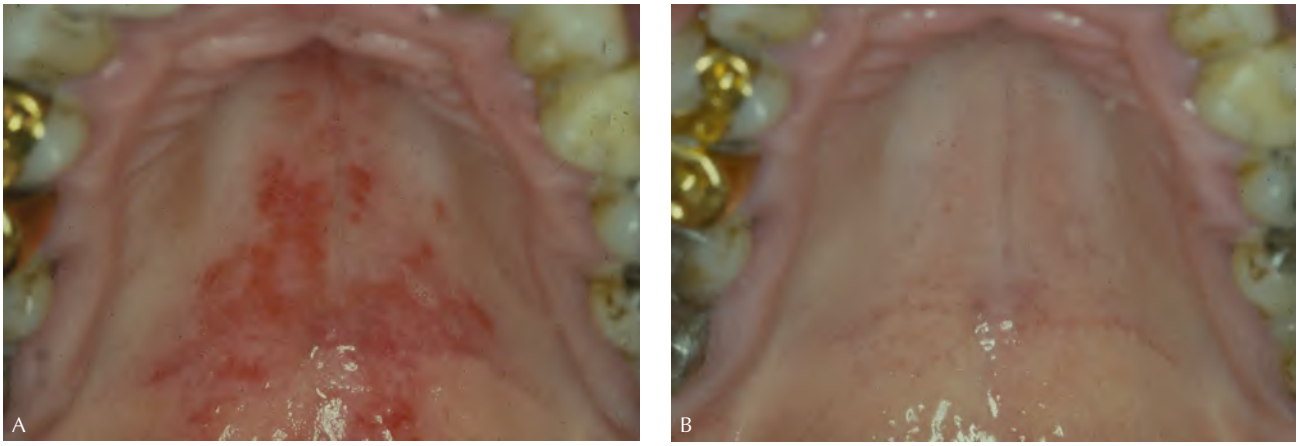

Figure 4-17 Palatal erythematous candidiasis in a cigarette smoker (A) before treatment; (B) after treatment.

Topical treatment with azoles such as miconazole is the treatment of choice for angular cheilitis, often infected by both *S. aureus* and candidal strains. This drug has a biostatic effect on *S. aureus* in addition to the fungistatic effect (but also augments warfarin). Antiseptic ointment can be used as a complement to the antifungal drugs if *Staphylococcus* is suspected. If angular cheilitis comprises an erythema surrounding the fissure, a mild steroid ointment may be required in addition to the antifungal to suppress the inflammation. To prevent recurrences, treatment of the intraoral reservoir of *Candida* is essential and patients may benefit from applying a moisturizing cream, which may prevent new fissure formation.

Systemic azoles may be used for deeply seated primary candidiasis, such as chronic hyperplastic candidiasis and median rhomboid glossitis with a granular appearance, and for therapy-resistant infections, mostly related to compliance failure. There are several disadvantages with the use of azoles. They are known to interact with warfarin, leading to an increased bleeding propensity. This adverse effect may also be present with topical application, as the azoles are fully or partly resorbed from the gastrointestinal tract. Development of resistance is particularly compelling for fluconazole in individuals with HIV disease. In such cases, ketoconazole and itraconazole have been recommended as alternatives. However, cross-resistance has been reported between fluconazole on the one hand and ketoconazole, miconazole, and itraconazole on the other. The azoles are also used in the treatment of secondary oral candidiasis associated with systemic

Table 4-8 Antifungal agents used in the treatment of oral candidiasis.

Drug	Form	Dosage	Comments
Amphotericin	Lozenge, 10 mg	Slowly dissolved in mouth 3–4 times/day after meals for 2 weeks minimum	Negligible absorption from gastrointestinal tract When given intravenously for deep mycoses may cause thrombophlebitis, anorexia, nausea, vomiting, fever, headache, weight loss, anemia, hypokalemia, nephrotoxicity, etc.
	Oral suspension, 100 mg/mL	Placed in mouth after food and retained near lesions 4 times/day for 2 weeks	
Nystatin	Cream	Apply to affected area 3–4 times/day	Negligible absorption from gastrointestinal tract Nausea and vomiting with high doses
	Pastille, 100,000 U	Dissolve 1 pastille slowly after meals 4 times/day, usually for 7 days	
	Oral suspension, 100,000 U	Apply after meals 4 times/day, usually for 7 days, and continue use for several days after postclinical healing	
Clotrimazole	Cream	Apply to affected area 2–3 times/day for 3–4 weeks	Mild local effects Also has antistaphylococcal activity
	Solution	5 mL 3–4 times/day for 2 weeks minimum	
Miconazole	Oral gel	Apply to affected area 3–4 times/day	Occasional mild local reactions Also has antibacterial activity
	Cream	Apply twice/day and continue for 10–14 days after lesion heals	Theoretically the best antifungal to treat angular cheilitis Interacts with anticoagulants (warfarin), terfenadine, cisapride, and astemizole Avoid in pregnancy and liver disease
Ketoconazole	Tablets	200–400 mg tablets taken once or twice/day with food for 2 weeks	May cause nausea, vomiting, rashes, pruritus, and liver damage Interacts with anticoagulants, terfenadine, cisapride, and astemizole Contraindicated in pregnancy and liver disease
Fluconazole	Capsules	50–100 mg capsules once/day for 2–3 weeks	Interacts with anticoagulants, terfenadine, cisapride, and astemizole Contraindicated in pregnancy and liver and renal disease May cause nausea, diarrhea, headache, rash, and liver dysfunction
Itraconazole	Capsules	100 mg capsules daily taken immediately after meals for 2 weeks	Interacts with terfenadine, cisapride, and astemizole Contraindicated in pregnancy and liver disease May cause nausea, neuropathy, or rash

Adapted from Ellepola AN, Samaranayake LP. Oral candidal infections and antimycotics. *Crit Rev Oral Biol Med*. 2000;11(2):172–198.

predisposing factors and for systemic candidiasis. Some suggested regimes for the treatment of local and systemic *Candida* infections are outlined in Table 4-8.

Prognosis of oral candidiasis is good when predisposing factors associated with the infection are reduced or eliminated. Persistent chronic plaque type and nodular candidiasis have been suggested to be associated with an increased risk for malignant transformation compared with leukoplakia not infected by candidal strains. Patients with primary candidiasis are also at risk if systemic predisposing factors emerge. For example, patients with severe immunosuppression, as seen in conjunction with leukemia and AIDS, may encounter disseminating candidiasis with a fatal course.[13]

Oral Hairy Leukoplakia

Oral hairy leukoplakia (OHL) is the second most common HIV-associated oral mucosal lesion. OHL has been used as a marker of disease activity, since the lesion is associated with low $CD4^+$ T lymphocyte counts.[14] It is caused by concurrent infection with the Epstein–Barr virus (EBV). The lesion is strongly associated with HIV disease, but other states of immune deficiencies, such as those caused by immunosuppressive drugs and cancer chemotherapy, have also been associated with OHL.

Etiology and Pathogenesis

OHL appears to be an EBV-induced lesion in patients with low levels of $CD4^+$ T lymphocytes. Antiviral medication, which prevents EBV replication, is curative and lends further support to EBV as an etiologic factor. There is also a correlation between EBV replication and a decrease in the number of $CD1a^+$ Langerhans cells, which, together with T lymphocytes, are important cell populations in the cellular immune defense of the oral mucosa.[15]

Epidemiology

The prevalence figures for OHL depend on the type of population investigated and vary around the world. Prior to the ART era, the mean prevalence was 25% of people living with HIV, but this figure has decreased considerably after the introduction of more effective therapies.[16] In contrast, patients who develop AIDS have an increased prevalence of greater than 50%. The prevalence in children is lower compared with adults and has been reported to be around 2%.[17] The condition is more frequently encountered in men, but the reason for this predisposition is not known. A correlation between smoking and OHL has also been observed.[18]

Clinical Findings

OHL is frequently encountered bilaterally on the lateral borders of the tongue (Figure 4-18), but may also be observed on the dorsum and in the buccal mucosa.[19] The typical clinical appearance is vertical white folds oriented as a palisade along the borders of the tongue. The lesions may also be seen as white and somewhat elevated plaque, which cannot be scraped off. OHL is asymptomatic, although symptoms may be present when the lesion is superinfected with candidal strains. As OHL may present in different clinical forms, it is important always to consider this mucosal lesion whenever the border of the tongue is affected by white lesions, particularly in immunocompromised patients.

Diagnosis

A diagnosis of OHL is usually based on clinical characteristics, but histopathologic examination and detection of EBV can be performed to confirm the clinical diagnosis (Table 4-9). It may most easily be confused with chronic trauma to the lateral borders of the tongue, but in that instance the corrugations are horizontal, not vertical.

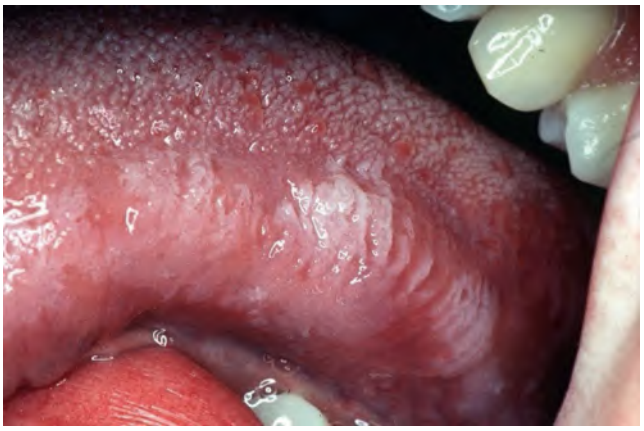

Figure 4-18 Hairy leukoplakia at the left lateral border of tongue in an AIDS patient showing vertical keratotic corrugations.

Pathology

The histopathology of OHL is characterized by hyperkeratosis, often with a chevron-pattern surface and acanthosis. Hairy projections are common, which is reflected in the name given to this disorder. Koilocytosis, with edematous epithelial cells and pyknotic nuclei, is also a characteristic histopathologic feature. The complex chromatin arrangements may mirror EBV replication in the nuclei of koilocytic epithelial cells. Candidal hyphae surrounded by polymorphonuclear granulocytes are a common feature. The number of Langerhans cells detected by immunostaining is considerably reduced. Mild subepithelial inflammation may also be observed. EBV can be detected by in situ hybridization or by immunohistochemistry. Exfoliative cytology may be of value and can serve as an adjunct to biopsy.

Management

OHL can be treated successfully with antiviral medication, but this is not often indicated, as this disorder is not associated with adverse symptoms. In addition, the disorder has also been reported to show spontaneous regression. OHL is not related to increased risk of malignant transformation. Medication with ART has reduced the number of OHL to a few percent in HIV-infected patients.[20]

ORAL POTENTIALLY MALIGNANT DISORDERS

Oral Leukoplakia

Definitions

Leukoplakia is defined as a white plaque of questionable risk for malignant transformation having excluded other known white lesions or disorders that carry no increased

Table 4-9 Features of the diagnosis of oral hairy leukoplakia.

Provisional diagnosis
Characteristic gross appearance of bilateral vertical corrugations on sides of tongue, with or without responsiveness to antifungal therapy
Presumptive diagnosis
Light microscopy of histologic sections revealing hyperkeratosis, koilocytosis, acanthosis, and absence of inflammatory cell infiltrate, or light microscopy of cytologic preparations demonstrating nuclear beading and chromatin margination
Definitive diagnosis
In situ hybridization of histologic or cytologic specimens revealing positive staining for Epstein–Barr virus DNA, or electron microscopy of histologic or cytologic specimens showing herpesvirus-like particles

risk for cancer. Leukoplakia is thus a diagnosis of exclusion. Erythroplakia is a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease. Both those diagnoses thus require exclusion of other similar-looking lesions of known causes or mechanisms before being applied.[21]

By far the majority of white and red lesions are benign. However, the two conditions with the greatest malignant potential in the oral cavity are leukoplakia (white plaque) and erythroplakia (red plaque). The relative importance of one versus the other is that leukoplakia is very common and can sometimes transform into cancer, whereas erythroplakia is rather uncommon but frequently represents a precursor to cancer. There is also a term erythroleukoplakia (nonhomogeneous, speckled leukoplakia), which has both white and red areas, and the sinister nature of erythroleukoplakia and erythroplakia should be considered alike.

Etiology and Pathogenesis

By definition, leukoplakia is idiopathic, having excluded white patches of known etiology. The exception to this rule is that smoking is recognized as an etiological or exacerbating factor and smoker's keratosis may regress when the irritant is removed (see later).[22] As smoking cessation can effectively reverse many tobacco-associated leukoplakia, appreciating its etiology and acting appropriately form the best approach to prevent oral cancer.[22]

Hairy leukoplakia is not considered a true leukoplakia, since the etiology and infective agent (EBV) are known and the risk of malignant transformation appears to be almost nonexistent.

The development of oral leukoplakia and erythroplakia as potentially malignant lesions involves different genetic events. This notion is supported by the fact that markers of genetic defects are differently expressed in different leukoplakias and erythroplakias.[23–25] Activation of oncogenes and deletion and injuries to suppressor genes and genes responsible for DNA repair will all contribute to a defective functioning of the genome that governs cell division. Following a series of mutations, a malignant transformation may occur. For example, carcinogens such as tobacco may induce hyperkeratinization, with the potential to revert following cessation, but at some stage mutations will lead to unrestrained proliferation and cell division.

Epidemiology

The prevalence of oral leukoplakia varies among scientific studies. A comprehensive global review points at prevalences between 1.5% and 2.6%.[26] Most oral leukoplakias are seen in patients beyond the age of 50 and are infrequently encountered below the age of 30. In population studies, leukoplakias are more common in men, but a slight majority for women has been found in some studies.[27]

Clinical Findings

Oral leukoplakia is defined as a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer. This disorder can be further divided into a homogeneous and a nonhomogeneous type. The typical homogeneous leukoplakia is clinically characterized as a white, often well-demarcated plaque with a similar reaction pattern throughout the lesion (Figure 4-19). Some lesions are uniformly presented in the entire area, but the surface texture can vary, even in a single case, from smooth and thin to a leathery appearance with surface fissures sometimes referred to as "cracked mud." Thus, different thicknesses and textures can, in the absence of red areas and frank verruciform parts, still allow styling leukoplakia as homogeneous. The demarcation is usually distinct, which is different from an oral lichen planus (OLP) lesion, where the white components have a more diffuse transition to the normal oral mucosa. Another difference between these two lesions is the lack of a peripheral erythematous zone in homogeneous oral leukoplakia. The lesions are asymptomatic.

The term "nonhomogeneous" is somewhat less precise. The term is ascribed to lesions with two different features, usually having both red and white areas (Figure 4-20A), but also to all those without redness but containing verruciform exophytic elements. Due to the combined appearance of white and red areas, the nonhomogeneous oral leukoplakia has also been called erythroleukoplakia and speckled leucoplakia (Figure 4-20B). The clinical manifestation of the white component may vary from large white verrucous areas to small nodular structures. If the surface texture is homogeneous but contains verrucous, papillary (nodular), or exophytic components, the leukoplakia is also regarded as nonhomogeneous.

It should be stressed that there is a marked difference in malignant potential between those two subtypes of nonhomogeneous leukoplakia. Those with red areas should be considered

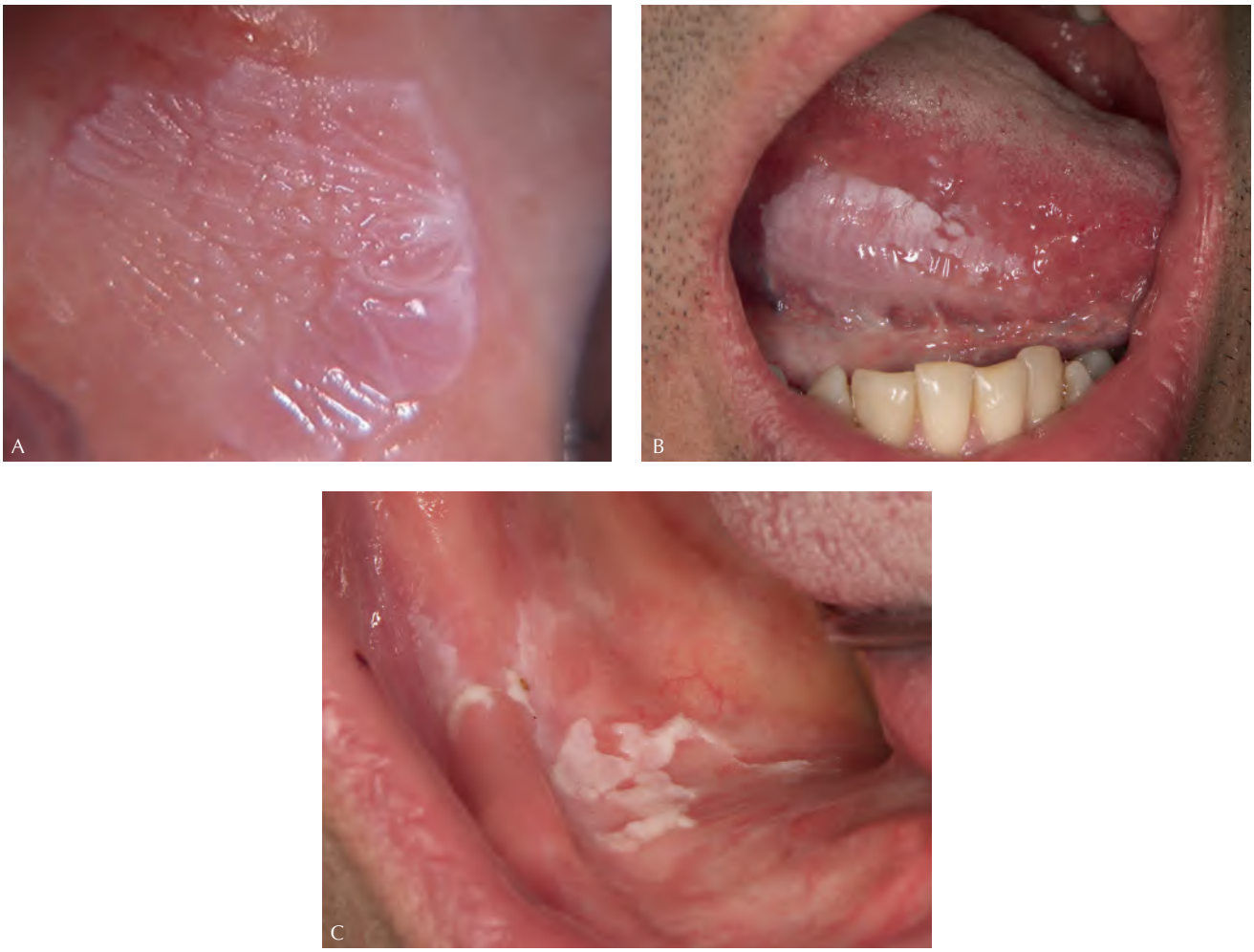

Figure 4-19 Clinical variations of homogeneous leukoplakias. (A) A homogeneous leukoplakia at the left buccal mucosa, (B) right side of tongue, and (C) upper buccal sulcus, which transformed into a squamous cell carcinoma two years later.

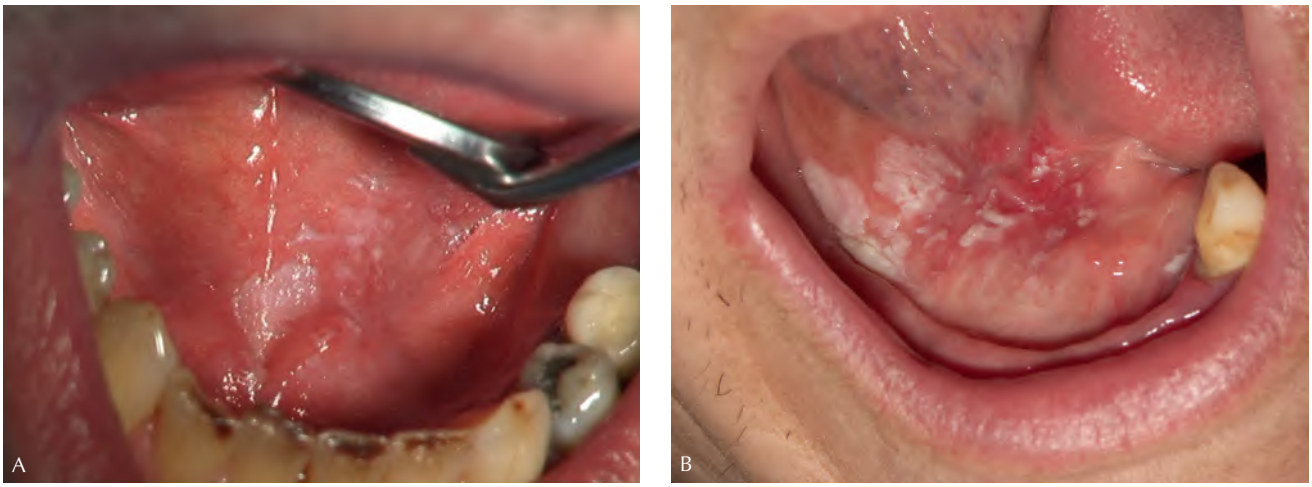

Figure 4-20 Nonhomogeneous leukoplakias of the floor of the mouth, which both transformed into squamous cell carcinomas.
(A) Nonhomogeneous leukoplakia in a heavy smoker at the floor of the mouth. The left part of the lesion has a speckled appearance.
(B) Nonhomogeneous leucoplakia showing a speckled appearance centrally, which transformed into squamous cell carcinoma over two years.

as an early cancer unless histopathologically proven otherwise. Those without red areas still have potential for malignant transformation, but less so. Oral leukoplakias, where the white component is dominated by papillary projections, similar to oral papillomas, are referred to as verrucous or verruciform leukoplakias.[28]

Oral leukoplakia may be found at all sites of the oral mucosa. The floor of the mouth and the lateral borders of the tongue are high-risk sites for malignant transformation (Figure 4-21). These sites have also been found to have a higher frequency of loss of heterozygosity compared with low-risk sites. However, the size of the lesion and the homogeneous/nonhomogeneous pattern are also decisive characteristics for the prognosis, whatever the site.

Proliferative Verrucous Leukoplakia

Proliferative verrucous leukoplakia (PVL) is an uncommon and serious condition where the pattern of clinical behavior does not match the histologic features. Diagnosis cannot usually be established at a single consultation. Histologically the lesion may appear benign, but clinically it behaves as a malignancy with gradually spreading leukoplakia, often gingivally. Oral leukoplakias with this clinical appearance but with a more aggressive proliferation pattern and high recurrence rate are designated as PVL (Figure 4-22).[29] This lesion may start as a homogeneous leukoplakia, but over time develops a verrucous appearance containing various degrees of dysplasia. PVL is usually encountered in older women, and the lower gingiva is a predilection site. The malignant potential is very high, and verrucous carcinoma or squamous cell carcinoma may be present at the primary examination. As the reaction pattern is similar to what is seen in oral papillomas, PVL has been suspected to have a viral etiology, although an association has not been confirmed.[30]

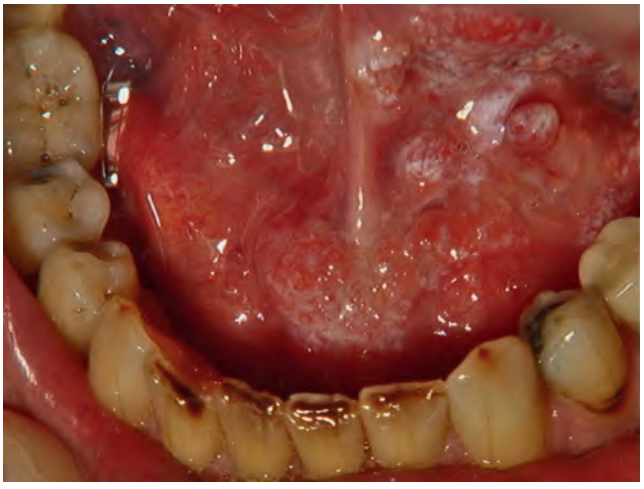

Figure 4-21 The patient with floor-of-mouth nonhomogeneous leukoplakia (Figure 4-20A) did not attend follow-up visits for three years and developed a squamous cell carcinoma.

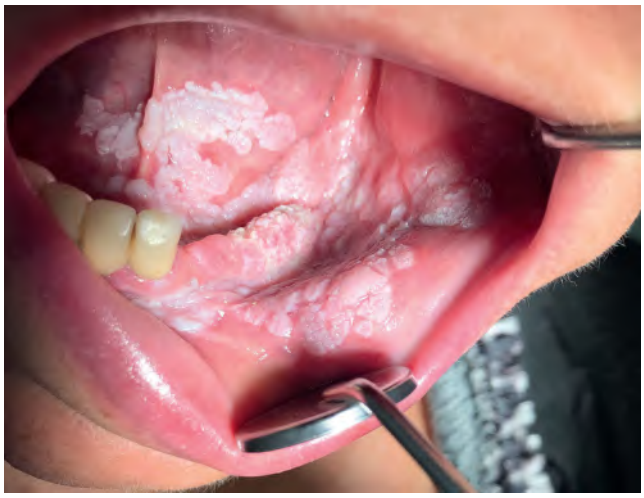

Figure 4-22 A proliferative verrucous leukoplakia progressively extending from the buccal mucosa, across the gingiva to the ventral surface of the tongue in a 48-year-old female.

Erythroplakia

Epidemiology

Oral erythroplakia is not as common as oral leukoplakia, and the prevalence in adults has been estimated to be in the range of 0.02% to 0.1%. The sex distribution is reported to be equal.

Oral erythroplakia has not been studied as extensively as oral leukoplakia, presumably because it is less common. Erythroplakia is initially a clinical diagnosis. It is defined as a red lesion of the oral mucosa that excludes other known pathologies (Figure 4-23). It comprises an irregular red lesion that is frequently observed with a distinct demarcation against the normal-appearing mucosa, sometimes with velvety granular surface texture.[31–33] Clinically, erythroplakia is different from erythematous OLP, as the latter has a more diffuse border and is surrounded by white reticular or papular structures. Erythroplakia is usually asymptomatic, although some patients may experience a burning sensation in conjunction with food intake.

It has been reported that 91% of histologically assessed homogeneous erythroplakias showed invasive carcinoma or carcinoma in situ, and in 9% there was moderate to severe dysplasia.[31] Another study showed severe dysplasia and frank carcinoma in 75% and mild to moderate dysplasia in 25%.[33] Thus, all erythroplakias should be considered as sinister. Any red mucosal lesion without an apparent local cause or not fitting into other known red lesions, and not regressing following removal of possible cause or two weeks of

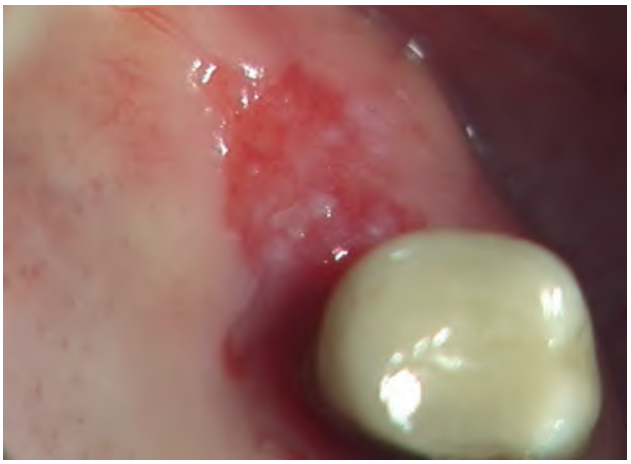

Figure 4-23 An erythroplakia on the upper alveolar ridge. Later on the patient developed a squamous cell carcinoma.

treatment, should be considered a cancer unless histologically proven otherwise.

A special form of erythroplakia has been reported that is related to reverse smoking of *chutta*, predominantly practiced in India. The lesion comprises well-demarcated red areas in conjunction with white papular tissue structures. Ulcerations and depigmented areas may also be a part of this particular form of oral lesion.

Diagnosis

The diagnostic procedure of oral leukoplakia and erythroplakia is identical. The provisional diagnosis is based on the clinical observation of a white or red patch that is not explained by a definable cause, such as trauma. If trauma is suspected, the cause, such as a sharp tooth or restoration, should be eliminated. If healing does not occur in two weeks, a tissue biopsy is essential to rule out malignancy. Realistically, differential diagnosis often requires considerable experience. As can be observed from referrals, clinicians not trained in an oral medicine specialty will rarely be able to perform clinical "fine print" distinction between various white lesions. Any similar white mucosal area will likely be initially indiscriminately proclaimed as "leukoplakia" instead of what it really may be (frictional hyperkeratosis, plaque-like lichen planus, habitual cheek biting, etc.). Sometimes there are cases when even specialists struggle with a final diagnosis, or change it over time.

Biopsies

Excisional biopsy is generally recommended if the leukoplakia diameter is less than 30 mm and the location allows (e.g., out of fine sublingual structures or not associated with marginal gingiva). Otherwise, in larger lesions incisional biopsies should be undertaken, sometimes from several sites. Selecting the appropriate site that will best represent the most severe aspect is of paramount importance, as underdiagnosing the lesion may be dangerous. New biopsies should be taken if new clinical features emerge. Following five years of no relapse, self-examination may be a reasonable approach.

Oral Leukoplakia and Erythroplakia: Pathology

The clinical appearance is a poor predictor of the histologic characteristics or behavior of oral leukoplakia, with the exception of the nonhomogeneous (speckled, erythroleukoplakia) type, which often displays a spectrum of occurrences from any degree of dysplasia to cancer. The biopsy should include representative tissue of the different clinical patterns. Hyperkeratosis without any other features of a definable diagnosis is compatible with homogeneous oral leukoplakia. If the histopathologic examination leads to another definable lesion, the definitive diagnosis will be changed accordingly. However, there is no uniform depiction of an oral leukoplakia and the histopathologic features of the epithelium may include hyperkeratosis, atrophy, and hyperplasia with or without dysplasia. When dysplasia is present, it may vary from mild to severe. Dysplasia may be found in homogeneous leukoplakias, but is much more frequently encountered in nonhomogeneous leukoplakias and in erythroplakias.

Epithelial dysplasia is defined in general terms as a precancerous lesion of stratified squamous epithelium characterized by cellular atypia and loss of normal maturation short of carcinoma in situ (Figure 4-24). Carcinoma in situ is defined as a lesion in which the full thickness of squamous epithelium shows the cellular features of carcinoma without stromal invasion.[34] A more detailed description of the features of epithelial dysplasia is presented in Table 4-10. The prevalence of dysplasia in oral leukoplakias varies from 1% to 30%, presumably due to various lifestyle factors involved and due to subjectivity in the histopathologic evaluation. The majority of erythroplakias display an atrophic epithelium with dysplastic features. The significance of epithelial dysplasia for predicting future development of oral cancer is not always clear.

Oral Leukoplakia and Erythroplakia: Management

There are two key unanswered questions that clinicians would consider the most challenging regarding management of oral leukoplakia. The first is how to estimate the risk of a particular case transforming into oral squamous cell carcinoma; that is, to assess the likelihood of malignant transformation and how soon it may happen. Clinical and histopathologic features are somewhat helpful, but the information obtained from them has limitations. In spite of major scientific efforts, universal markers that reliably and efficiently identify lesions with higher risk and that could predict their malignant transformation have not been discovered.[35,36]

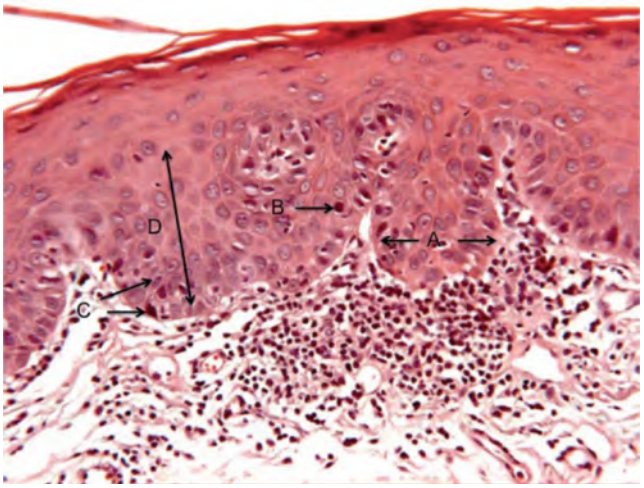

Figure 4-24 Histopathology of a leukoplakia with several characteristics of dysplasia in the oral epithelium (Table 4-9): drop-shaped rete ridges, nuclear hyperchromatism, presence of more than one layer of cells having a basaloid appearance, and irregular epithelial stratification.

Table 4-10 Criteria used for diagnosis of epithelial dysplasia.

Loss of polarity of basal cells
Presence of more than one layer of cells having a basaloid appearance
Increased nuclear–cytoplasmic ratio
Drop-shaped rete ridges
Irregular epithelial stratification
Increased number of mitotic figures
Mitotic figures that are abnormal in form
Presence of mitotic figures in the superficial half of the epithelium
Cellular and nuclear pleomorphism
Nuclear hyperchromatism
Enlarged nuclei
Loss of intercellular adherence
Keratinization of single cells or cell groups in the prickle cell layer

Since leukoplakias are asymptomatic, the main purpose of treatment is to prevent the development of cancer (or sometimes esthetics). Thus, a key question is whether anything can be done so that leukoplakia does not transform to cancer. Several approaches have been suggested, including chemoprevention with nonsteroidal anti-inflammatory drugs (NSAIDs) and metformin, but neither medications nor surgical approaches seem to be effective in preventing cancer development in patients with leukoplakia.[37–39]

As we do not have answers to those two pertinent questions, management of leukoplakia follows certain non-evidence-based protocols, but optimal management approaches are on a case-by-case basis and sometimes require numerous, lifelong, and frequent follow-up visits, including repeated biopsies.[40] Every oral health professional has a major role in identifying and diagnosing leukoplakia. Due to its unpredictable nature and the fact that even specialists find leukoplakia challenging, once it is suspected it is best referred to an oral medicine specialist. Oral medicine specialists will monitor patients closely and in a structured manner. Furthermore, specialists in hospitals have direct access to other clinicians, including head and neck surgeons, in case malignancy occurs and aggressive surgical intervention is required.

In contrast to leukoplakias, where close monitoring for years is a sensible alternative to surgical treatment, in erythroplakias biopsy and then excision constitute the normal recommended approach. Since such a high proportion of erythroplakias show severe dysplasia or carcinoma in situ on biopsy, excision usually follows. Usually, erythroplakias are not extensive, and thus neither will the surgery be.

In general, *clinical management* of leukoplakia relates to a combination of clinical (site, homogeneity, size, behavior) and histologic features (presence and degree of dysplasia and inflammation). While those leukoplakias that are homogeneous, stable, on lower-risk sites such as the buccal mucosa and show no dysplasia, can be reviewed annually (assuming no change in clinical characteristics), those showing clinical characteristics of mixed appearance, on high-risk sites, changing in size, in smokers, and histologically showing a degree of dysplasia will need to be reviewed more regularly. It can be deduced that a reproducible risk score from this combination of features would be very helpful for clinicians. An algorithm for management is shown in Figure 4-25.

If dysplasia is not present, follow up at six-month intervals is recommended. In case of dysplasia, the decision whether to surgically remove the whole lesion or not will depend upon its severity and the size and location of the lesion. Mild dysplasia may regress, and thus watchful waiting is appropriate. However, moderate to severe dysplasia is not likely to regress, but the rate of its progression cannot be estimated. In such cases, the premalignant site irrespective of surgical excision should be reexamined every three months, at least for the first year. If the lesion does not relapse or change in clinical pattern, the follow-up intervals may be extended to once every six months, with the patient advised with regard to self-examination. Oral leukoplakia is a lesion with an increased risk of malignant transformation, which has great implications for the management of this oral mucosal disorder (Figure 4-25). Since alcohol and smoking are well-established risk factors for the development of oral squamous cell carcinomas, measures should be taken to influence patients to modify or discontinue such habits.

Cold-knife surgical excision, as well as laser surgery, is widely used to eradicate leukoplakias and erythroplakias, but

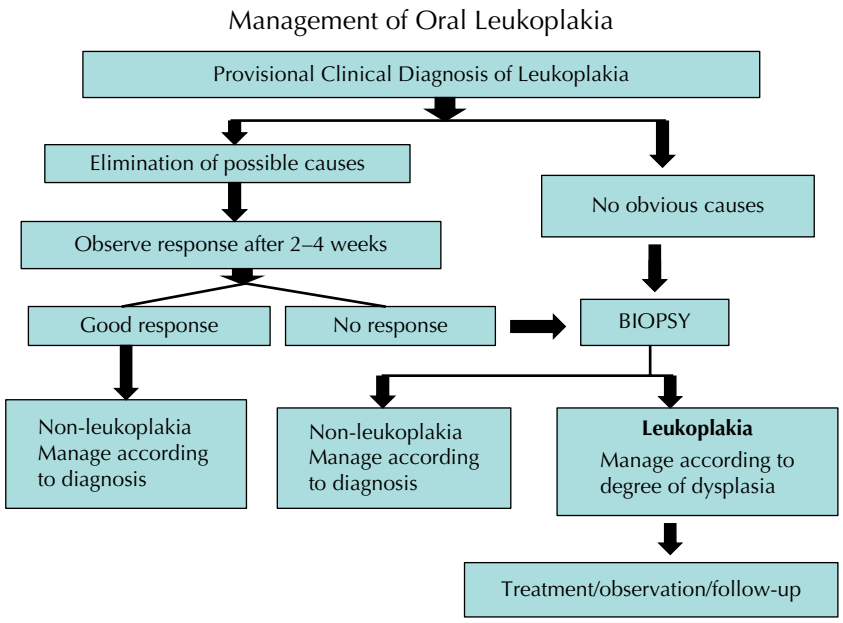

Figure 4-25 An algorithm for the management of oral leukoplakias.

will not prevent all premalignant lesions from malignant development. On the contrary, surgery has been strongly questioned, as squamous cell carcinomas are almost equally prevalent in patients subjected and not subjected to surgery.[41] This may be explained by genetic defects even in clinically normal mucosa surrounding the removed lesion and is supported by a concept referred to as field cancerization.[42] Field cancerization is caused by simultaneous genetic instabilities in the epithelium of several extralesional sites that may lead to squamous cell carcinomas. However, in the absence of evidence-based treatment strategies for oral leukoplakias, surgery will remain the treatment of choice for oral leukoplakias and erythroplakias where intervention is indicated. Such a treatment regimen is supported by the fact that serial sections of the total lesion after surgical removal have shown that as many as 7% of the lesions contained frank squamous cell carcinomas, which had not been revealed by an incisional biopsy.[37]

Malignant transformation of oral leukoplakias has been reported to be up to 20% over 30 years, depending on site and habits. According to available epidemiologic data, studies report an incidence that varies from less than 1% up to higher than 2% per year.[43] One study reported the incidence of malignant transformation of 2.6% per year among 144 cases. From that cohort, a total of 11% of cases transformed within the observation period of between two and seven years.[38] A recent meta-analysis of 23,498 pooled cases showed a mean malignant transformation rate of included studies of 9.7% over 2–10 years, with a slight preponderance in females, in patients followed up for a longer time, in older patients, and in lesions localized on the tongue and floor of the mouth.[44]

Over half of oral carcinomas have been reported to be associated with leukoplakias at the time of diagnosis, while in some countries such as India 80% of oral cancers were reported to be preceded by oral precancerous disorders. Until biomarkers are developed, management of oral leukoplakias and erythroplakias has to rely on traditional clinical and histopathologic criteria. Homogeneous oral leukoplakias are associated with a lower risk for malignant transformation than nonhomogeneous leukoplakias and erythroplakias, and lesions not exceeding 200 mm^2 appear to have a better prognosis than larger lesions

Oral Submucous Fibrosis

Oral submucous fibrosis (OSMF) is a chronic disease affecting the oral mucosa, as well as the pharynx and the upper two-thirds of the esophagus. There is substantial evidence that lends support to a critical role of areca nuts in the etiology behind OSMF.

Etiology and Pathogenesis

There is dose dependence between an areca quid chewing habit and the development of this oral mucosal disorder. Areca nuts contain alkaloids, of which arecoline seems to be a primary etiologic factor.[45] Arecoline has the capacity to modulate matrix metalloproteinases, lysyl oxidases, and collagenases, all affecting the metabolism of collagen, which leads to increased fibrosis.[46] During the development of fibrosis, a decrease in water-retaining proteoglycans will occur in favor of increased collagen type I production.[47] There is also evidence of a genetic predisposition of importance for the etiology behind OSMF. Polymorphism of the gene, which is coding for tumor necrosis factor α (TNF-α), has been reported to promote the development of the disorder. Fibroblasts are stimulated by TNF-α,

thereby participating in the development of fibrosis. Aberrations of other cytokines of importance are transforming growth factor β and interferon-γ, which may lead to increased production and decreased degradation of collagen.

Epidemiology

Areca nut–derived products are commonly used by several hundred million individuals in the southern parts of Asia. Regional variations exist regarding the preference for areca nut use, which also accounts for variation in the oral sites affected. Oral complications are most commonly observed on the lips, buccal mucosa, retromolar area, and soft palatal mucosa. The habit of chewing betel quid, containing fresh, dried, or cured areca nut and flavoring ingredients, is widespread in India, Pakistan, Bangladesh, and Sri Lanka and in emigrants from these regions. Tobacco is often used in conjunction with betel quid. The habit is more common among women in some geographic areas, which is also reflected in the sex distribution of oral submucous fibrosis.

The global incidence of OSMF has been estimated at 2.5 million individuals.[48] The prevalence in Indian populations is 5% for women and 2% for men. Individuals less than 20 years old are commonly affected by OSMF, probably reflecting the advertising of areca nut products, which is directed to younger age groups.

Clinical Findings

The first signs of OSMF are erythematous lesions, sometimes in conjunction with petechiae, pigmentations, and vesicles. These initial lesions are followed by a paler mucosa, which may comprise white marbling (Figure 4-26). The most prominent clinical characteristics will appear later in the course of the disease and include fibrotic bands located beneath an atrophic epithelium. Increased fibrosis eventually leads to loss of resilience, which interferes with speech and tongue mobility, and leads to a decreased ability to open the mouth. The atrophic epithelium may cause a smarting sensation and an inability to eat hot and spicy food. More than 25% of patients also exhibit oral leukoplakias.

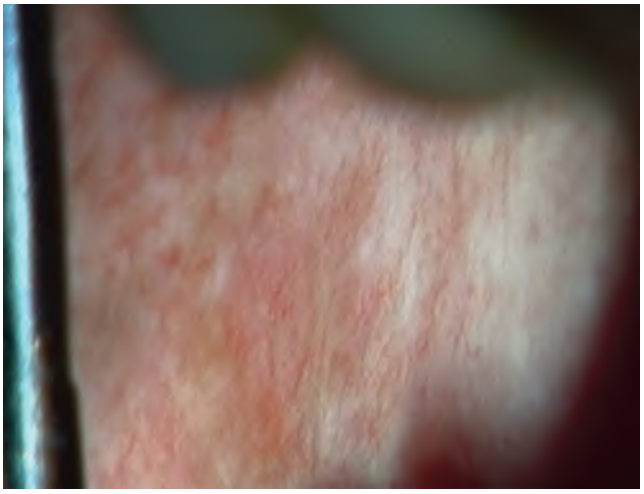

Figure 4-26 Marble-like appearance of the right buccal mucosa in a patient with submucous fibrosis with restricted ability to open her mouth. Similar changes were present in the left buccal mucosa.

Diagnosis

The diagnosis of OSMF is based on the clinical characteristics and on the patient's report of a habit of betel chewing. An international consensus has been reached where at least one of the following characteristics should be present:

- Palpable fibrous bands.
- Mucosal texture that feels tough and leathery.
- Blanching of mucosa together with histopathologic features consistent with oral submucous fibrosis (atrophic epithelium with loss of rete ridges and juxtaepithelial hyalinization of lamina propria).

Pathology

The early histopathologic characteristics for OSMF are fine fibrils of collagen, edema, hypertrophic fibroblasts, dilated and congested blood vessels, and an infiltration of neutrophilic and eosinophilic granulocytes. This picture is followed by a downregulation of fibroblasts, epithelial atrophy, and loss of rete pegs, and early signs of hyalinization occur in concert with an infiltration of inflammatory cells. Epithelial dysplasia in OSMF tissues appeared to vary from 7% to 25% depending on the study population.[49]

Management

Products derived from areca nuts are carcinogenic, regardless of the concomitant use of tobacco products. Thus, treatment of OSMF should be focused on cessation of the chewing habit. If this is successfully implemented, early lesions have a good prognosis as they may regress. A plethora of treatment strategies have been tried, such as topical and systemic steroids, hyaluronic acid, interferon-γ, supplementation of vitamins and nutrients, repeated dilatation with physical devices, and surgery. None of these treatments has reached general acceptance and the long-term results are dubious.

Malignant transformation of OSMF has been estimated in the range of 0.7% to 1.3% per annum and the incidence over a 10-year period at approximately 8%.[50]

IMMUNOPATHOLOGIC DISEASES

Lichen Planus

This is a family of lesions with different etiologies and a common clinical and histologic appearance. Neither clinical nor histopathologic features enable reliable discrimination

between them, but may be used to distinguish any of them from other pathologic conditions of the oral mucosa. This group of reactions includes the following disorders:

- Oral lichen planus.
- Oral lichenoid contact reactions.
- Oral lichenoid drug eruptions.
- Oral lichenoid reactions of graft-versus-host disease.

OLCRs are included in the later section where allergic reactions are discussed, since these lesions represent a delayed hypersensitivity reaction to constituents derived from dental materials or flavoring agents in foods and other ingested substances.

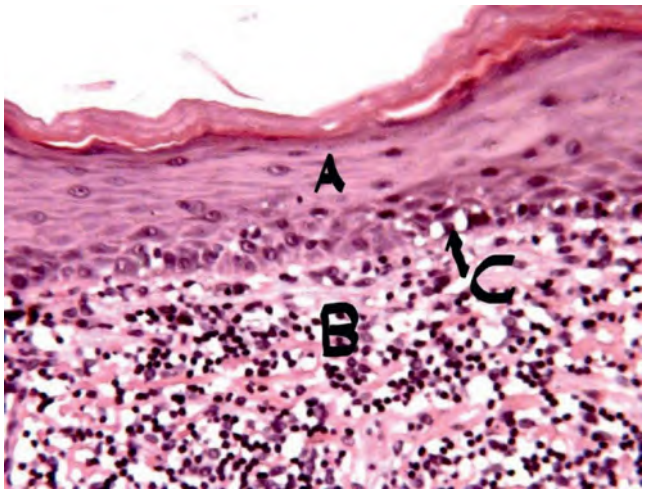

Figure 4-27 Lichenoid reaction with a subepithelial infiltrate of inflammatory cells and apoptosis of epithelial cells in the basal cell layer. (A) Epithelium, (B) subepithelial infiltrate, and (C) apoptopic epithelial cells.

Oral Lichen Planus

OLP is a chronic inflammatory cell-mediated immune disease of unknown etiology. Skin and mucous membranes are most commonly involved. In addition to oral mucosa, other mucous membranes (e.g., genitals in women, esophagus, rectal area) as well as scalp and nails can be affected. Several sites may be involved, consecutively or simultaneously. Typically, OLP is bilateral (symmetric) and can appear both white and red, depending on disease activity. It is striking because of its versatile presentation between individual patients. Some have long periods of remission, while others have frequent exacerbations and are not very responsive to treatment.

Etiology and Pathogenesis

The precise etiology of OLP is not known, but something is known about its pathogenesis.[51] The immune system has a primary role in the development of this disease and it is now considered to be an autoimmune cell-mediated disease targeted against epithelial cells, mainly in the basal layer. This is supported by the histopathologic characteristics of a subepithelial band–formed infiltrate dominated by T lymphocytes and macrophages and apoptosis of basal cells (Figure 4-27). There is no evidence that antibodies play a role.

A diagrammatic representation of the disease mechanism in lichen planus is shown in Figure 4-28. Cytotoxic $CD8^+$ T lymphocytes are responsible for apoptosis of the keratinocytes in the basal cell layer. These lymphocytes are a major component of the subepithelial inflammatory infiltrate in the mucosal lamina propria. The tissue destruction originates from the lymphocytic infiltrate and production of cytokines, characteristic of T-helper type 1 immune cellular response (IL-12, TNFα, interferons). They activate keratinocytes for increased expression of ICAM1 and the class II major histocompatibility complex (MHC) antigens. Other cells participating are CD4 cells, dendritic cells, natural killer (NK) cells, and mast cells. B cells and antibodies are not contributory. Activation of the autoreactive T lymphocyte is a process that may arise in other parts of the body than the oral mucosa and may not even occur in concert with the onset of the mucosal lesion. Autoantibodies do not appear to be involved in the pathogenic process.

The antigen that would trigger the onset of OLP is still unknown. Most likely, it is not one single peptide that has the potential to evoke the inflammatory response but several, depending on the specificity of the autoreactive T lymphocytes (Figure 4-28). It has not been possible to identify a single etiologic factor behind OLP, especially to explain the bilateral and symmetric nature of the clinical presentation. Other factors, such as stress, may also be of importance in establishing this inflammatory process. It is not unusual for patients to report that they have been exposed to negative social events months before the onset of the disease. Altogether, this makes the etiology behind OLP a multifactorial process comprising events that may take place at different time points and therefore difficult to investigate.

The exact influence of possibly associated etiologic factors remains controversial. Studies have found associations with hepatitis C virus (HCV), but this appears to relate to a small proportion of cases of OLP, possibly geographically based; OLP prevalence is also enhanced in those with thyroid diseases. However, at present the stimulus for cellular recognition of host antigens is unknown, so OLP remains in the idiopathic category.

Epidemiology

In the literature, a wide range of prevalence figures for OLP has been reported, but prevalence appears to be between

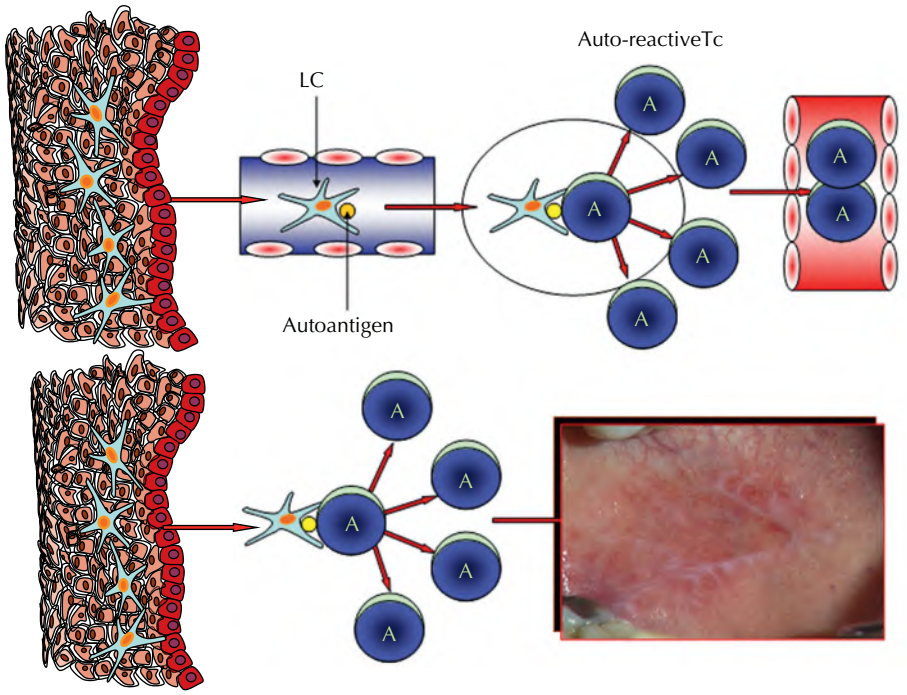

Figure 4-28 Diagrammatic representation of possible pathogenic mechanisms in oral lichen planus, a cell-mediated autoimmune disease where cytotoxic $CD8^+$ T lymphocytes are responsible for apoptosis of the keratinocytes in the basal cell layer. Autologous antigen peptides from basal cells or elsewhere are presented by Langerhans cells (Lc) to autoreactive T cells (Tc), which clonally expand and induce apoptosis in the basal cell layer and lead to the clinical lesions of oral lichen planus.

0.5% and 2% in different populations.[52] Oral lesions occur in around 50–60% of patients with cutaneous lichen planus. Conversely, cutaneous lesions occur in 10–15% of persons with OLP. The proportion of women is higher than that of men, with a ratio of 3:2. The condition usually occurs in people older than 40 years, the mean age of onset being 53 years. It is very rarely encountered in children, and does not seem to have a hereditary predisposition.

Clinical Findings

OLP may contain both red and white elements and these, together with the different textures, provide the basis for the clinical classification of this disorder. Oral lesions are typically multifocal, bilaterally distributed, most commonly symmetrically on the buccal mucosa, on lateral sites of the tongue, and on gingiva. However, they may appear anywhere in the mouth, including the lip vermilion. Palatal lesions are less common. The white and red components of the lesion can be a part of several clinical phenotypes:

- Reticular (and papular as its close clinical variant).
- Erythematous (also referred to as atrophic).
- Ulcerative (also referred to as erosive).
- Plaque-like.
- Bullous—very uncommon and usually associated with one of the other phenotypes.

The explanation of the different clinical manifestations of OLP is presumably related to the magnitude of the subepithelial inflammation. A mild degree of inflammation may provoke the epithelium to produce hyperkeratosis, whereas more intense inflammation will lead to partial or complete deterioration of the epithelium, histopathologically perceived as atrophy, erosion (thinning), or ulceration. This corroborates the fact that most erythematous and ulcerative lesions are surrounded by white reticular or papular structures. An inflammatory gradient may be formed where the central part comprises an intense inflammatory process, whereas the periphery is less affected and the epithelial cells are able to respond with hyperkeratosis.

Of the listed phenotypes, OLP most commonly presents in three of them: reticular/papular, erythematous/atrophic, or ulcerative/erosive forms.[53–56]

In the *reticular* form, hyperkeratotic white striations ("Wickham's striae"), which are a hallmark of the condition, form an interlacing or net-like (Latin "rete"; hence the name) pattern of linear white areas (Figure 4-29). This type is frequently present without symptoms. The reticular pattern tends to diminish with the duration of the condition.

The *papular* type of OLP is usually present in the initial phase of the disease (Figure 4-30). Small and densely distributed hyperkeratotic papules are present. These papules may coalesce and form a more reticular type, which is a variant of

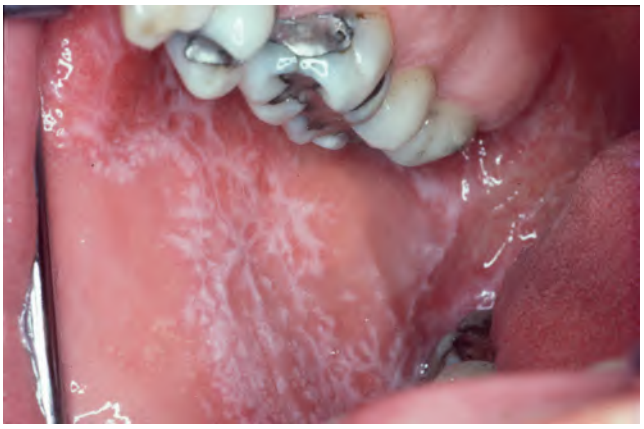

Figure 4-29 Reticular form of oral lichen planus at the right buccal mucosa with an almost identical clinical appearance in the left buccal mucosa.

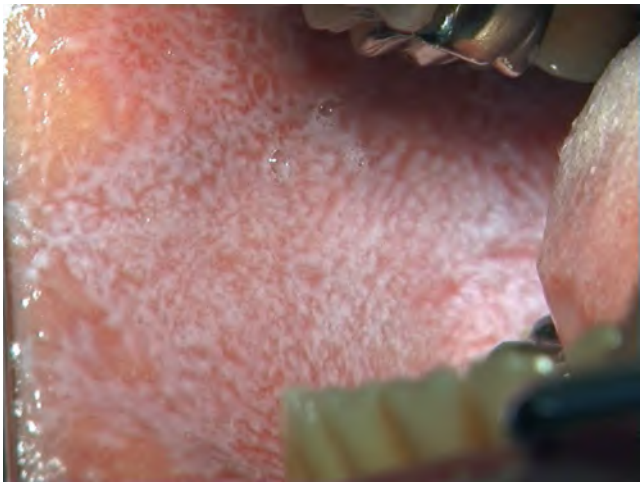

Figure 4-30 Papular oral lichen planus with dense cover of papules at the right buccal mucosa. The lesion has started to form a more reticular pattern on the anterior aspect. Bilateral presentation.

the other, since papular elements merge into striae as part of the natural course of OLP.

In *erythematous* (or *atrophic*) OLP, frank red lesions of atrophic mucosa appear as a result of hyperemia, reflecting clinical inflammation as well as some thinning of the epithelium. These usually affect the buccal mucosa, but may also be present on lateral parts of tongue and any other oral site. Although thinned and atrophic, the epithelium is not completely disrupted. Erythematous patches may be concomitant with hyperkeratotic lesions. However, erythematous lesions frequently occur with only discrete and gentle features typical of OLP, which may be unnoticed by the less experienced clinician, making clinical diagnosis more difficult.

When this type of OLP is present in the buccal mucosa or palate, striae are frequently seen in the periphery of the lesion. Some patients may display erythematous OLP exclusively affecting the attached gingiva (Figure 4-31). This form of lesion may occur without any papules or striae and presents as desquamative gingivitis (in more detail later). Therefore, erythematous OLP may require a histopathologic examination in order to arrive at a correct diagnosis and to distinguish it from mucous membrane pemphigoid.

The *ulcerative form* is characterized by grayish/yellowish fibrin pseudomembranes overlying breaches of the mucosa (ulceration). It is assumed that damage or loss of basal epithelial cells leads to loss of integrity of the epithelium above, which manifests as single or multiple lesions that are ulcers (ulcerative lichen planus) and often incorrectly described as erosions (erosive lichen planus). Ulcerative lesions are the most disabling form of OLP (Figures 4-32 and 4-33). Clinically, the fibrin-coated ulcers are surrounded by an erythematous zone with white striae in the periphery. This appearance may reflect a gradient of the intensity of subepithelial inflammation that is most prominent at the center of the lesion. The affected patient complains of chronic sensitivity, increased in conjunction with food intake. In the absence of treatment, clinical phenotypes appear to be relatively stable, but in time, inflammatory activity wanes and keratosis may become more prominent.

In addition to the three main clinical OLP presentations, there is *a plaque-like* form, which often represents a clinical challenge, as it is not easy to differentiate from homogeneous leukoplakia. In those lesions, solid hyperkeratotic patches are present instead of net-like striations and are usually bilateral. Plaque type OLP shows a homogeneous, well-demarcated white plaque that occurs in conjunction with striae (Figure 4-34).

One typical presentation of OLP is on the dorsal tongue, in the form of bilateral hemilunar whitish plaque areas, substituting for lost filiform papillae (Figure 4-35). These hemilunar areas can meet or involve much of the dorsum of the tongue. This large depapillated area may form perpendicular fissures, giving it a pattern resembling tiles (Figure 4-36). This typical presentation helps diagnose OLP if only the dorsal tongue is involved.

To distinguish plaque type lesions from homogeneous oral leukoplakias, it is often possible to identify reticular or papular structures besides plaque-like lesions in OLP (at least histologically), as well as the fact that they are usually bilateral. Some scientific reports lend support to the premise that a proportion of leukoplakias are derived from "burnt-out" lichen planus, supporting the view that OLP has an increased malignant transformation rate. Plaque type OLP is more often encountered in smokers, presumably reflecting the increased smoke-induced keratosis, and following cessation the plaque may disappear and convert into the reticular type of OLP.

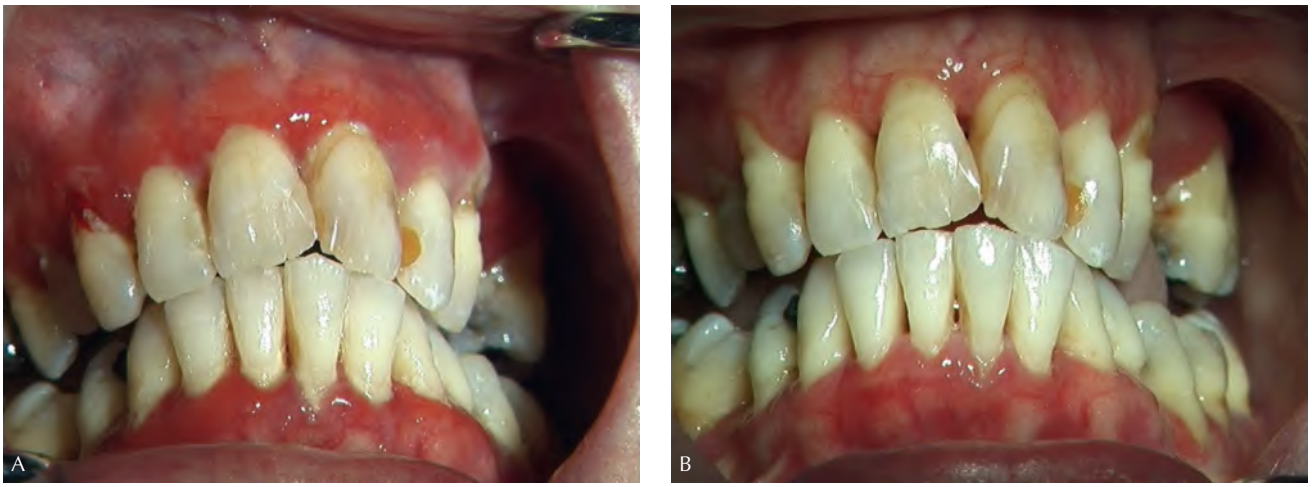

Figure 4-31 (A) Erythematous gingival oral lichen planus. (B) Improvement of the lesion following optimal oral hygiene.

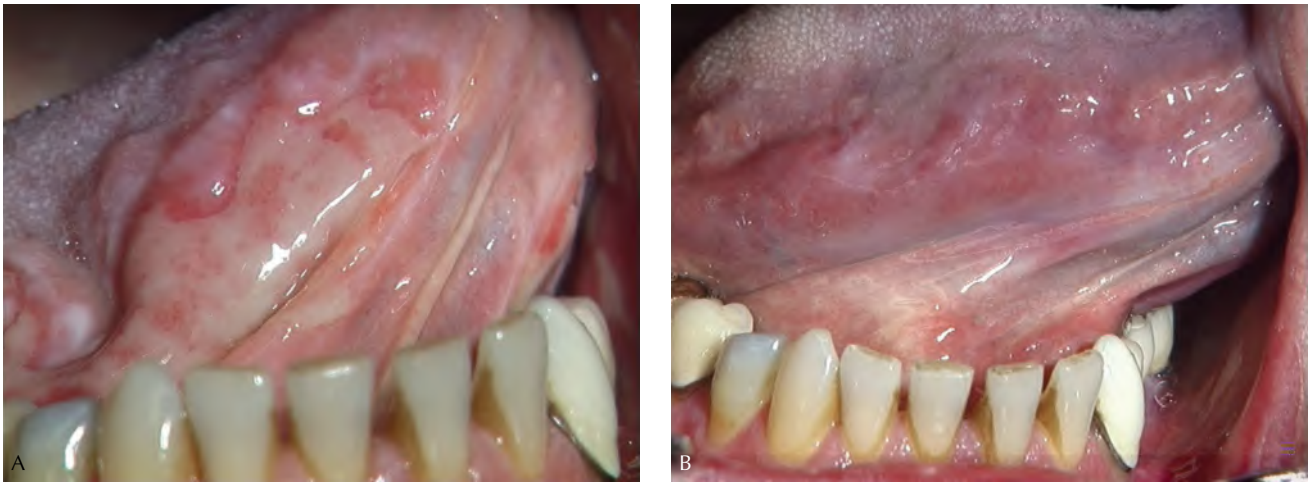

Figure 4-32 (A) Ulcerative oral lichen planus at the ventral surface of the tongue. (B) Complete epithelialization following three weeks of treatment with 0.025% clobetasol propionate gel, twice a day.

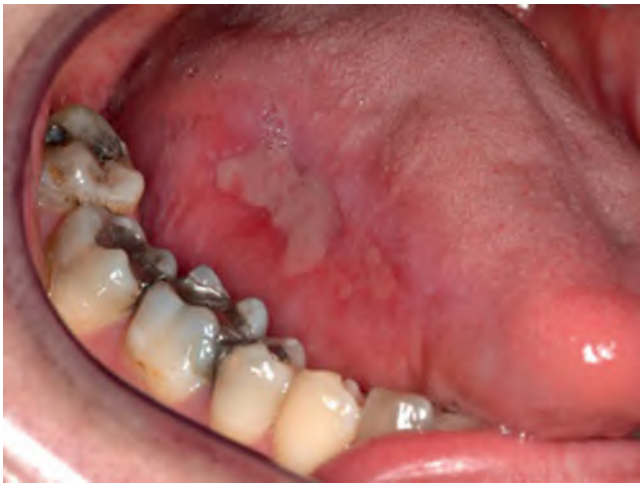

Figure 4-33 Ulcerative lichen planus on the right side of the tongue showing peri-ulcer erythema but little evidence of striae. Diagnosis confirmed on biopsy.

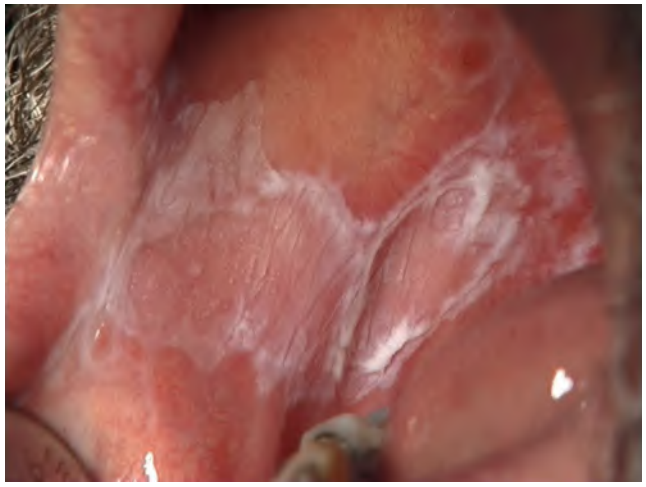

Figure 4-34 A plaque-like oral lichen planus with a plaque in the anterior part of the right buccal mucosa. In the posterior part, the lesion has features that are compatible with the reticular form.

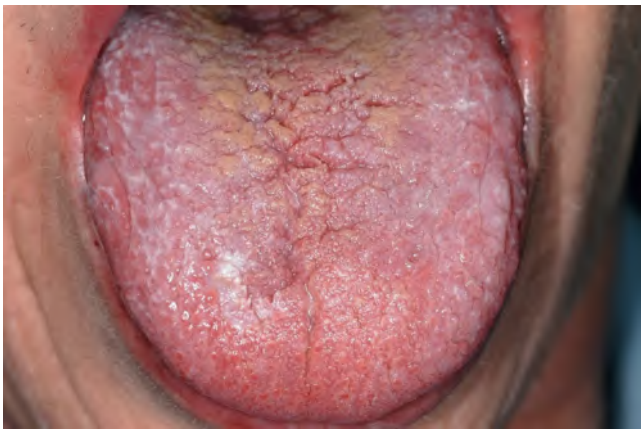

Figure 4-35 Lichen planus of the tongue, showing bilateral hemilunar areas, with the distal dorsum and anterior tip of the tongue apparently unaffected.

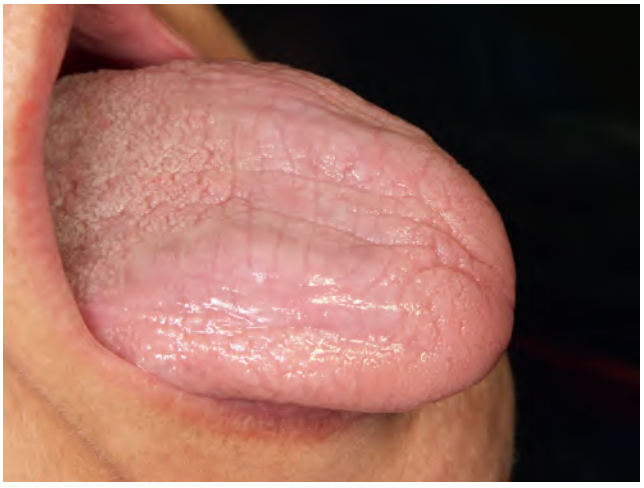

Figure 4-36 Tongue lichen planus showing bilateral depapillation with mild fissures, giving rise to a clinical picture resembling tiles.

The *bullous* form of OLP is very unusual. While sporadic case reports describe rare cutaneous lesions of bullous OLP, it is possible that this form does not exist at all as a separate phenotypic entity, but rather that occasionally bullae may be seen in the ulcerative or erythematous forms. Several contributory conditions may be misinterpreted as bullous OLP, including a clinically thick fibrin pseudomembrane of ulcerative OLP that resembles a wheal as it sticks out above the mucosal level, the small superficial mucoceles that frequently occur in mucosa affected by OLP, and a very rare condition called lichen planus pemphigoides,

Desquamative Gingivitis as a Manifestation of Oral Lichen Planus

OLP may appear as diffusely erythematous fragile gingiva that easily erodes. Gingival erythema with epithelial atrophy yields painful areas. It also may contain whitish, hazy, or lichenoid

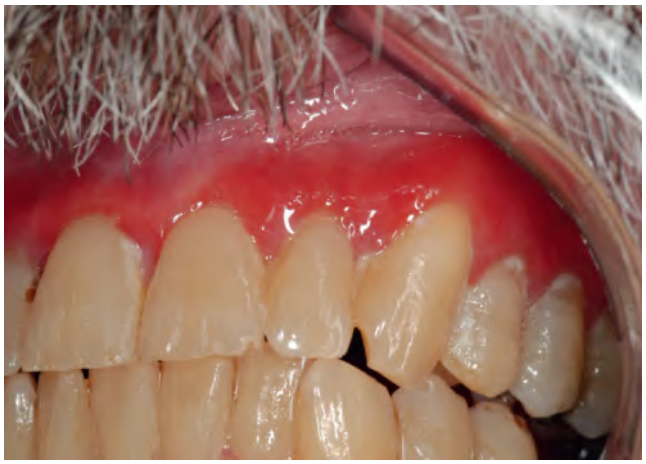

Figure 4-37 Classic desquamative gingivitis of lichen planus, with apparent absence of any striae.

lace-like epithelial film, but the presentation is usually just red. Frequently, gingival lesions are present in addition to other oral mucosal sites, but they also can be restricted to the gingivae alone in up to 10% of cases, meaning that no other more typical features of OLP are present (Figure 4-37). In those patients, a solid amount of caution and even clinical experience is required not to miss the diagnosis.

For these lesions, we use the term *desquamative gingivitis*. This is a clinical descriptive term for a non-biofilm-related, immune-mediated inflammatory condition affecting marginal, attached, and free gingivae. It is more prominent on the vestibular surface. Desquamative gingivitis is not a specific diagnosis. It most frequently represents OLP (typically indicating multimucosal disease, see later), but differentially it may be a consequence of several blistering diseases, most important among them a mucous membrane pemphigoid (MMP). Less probably, it may occur as a consequence of pemphigus vulgaris (PV), other subepithelial autoimmune blistering conditions (e.g., linear immunoglobulin A [IgA] disease), and hypersensitivity reactions (plasma-cell gingivitis).

Most commonly, it is mistaken for biofilm-related simple gingivitis. Misdiagnosis as such may lead to inadequate and too aggressive mechanical periodontal treatment, resulting in inadvertent exacerbation.

Extraoral Clinical Manifestations of Oral Lichen Planus

Patients with OLP may develop or already have lesions in extraoral locations. One or more sites can be involved, either sequentially or concomitantly, without a specific order or pattern. Cutaneous lesions may be encountered in approximately 15% of patients with OLP. The classic appearance of skin lesions consists of pruritic erythematous to violaceous papules that are flat topped. The predilection sites are the trunk and flexor surfaces of arms and legs (Figure 4-38). The papules may be discrete or coalesce to form plaques. Patients report

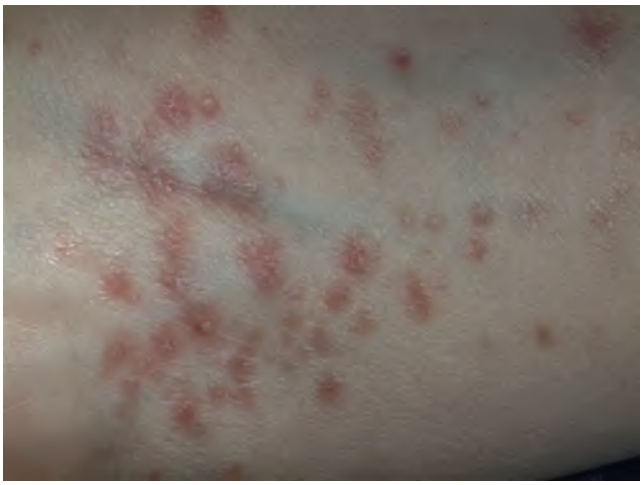

Figure 4-38 Cutaneous lichen planus on the flexor side of the forearm of a 45-year-old male.

relief following intense scratching of the lesions, but trauma may aggravate the disease, which is referred to as a Koebner phenomenon.

This phenomenon may also be of relevance for OLP, which is continuously exposed to physical trauma during mastication, toothbrushing, and denture wearing. Unlike OLP, cutaneous lichen planus is of short duration and, according to dermatologists, even untreated achieves full remission within a year or two, as opposed to OLP, which is long-lasting, frequently throughout life. It is very peculiar that the same disease acts so differently depending on the epithelial site it affects. If desquamative gingivitis is present in OLP, clinicians should be alert to ascertain if the patient has disease elsewhere.

Vulvovaginal-Gingival Syndrome

The most frequent extraoral mucosal site involved is the genital mucosa. Close to 25% of women presenting with OLP also have genital involvement, though not always symptomatic, and frequently misdiagnosed. Within this cohort is a distinct group of patients with a specific presentation of gingival, vulval, and vaginal lichen planus with genital and oral (usually buccal mucosa) scarring and loss of sulcular depth, known as vulvovaginal-gingival (VVG) syndrome.[57] The rare equivalent in men is peno-gingival syndrome. Symptoms in female patients include burning, pain, vaginal discharge, and dyspareunia, which are frequently noted, especially with the erythematous or ulcerative forms of the disease. No relationship seems to exist between the degree of severity in oral and genital sites.

Genital lichen planus has been reported in men, but the association with OLP is not as frequent as for women. In addition to standard treatment of oral lesions, erosions or desquamation of vulval and vaginal mucosae require timely therapeutic measures for preservation of vulval architecture in order to minimize vaginal stenosis. Cases of women with undiagnosed lichen planus undergoing inappropriate vulvovaginal surgery are not uncommon. OLP is an immune-mediated inflammatory condition, and any surgical approach should not be entertained until attempts to control the disease medically have been exhausted.

In up to 5% of OLP patients three or more sites are involved. In addition to the genital region, potential locations include skin, conjunctival mucosa, ears, scalp (causing alopecia), nails, and esophagus (causing dysphagia). All these associations will be revealed by a good medical history.

Diagnosis

Although OLP is a common disease, its diagnosis can be challenging due to overlapping clinical as well as histopathologic features with other oral conditions. Papules or reticular components have to be present in order to establish a correct clinical diagnosis. These pathognomonic components may exist together with plaque-like, erythematous, or ulcerative lesions. In patients with gingival erythematous lesions, it may be difficult to find striae or papules. A biopsy is usually required for an accurate diagnosis of this type of OLP and indeed for all cases of OLP, except those that have a low disease severity score, both to confirm the diagnosis and to exclude any early dysplasia. It is important that the biopsy is taken as far as possible from the gingival pocket to avoid inflammatory changes due to periodontal disease.

Conditions that need to be considered in a differential diagnosis for OLP include oral lichenoid lesions (see later). There are reactions to dental restorative materials, mainly amalgam, called oral lichenoid contact reactions (OLCR), which are frequently encountered; and drug reactions to medications, called oral lichenoid drug eruptions (OLDE), which are very rare although strongly represented in textbooks and literature. They both are likely to represent type IV immune delayed hypersensitivity reactions.

OLP can often be clinically separated from OLCRs to dental materials, which are most often detected on the buccal mucosa and the lateral borders of the tongue. OLP, on the other hand, usually displays a more general involvement. OLP is universally bilateral and frequently symmetrically distributed on oral mucosa, while OLCR is in close topographic contact with dental material and usually unilaterally present.

OLDEs have been reported to have similar histopathologic characteristics as OLP. The patient's disease history may give some indication as to which drug is involved, but OLP may not start when the drug is first introduced. Withdrawal of the drug and rechallenge are the most reliable ways to diagnose OLDEs, but may not be possible to carry out. OLP should also be distinguished from oral chronic graft-versus-host disease (GVHD) and discoid and systemic lupus erythematosus (DLE and SLE, respectively), and the medical history normally will guide the diagnosis.

Oral GVHD has the same clinical appearance as OLP, but the lesion is usually more generalized. The lichenoid reactions are frequently seen simultaneously with other characteristics, such as xerostomia and the presence of localized skin involvement and liver dysfunction, even if an oral lichenoid reaction may emerge as the only clinical sign of GVHD (see later).

DLE shows white radiating striae, sometimes resembling those of OLP but with a brush border of short striae. The striae present in DLE are typically more prominent, with a more marked hyperkeratinization, and may abruptly terminate against a sharp demarcation (Figure 4-39). Histopathologic criteria for lupus erythematosus (LE) have been reported to discriminate against OLP with a sensitivity of 92% and a specificity of 96% (see "Diagnosis" in the "Lupus Erythematosus" section). Direct immunofluorescence for IgM on biopsies of the clinically normal oral mucosa (lupus band test) may also be used, although it is only positive in about 45% of SLE cases.

Several other conditions need to be included in differential diagnosis of OLP. Erythematous OLP of the gingiva exhibits a similar clinical presentation to MMP. Thus, in cases of desquamative gingivitis, MMP should also be suspected. In pemphigoid lesions, the epithelium is easily detached from the connective tissue by a probe or a gentle searing force (Nikolsky's phenomenon). A biopsy for routine histology and direct immunofluorescence are required for an accurate differential diagnosis. Plaque-form OLP can be clinically similar to homogeneous oral leukoplakia, especially from the early stage of PVL (see earlier).

As was discussed in Chapter 3, "Ulcerative, Vesicular, and Bullous Lesions," in more severe ulcerative OLP cases, differential diagnosis should also include MMP and chronic ulcerative stomatitis (a rare condition in which stratified epithelium-specific antinuclear antibodies develop). PV and erythema multiforme may be included in a broader list of differential diagnoses of erosive OLP, but more precise assessment of their clinical features and the acute nature of erythema multiforme will allow even clinical distinction in most cases. Furthermore, the former lesions do not typically appear with reticular or papular elements in the periphery of the ulcerations.

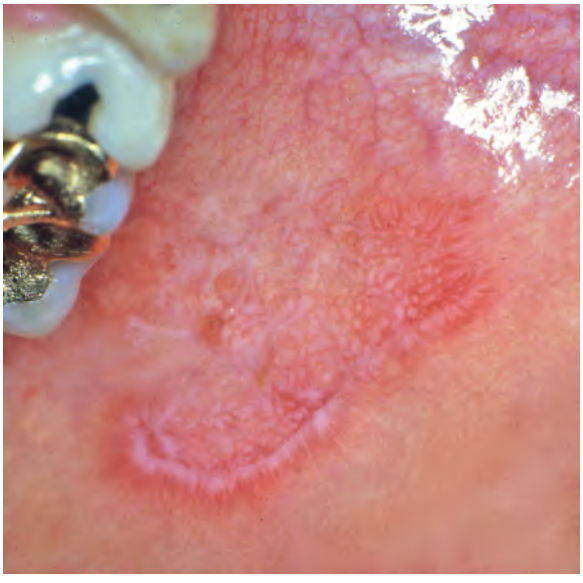

Figure 4-39 Unilateral lesion of discoid lupus erythematosus of the left buccal mucosa showing the typical brush border.

Immunofluorescence is useful in distinguishing lichen planus from the extremely rare chronic ulcerative stomatitis, as well as from vesiculo-bullous immune-mediated diseases. Histopathologic and immunofluorescence investigations combined with finer assessment of clinical presentation provide the most precise diagnosis (see Chapter 5).

Investigations

Routine Investigations

The presence of bilateral white and red areas of mucosa, often with the typical clinical presentation of some reticular and/or ulcerative component, is diagnostic for OLP. However, frequently and in less typical cases, biopsy is needed for histopathologic confirmation. Biopsy is also advised if red lesions persist despite treatment.

The most prominent and important histopathology feature is "interface mucositis" around the basement membrane, characterized by a dense "band-like," predominantly T-lymphocytic subepithelial infiltrate in the lamina propria (upper corium; see Figure 4-27).[58] T lymphocytes from the lamina propria penetrate epithelium and cause apoptosis of epithelial basal cells, which is sometimes described as vacuolar (hydropic) degeneration and lysis of basal cells, seen under a microscope as scattered cytoid (hyaline, colloid) Civatte bodies along the epithelial interface. Eosinophils and fibrin may be seen just beneath the basement epithelial layer covering the lamina propria. The basal epithelium may display "sawtooth" rete pegs, but this feature, although typical for cutaneous lichen planus, is not so frequently present in OLP.

The epithelium shows hyperorthokeratosis and hyperparakeratosis (stratum corneum), often with a thickening of the granular cell layer and acanthosis (thickening of stratum spinosum). In addition, melanin "incontinence" and melanophages also may be seen, especially in postinflammatory hyperpigmentation, but are not specific to OLP.

Depending on the nature of the clinical lesion and the site selected for biopsy, atrophy and ulceration may be seen. However, biopsy samples should be taken from the nonulcerated adjacent full-thickness epithelium, including basement membrane and subepithelial connective tissue, so that pathologic changes around the basement membrane can be identified, which may be lacking if the biopsy is taken from ulcerated areas.

There is very high but not always absolute clinico-pathologic agreement in OLP. Histopathology findings can (1) be confirmatory for clinical diagnosis; (2) be compatible with diagnosis (fitting in its spectrum); or (3) be considered not to have histologic features of OLP. Since pathologic diagnoses should not be made in a vacuum, clinicians must provide the pathologist with all clinical details available including the behavior, site, and size of the lesion, as well as a provisional and differential diagnosis. In the case of a mismatch, the clinical diagnosis prevails, but the case should be more closely monitored and reviewed in the future.

Some pathologists, less experienced in oral and mucosal pathology, may describe the inflammatory changes in OLP as cellular atypia, especially if the sectioning has not been performed perpendicular to the mucosal surface, but the changes only mimic it. Conversely, real cellular atypia in dysplastic and even malignant lesions is sometimes described as "lichenoid." "Interface mucositis" is also seen in oral LE and other lichenoid lesions, complicating histologic interpretation.

Histopathologic examination alone is of modest diagnostic value in the differentiation between OLP and the other four types of oral lichenoid lesions—that is OLCRs, OLDEs, oral lichenoid reactions of GVHD, and oral DLE or SLE—since all five lesions display similar histopathologic features. The diagnosis is dependent on the combination of clinical and histologic features. However, histopathology is a valuable tool when lichenoid reactions are to be discriminated from other mucosal lesions. Explicit guidelines on the necessity of a biopsy to arrive at an accurate diagnosis of OLP have not been universally approved, but most clinicians would accept the need for biopsies when the disease severity is moderate or severe or when the diagnosis is uncertain.

Special Investigations

Direct immunofluorescence (DIF), otherwise essential for vesiculobullous diseases (see Chapter 3), is rarely performed in OLP, as it is nonspecific. However, DIF helps us in differentiating OLP from MMP or PV in cases of desquamative gingivitis, or it can help differentiate OLP from lupus. In OLP, DIF can be positive in about two-thirds of cases. DIF shows accumulation of shaggy fibrinogen along the basement membrane zone (BMZ) and in approximately one-third of cases it reveals granular deposits of IgM, IgA, complement c4, and fibrinogen, corresponding to apoptotic Civatte corpuscles (a consequence of apoptosis and degeneration of epithelial cells due to an autoimmune T lymphocyte reaction). Shaggy deposition of fibrinogen along the BMZ is not restricted to OLP, and can also be seen in other premalignant and malignant oral lesions.

Epicutaneous patch testing can be useful for identifying causative allergens if OLCR is suspected, which can then be avoided. Standard series of allergens (e.g., the European series) ensure consistency of preparations, but training is needed for application, reading, and interpretation of positive results. Skin tests represent delayed (contact) hypersensitivity and are most frequently conducted in dermatology departments. Positive skin tests can be helpful, but lesions may resolve after replacement of dental materials even if the test is negative.

Hematological investigations are sometimes performed in OLP not to make a diagnosis, but to screen for possibly associated systemic diseases, especially hematologic. Since OLP is considered an idiopathic condition, there are no specific hematologic tests to confirm the diagnosis, but deficiency of iron and other hematinics may contribute to exacerbation of symptoms. There are reports of potentially relevant associations between OLP thyroid disease and also hepatitis B or C virus infection. Therefore, liver function tests—aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyl-transpeptidase (GGT)—and thyroid hormones are sometimes performed in OLP patients. However, repeated hematologic investigations are rarely justified.

Photographic records of lesions can be very helpful to assist in the determination of any response to therapy and can become part of the evidence of clinical outcomes (see later).

Management

Current therapies are directed largely against (1) the presumed immune mechanisms using immunosuppressives; (2) the cellular inflammatory response using anti-inflammatories; and (3) reducing or eliminating symptoms.[59]

Careful oral hygiene to reduce biofilm-associated supplementary inflammation is extremely important in OLP patients with symptoms.[60] Therefore, training patients in gentle, careful oral hygiene procedures is recommended. Physical trauma to the gingival tissue should be reduced to avoid pain and exacerbation of gingival lesions.

Preventive therapies are lacking, and no sound strategy at present exists for their development. Pain as a symptom in OLP has a major role in deciding whether to treat or to observe. Typically, the reticular, papular, and plaque-like forms of OLP are asymptomatic, although the patient may experience a feeling of roughness when touched by the tongue or increased sensitivity to spicy or hot foods. However, pain is a very relevant symptom in the ulcerative (erosive) and erythematous (atrophic) forms of OLP. At the mild end of the spectrum, pain appears as burning in contact with irritating agents, acidic, coarse and hot foods and beverages, alcohol, and so on, but intense and persistent pain can be found in the ulcerative forms, directly related to the degree of ulceration. Pain is thus a relevant element in quantification of the intensity of the condition.

The decision about whether to prescribe local or systemic therapy depends on the disease severity, the extent of pain, and the individual patient's needs and ability to cope.

Oral Disease Severity Scoring

Disease severity scoring systems are tools that can help clinicians assess both the severity of objective clinical findings as well as the subjective features of a disease, including its impact on patients' lives. There are three essential aspects that are important in defining the intensity of a disease: (1) a clinical score measuring the level of inflammation, area, and specific clinical features (e.g., ulceration); (2) subjective reporting of pain that the disease is inflicting; and (3) a questionnaire relating to how the condition affects patients' functioning and their lives, or oral health-related quality of life (OHRQoL). There are now several validated and universally used tools for oral diseases that should be used at every patient visit.

It is a sad truism and a reflection on the field that few oral medicine treatments are evidence based, even those regarded as standard therapies. Until the last few years, there had been a lack of any method to routinely assess disease severity and thus of quantifying responses to therapies. This led to the obvious need to devise and validate oral disease severity scores for a variety of conditions seen in routine clinical practice that could also be used for assessing treatment responses.

The benefits of a scoring system for mucosal disease severity are that (1) they can indicate the severity of disease; (2) they are needed to indicate the efficacy of any treatments; (3) they may distinguish between or reveal subgroups of activity; (4) they may assist in deciding to implement or withhold treatment; and (5) they are a routine clinical audit tool that can also be used for research. Any such oral disease scoring system must be objective, reproducible, easy to use, and widely applicable. Fortunately, such scoring systems have been created and validated and are in use for recurrent aphthous ulceration, OLP, pemphigus, MMP, orofacial granulomatosis, and dry mouth assessment.

Oral Disease Severity Score for Oral Lichen Planus

The Oral Disease Severity Score (ODSS) is a comprehensive oral scoring system previously validated for OLP (Figure 4-40).[61,62] In the ODSS, the oral cavity is divided into 17 sites. These sites include outer and inner lips, buccal mucosae, soft and hard palates, oropharynx, floor of the mouth, and the gingivae in sextants. Each site receives a *site score* of 1 if disease is present, with larger sites such as the buccal mucosa, tongue, and palate being doubled if greater than 50% of the area is involved or if lesions are bilateral. An *activity score* between 0 and 3 is assigned to describe the severity of disease at each site, for example no activity = 0 (keratosis only), mild inflammation (erythema or healing areas) = 1, marked erythema = 2, and ulceration = 3. If the site score is 2 (i.e., affecting >50%), the activity score is doubled. A *pain score* (subjective score provided by the patient between 0 and 10) is then added to provide the *total score*. The theoretical maximum total score is 106; however, more than 95% of patients have scores between 0 and 60, representing a clinical range from remission to severe disease. The ODSS takes an average of 90 seconds to complete.

OLP is not only the most common oral mucosa disease affecting approximately 1–2% of the adult population at any one time, but can also present in a wide variety of clinical appearances. The ODSS or any scoring system needs to be able to embrace this wide variety of appearances. The 17 individual sites are examined and assessed for the presence of disease, the disease severity at each site, along with a subjective pain score, and these three scores give an overall ODSS for lichen planus (Figure 4-40). Different clinical phenotypes appear to be relatively consistent over many years and clinical photographs form an additional tool for recording outcomes (Figure 4-41).[63]

Pain Score

The most widely used tool for pain is the numeric pain rating scale (NPRS), which lets the patient subjectively relate their current perception of pain on a scale from 0 to 10, if 0 is "No pain" and 10 represents "Worst imaginable pain." Similar, and perhaps more sensitive, is the visual analogue scale (VAS), which is a straight line on a piece of paper, usually 100 mm in length, with only two extremes listed: "No pain" to the left of the line and "Worst imaginable pain" to the right. The patient marks their current pain level on the line with a pen.

Oral Health-Related Quality of Life

OHRQoL is assessed by using validated questionnaires that measure a patient's oral health self-perception of their capability for daily activities.[64] The Oral Health Impact Profile (OHIP-14) is a widely accepted tool in the form of a questionnaire (it is a short version of the original OHIP-49), showing good sensitivity to any improvement of OHRQoL in relation to clinical improvement (e.g., due to treatment). OHIP-14 is the most commonly used instrument for assessing OHRQoL. It should be noted that OHIP is generic for any oral, dental, or denture-related condition that may impair quality of life, and thus it was not intended only for mucosal diseases. An OHRQoL questionnaire specific for oral mucosal diseases would provide more precise and relevant information, as reported by our patients. Therefore, a questionnaire specific for mucosal diseases, the Chronic Oral Mucosal Diseases Questionnaire-15 (COMDQ-15), was recently devised.[65] Patients respond to 15 questions (Figure 4-42) by selecting one of the answers from a 5-point scale (from "not at all" to "extremely"). Scores are then added and may range from 0 to 60.

Both COMDQ-15 and NPRS/VAS are considered valuable tools for quantifying what are called "patient-related outcome measures" (PROMs). It has been observed that the clinical severity of any medical condition and a response to treatment

Site	Site Score	Activity score (0–3), Double if site = 2
L Buccal mucosa <50% = 1, >50% = 2		
R Buccal Mucosa (1 or 2)		
Outer lips (1)		
Inner lips (1)		
Gingivae (1 each segment)		
Lower R (distal)		
Lower central		
Lower L (distal)		
Upper R (distal)		
Upper central		
Upper L (distal)		
Dorsum tongue (1 or 2)		
R lateral tongue (1)		
L lateral tongue (1)		
Floor of mouth (1 or 2)		
Hard palate (1 or 2)		
Soft palate (1 or 2)		
Oropharynx (1 or 2)		

Activity Score

- 0 = keratosis only
- 1 = mild erythema. (e.g., on gingivae, papillae only, or less than 3 mm along margins)
- 2 = marked erythema (e.g., full thickness on gingivae, extensive with atrophy, or edema on nonkeratinised mucosa)
- 3 = ulceration at this site

Site score

- 0 if no lesion at site
- 1 if less than 50% of area affected,
- 2 if greater than 50% of area affected. Not defined anatomically

Pain score

- Analogue scale from 0 (no discomfort) to 10 (unbearable pain).

Figure 4-40 Oral disease scoring for site and activity elements for oral lichen planus. The Oral Disease Severity Score for an individual patient visit is the sum of sites, activity at each site, and a pain score. Site score = 1 for each site affected, 2 for large sites. Activity score = 0–3 at each site. Pain = average pain over last week, from 0 (no discomfort) to 10 (unbearable/the most severe pain imaginable). *Source:* Reproduced with permission from Challacombe SJ, McParland H, Proctor G, et al. How cross-disciplinary research has increased our understanding of oral mucosal diseases. In: Meurman JH (ed.), *Translational Oral Health Research*. Berlin: Springer International; 2018: 1–12.

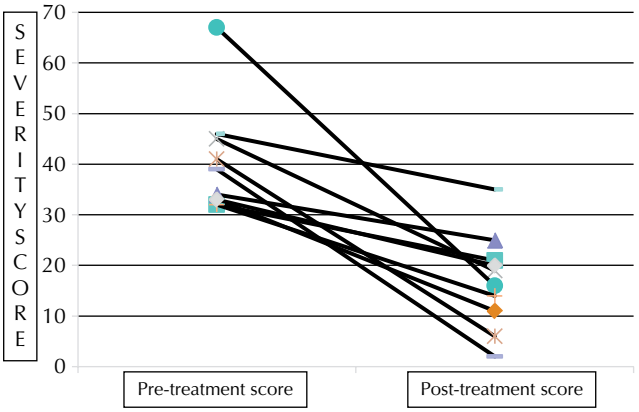

Figure 4-41 Example of an Oral Disease Severity Score (ODSS) of oral lichen planus (OLP) before and after treatment with mycophenolate in 10 vulvovaginal-gingival-OLP patients. Total ODSS for each patient before and after treatment includes disease activity, sites affected, and pain score. *Source:* Reproduced with permission from Wee J, Shirlaw PJ, Challacombe SJ, Setterfield JF. Efficacy of mycophenolate mofetil in severe mucocutaneous lichen planus: a retrospective review of 10 patients. *Br J Dermatol*. 2012;167:36–43.

does not always reflect a patient's subjective feeling. Thus, the addition of complementary PROMs in the assessment of the complexity of diseases is a mandatory part of a responsible clinical approach. Additionally, it is valuable feedback information on our therapeutic approaches.

Treatment

Treatment depends on the severity of the case and on the mucosal area involved. Most cases of OLP are not symptomatic and do not require active treatment. The area affected by hyperkeratosis may increase over time, but as long as there is no pain, only reassurance and regular follow-up are needed. Explanation of the condition along with information leaflets is important for wellbeing and for future compliance with follow-up. Patients need to understand that treatment is not curative, but rather serves to alleviate the inflammation and symptoms when needed, and that it may take even a week before response to therapy is observed. Additionally, patients must comprehend that the condition is chronic and that

Chronic Oral Mucosal Disease Questionnaire-15 (COMDQ-15)

Instructions: Please answer the following questions by ticking one of the following boxes for each.

Physical discomfort	**Not at all**	**Slightly**	**Moderately**	**Considerably**	**Extremely**
How much do certain *types of food/drink* cause you discomfort (spicy food, acidic food)?	0	1	2	3	4
How much do certain *food textures* cause you discomfort (rough food, crusty food)?	0	1	2	3	4
How much does the *temperature of certain foods/drinks* cause you discomfort?	0	1	2	3	4
How much does your oral condition lead to discomfort when *carrying out your daily oral hygiene routine* (brushing, flossing, mouthwash usage)?	0	1	2	3	4
How much do you feel you *need medication* to help you with activities of daily life (talking, eating etc.)?	0	1	2	3	4
Medication and Treatment					
How concerned are you about the possible *side effects of the medications* used to treat your oral condition?	0	1	2	3	4
How much does it frustrate you that there is *no single standard medication* to be used in your oral condition?	0	1	2	3	4
How much does *the use of the medication limit* you in your *every day life* (routine / the way you apply or take your medications)?	0	1	2	3	4
Social and Emotional					
How much does your oral condition get you *down*?	0	1	2	3	4
How much does your oral condition cause you *anxiety*?	0	1	2	3	4
How much does the *unpredictability* of your oral condition bother you?	0	1	2	3	4
How much does your oral condition make you *pessimistic about the future*?	0	1	2	3	4
How much does your oral condition *disrupt social activities* in your life (social gatherings, eating out parties)?	0	1	2	3	4
Patient Support					
How satisfied are you with the *level of support and understanding* shown to you by *family* regarding this oral condition?	4	3	2	1	0
How satisfied are you with the *level of support and understanding* shown to you by *friends/work colleagues* regarding your oral condition?	4	3	2	1	0

Figure 4-42 Chronic Oral Mucosal Diseases Questionnaire-15. *Source:* Reproduced with permission from Wiriyakijja P, Porter S, Fedele S, et al. Development and validation of a short version of Chronic Oral Mucosal Disease Questionnaire (COMDQ-15). *J Oral Pathol Med.* 2020;49(1):55–62.

long-term treatment or follow-up is sometimes necessary. Patients with symptomatic OLP will usually require active treatment, but if mild then the question of whether to treat or not may depend on whether symptoms are induced only while eating (see Figure 4-42).

Topical Treatment

Several topical drugs have been suggested, including steroids, calcineurin inhibitors (cyclosporine and tacrolimus), retinoids, and ultraviolet phototherapy. Among these, topical steroids (ointment, adhesive paste, gel, spray, or rinse) are widely used and accepted as the primary treatment of choice (Figure 4-43). Although systematic reviews of treatment modalities for OLP have not strongly confirmed several accepted standard therapies, OLP can usually be very successfully treated.[66–68] There is an evidence base for significant reduction in disease severity (reducing and stopping pain) using high- or moderate-potency topical corticosteroids (e.g., clobetasol propionate, fluocinonide, betamethasone, and triamcinolone acetonide).[66]

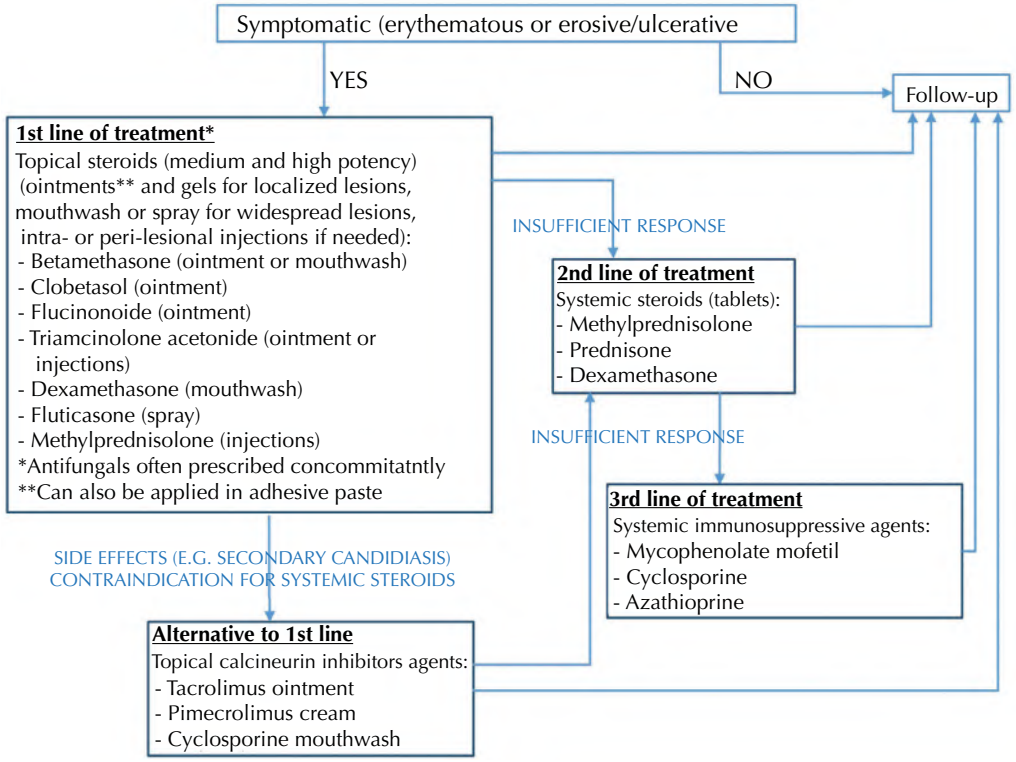

Figure 4-43 Algorithm for the management of oral lichen planus. Treatment is dependent on symptoms, the oral disease severity score, and previous response to therapy.

Although no systematic studies have compared different frequencies of application, a reasonable approach may be to apply the drug two to four times a day for one to two months, followed by tapering during the following eight weeks until a maintenance dose of two to three times a week is reached. For specific lesions, treatment with betamethasone dipropionate 0.5 mg/g ointment or triamcinolone acetonide 1 mg/g in adhesive paste or steroid sprays is appropriate. For more widespread lesions, betamethasone mouthwash is more useful. Adhesive pastes consisting of pectin, gelatin, and carboxymethyl cellulose containing topical steroids (e.g., triamcinolone) have been formulated for use on moist oral mucosal surfaces. Ointments containing steroids can also be effective, but as they are hydrophobic they require drying of the mucosal surface before application.

It should be noted that extended application of topical steroids to mucosa does not appear to result in adrenal suppression. However, since OLP is a chronic condition with alternating episodes of remissions and flare-ups, patients can self-regulate according to symptoms. In more severe rare cases, corticosteroids may need to be regularly applied over several months. In the absence of considerable clinical improvement after four weeks (e.g., marked pain reduction and significant reduction in severity score), higher-potency topical corticosteroid clobetasol propionate 0.5 mg/g ointment can be applied twice a day, and only occasionally three times a day. Gingival OLP lesions appear to be more resistant to treatment, and if there is no response to improved oral hygiene[60] clobetasol is usually the first line of topical therapy. However, no randomized clinical trials exist where different formulas, strengths, and classes of topically applied steroids have been compared. In the case of widespread lesions, dexamethasone 0.5 mg/5 mL rinse can be applied three times a day for three minutes, gradually decreasing the number of applications following the improvement as already described.

Topical application of cyclosporine and tacrolimus has been suggested as a substitute topical therapy in OLP patients who develop candidiasis regardless of antimycotic therapy. Cyclosporine has been reported to be less effective than clobetasol propionate and not significantly better than 1% triamcinolone paste. No adverse effects related to these two drugs have been reported, except for a temporary burning sensation following the use of cyclosporine. Topical tacrolimus 0.1% ointment has been reported to have a better initial therapeutic response than triamcinolone acetonide 0.1% ointment.[69–71] However, there are concerns about extended use of tacrolimus in OLP due to the increased risk of malignancy (squamous cell carcinoma and lymphoma).[72] These agents should therefore be used in limited circumstances,

and patients made aware of such concerns.[73] Current data are reassuring and show acceptable safety for short-term use of tacrolimus or pimecrolimus.[74,75]

In conclusion, topical steroids should be used as the primary therapeutic choice for symptomatic OLP (see the algorithm for OLP treatment in Figure 4-43). Cyclosporine may be considered a second choice, although the efficacy has been questioned. Tacrolimus should only be used by experts when symptomatic OLP lesions are recalcitrant to topical steroids or cause side effects related to the use of steroids. Relapses are common, and the general approach should be to use steroids at the lowest level to keep the patient free of symptoms. This approach necessitates an individual amendment of the steroid therapy to each patient. When potent topical steroids are used, a fungal infection may emerge, and a parallel treatment with antifungal drugs may be necessary when the number of applications exceeds one a day; antifungal treatment itself may result in significant improvement of symptoms and clinical features. Since half of OLP lesions exhibit candidal infection, antifungal treatment may be used concurrently with steroids. More routine assessment of outcome measures using disease severity scoring would enable a more robust evidence base for many of the therapies discussed.

Systemic Therapy

Although topical steroids are usually able to keep OLP patients free of symptoms, systemic steroids are justified to control symptoms from recalcitrant lesions. A dose of 0.5–1 mg/kg prednisolone daily for seven days has been suggested, followed by a reduction of 5 mg each subsequent day. A maintenance dose with topical steroids may be commenced during tapering of systemic steroids.

However, before switching to systemic steroids, the use of peri- or intralesional steroids should be considered. Usually, 0.2–0.5 mL of 40 mg/mL methyl prednisolone or triamcinolone suspension is injected around and under the erosive lesion of OLP. This treatment is usually a sufficient supplement to regain control of OLP with topical steroids, even if performed once, but can be occasionally repeated (weekly or bi-weekly) if required.[76] Mycophenolate mofetil or azathioprine can be used in very severe OLP or in VVG syndrome, as seen in Figure 4-41.

Erythematous (desquamative) OLP of the gingiva constitutes a therapeutic challenge. It is critical to remove both sub- and supragingival plaque and calculus (Figure 4-31). If microbial plaque–induced gingivitis is present, it seems to work in concert with gingival lichen planus and make the latter more resistant to pharmacologic treatment. Thus, oral hygiene should be optimized together with commencement of steroid treatment. Some patients experience a decrease in or even elimination of symptoms with oral hygiene and steroid treatment is no longer necessary. If symptoms persist, steroid gels in prefabricated plastic trays may be used for 30 minutes at each application to increase the concentration of steroids in the gingival tissue.

As part of OLP lesions, ulcerative areas may be found in close contact with dental materials, similar to what is observed in OLCRs. This only accounts for cases in which amalgam restorations are in direct contact with lesions, but not in those where OLP lesions were not in close contact with the restorations. When symptomatic ulcerations of this kind are present as part of the OLP lesion, replacement of the dental material, usually amalgams, may convert a symptomatic to a nonsymptomatic lesion.

Prognosis

Patients have periods of remission and exacerbation. These may correspond to psychologic factors and stress levels, but the topic is not well investigated. There have been few very long-term follow-up studies of OLP, but those that have been done suggest that a proportion of OLP "burn out" and turn into leukoplakia-like lesions without underlying mucosal inflammation.

OLP is considered to be a potentially premalignant disorder with an increased risk of malignant transformation at some site of the oral mucosa, not necessarily associated with a preexisting lesion (Figure 4-44). It is widely accepted that patients with OLP are predisposed to develop oral carcinomas. A recent systematic review pooled 7806 OLP patients from 16 follow-up studies on the risk of malignant transformation in OLP.[77] The mean was 0.4% per year, with a wide variation (0.03% to 1.3%) against age-matched controls of 0.02% per year. Patients thus need to be realistically informed about a small but increased risk of developing oral carcinoma. No clear relationship with the clinical phenotype has emerged, and the site as well as the severity appears to be important.

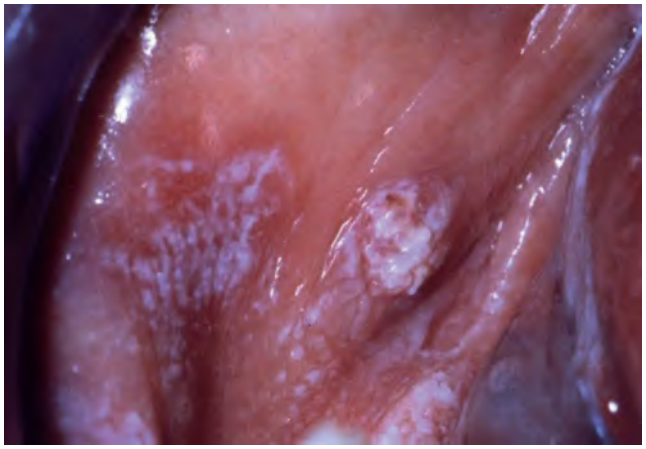

Figure 4-44 An exophytic squamous cell carcinoma developed in reticulo-papular oral lichen planus in the right buccal mucosa. The contralateral side showed only lichen planus.

We cannot clinically or histologically predict the malignant potential of any particular OLP case. Long-lasting inflammation of OLP may lead to secondary cellular atypia, which might be histopathologically interpreted as mild to moderate dysplasia. There is a quest for the discovery of molecular markers that would ideally help identify the premalignant nature of a lesion before the development of the corresponding clinical and pathologic alterations. With such information, we would be able to select patients who would undergo closer follow-up for secondary prevention. Many specific molecular features of OLP are being studied as potential markers for increased risk of malignant transformation. Among them, genetic (p53 mutation), epigenetic (DNA methylation, histone modification, miRNAs), and cytogenetic (loss of heterozygosity) occurrences were postulated and are still being investigated.[78] There is no current reliable risk marker for malignant transformation of OLP. While DNA aneuploidy (i.e., abnormal genetic content in the form of changes in chromosome number and structure) might be a promising predictor for oral lesions in a broader sense, it is rarely observed in OLP tissues and is not a consistent predictor of a lesion's behavior. Nevertheless, when DNA aneuploidy is performed on "high-risk" OLP lesions, around a third with positive findings will develop oral cancer.

Albeit the risk for patients with OLP of contracting oral squamous cell carcinomas is low (0.4% per annum), a minimum of annual monitoring has been suggested in conjunction with routine dental examination by the general dental practitioner. For patients with symptomatic OLP, examination for malignancies will be a part of treatment. In countries with limited healthcare resources, it may be difficult to conduct annual monitoring, but at the time of diagnosis, patients need to be properly educated on the malignant potential of OLP.

Oral Lichenoid Drug Eruptions

Etiology and Pathogenesis

In certain individuals, it has been reported that OLDE develops secondary to the use of medications. The mechanisms behind OLDEs are poorly understood. As the clinical and histopathologic appearances resemble a delayed hypersensitivity reaction, it has been hypothesized that drugs or their metabolites, with the capacity to act as haptens, trigger a lichenoid reaction. Penicillin, gold, NSAIDs, and sulfonamides are examples of drugs that have been related to the development of OLDEs. However, sulfonamides are much more relevant as a factor behind the development of erythema multiforme (see Chapter 5). Penicillin and gold may bind directly to self-proteins, which will be presented by antigen-presenting cells (APCs) and perceived as foreign by specific T lymphocytes, similar to a delayed hypersensitivity reaction. Drugs such as sulfonamides haptenate self-proteins indirectly, through the formation of reactive metabolites, which will covalently bind to proteins present in the oral mucosa.[79] It has been postulated that OLDEs may result from poor drug metabolism because of genetic variation of the major cytochrome P-450 enzymes.

Epidemiology

No prevalence figures are available for OLDEs; most likely, they are unusual and constitute a minority of cases. Some recent publications have questioned their existence, due to an extremely low occurrence and because only case reports are available.[80]

Clinical Findings

Our knowledge about oral OLDEs is limited and primarily based on case reports. It has been suggested that OLDEs are predominantly unilateral and present with an ulcerative reaction pattern. These characteristics are far from consistent and not useful to discriminate between OLP and OLDEs (Figure 4-45A). At present, OLDEs are often clinically indistinguishable from OLP[81] with hyperkeratotic striations and an erythematous base. They are frequently found in the form of a single oral lesion and are often unilateral. However, many oral drug reactions, such as nicorandil and lingual ulceration, do not present with any obvious lichenoid component. The history of any temporal relationship between taking medications and clinical manifestations is of paramount importance diagnostically.

Diagnosis

Although diagnostic testing methods exist, in general they are of limited clinical value. One major problem that affects the use of diagnostic tests for drug hypersensitivity is that the immune pathogenesis for most drugs, except for penicillin and gold, is virtually unknown. To be clinically classified as an OLDE, the oral lesions should comprise a white reticulum or papules. These characteristics may be observed concurrently with erythematous and ulcerative lesions. OLDEs are often a diagnostic challenge, as the condition has been associated with a large number of drugs (Table 4-11). A correct diagnosis is easier to establish when a patient develops OLDE after starting a new drug (see Figure 4-45A). Discontinuation of the offending substance is the mode of treatment and also of confirming the diagnosis. For practical reasons, it is difficult to conduct withdrawal unless a patient has a severe symptomatic case. An OLDE may not develop for several months after a new drug is started. It may also take several weeks before an OLDE disappears following withdrawal (Figure 4-45B). The delay between exclusion of the offending drug and regression of the lesion indicates that the molecule has sensitized the epithelium, which may persist regardless of drug withdrawal.

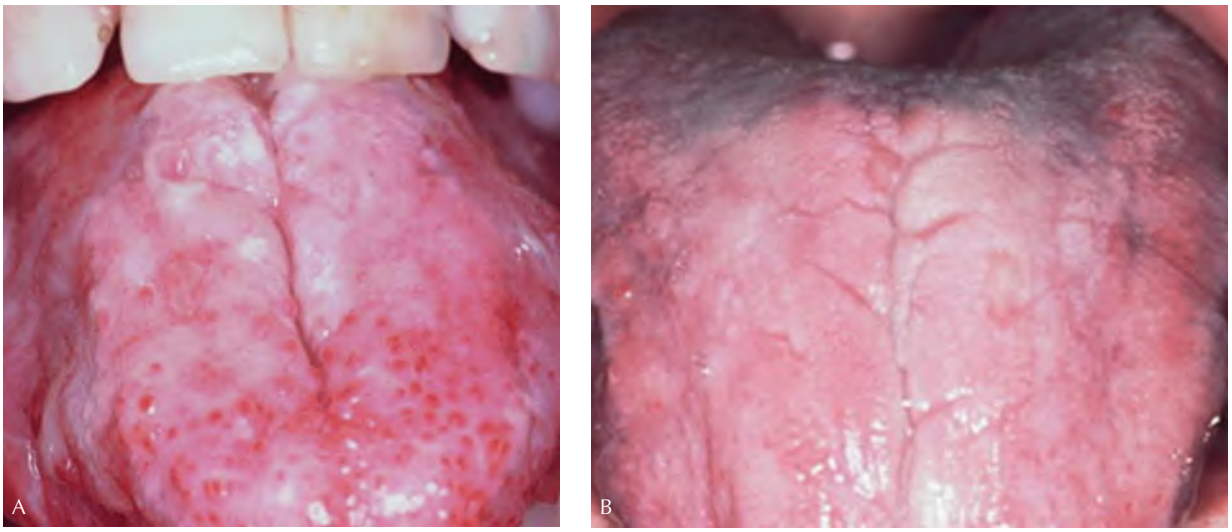

Figure 4-45 (A) Drug-induced lichenoid reaction at the dorsum of the tongue following one month of medication with a cholestyramine-containing drug. (B) Three weeks following withdrawal of the drug.

Table 4-11 Examples of drugs which have been associated with lichenoid reactions.

Angiotensin-converting enzyme inhibitors
Allopurinol
Antimalarials
Barbiturates
Chlorpropamide
Colchicine
Dapsone
Gold
Hydroxychloroquine
Metformin
Nonsteroidal anti-inflammatory drugs
Penicillamine
Phenothiazines
Phenylbutazones
Phenytoin
Propranolol
Protease inhibitors
Sulfonamide
Tetracyclines

Management

Discontinuance of the drug and symptomatic treatment with topical steroids would be sufficient. The patient should be properly educated about the responsible drug to prevent future OLDEs. Altering medication regimen requires communication with the patient's physician. Nevertheless, if a patient has idiopathic OLP and happens to take one of the allegedly lichenoid reaction-causing medications, we might needlessly try to substitute a suspect medication.

Lichenoid Reactions of Graft-versus-Host Disease

Etiology and Pathogenesis

The major cause of GVHD is allogeneic hematopoietic cell transplantation, even if an autologous transplant may also entail GVHD. In GVHD, it is the transplanted immunocompetent tissue that attempts to reject the tissue of the host. As a first step, conditioning of the host by chemotherapy and radiation will generate host cell damage, release of cytokines, and upregulation of adhesion and MHC molecules, which all facilitate recognition of alloantigens by donor T lymphocytes. A second step comprises an interaction between the recipient's APCs and the donor's T lymphocytes, which will perceive the histocompatibility antigens, expressed by APCs as foreign. This interaction may in fact be considered as the donor T lymphocytes recognizing the recipient's APCs as self-APCs expressing non-self-peptides. This interaction resembles the interaction between autoreactive T lymphocytes and APCs, hypothesized to play a role in the development of OLP. In a third step, the inflammatory cascade that follows the APC–T lymphocyte reaction will stimulate the proliferation of stromal cells, resulting in clinical features compatible with a lichenoid reaction.[82]

Epidemiology

Chronic GVHD occurs in 15–50% of patients who survive three months after transplantation and varies in incidence

from 33% of human leukocyte antigen (HLA)-identical sibling transplants to 64% of unrelated donor transplants. The risk for GVHD increases with the age of the marrow recipient. Chronic GVHD is defined as occurring more than 100 days post hematopoietic stem cell transplantation (HSCT), most commonly as a transition from acute GVHD. In 20–30% of patients, chronic GVHD may occur de novo.

Clinical Findings

Oral lichenoid reactions as part of GVHD may be seen both in acute and chronic GVHD, although the latter are more often associated with typical lichenoid features. The clinical lichenoid reaction patterns are indistinguishable from what is seen in patients with OLP—that is, reticulum, erythema, and ulcerations—but lichenoid reactions associated with GVHD are typically associated with a more widespread involvement of the oral mucosa (Figure 4-46).

Extraoral Clinical Manifestations

The skin lesions often present with a pruritic maculopapular and morbilliform rash, primarily affecting the palms and soles. Violaceous scaly papules and plaques may progress to a generalized erythroderma, bulla formation, and, in severe cases, a toxic epidermal necrolysis–like epidermal desquamation.[83]

Diagnosis

The presence of systemic GVHD facilitates the diagnosis of oral mucosal changes of chronic oral GVHD. However, the oral cavity may, in some instances, be the primary or even the only site of chronic GVHD involvement. Lichenoid eruptions are important in the diagnostic process of oral GVHD and have the highest positive predictive value of all reaction patterns. It is not possible to distinguish between OLP and oral GVHD based on clinical and histopathologic features. Although oral chronic GVHD is both clinically and histologically strikingly similar to OLP, a positive medical history of previous allogeneic HSCT will remove any doubt—that is, if the clinician asks the proper questions.

Management

The same treatment strategy as for OLP may be used for chronic oral GVHD; that is, topical steroid preparations, such as fluocinonide and clobetasol gel, or topical tacrolimus ointment or rinse. Intensive dexamethasone rinse (0.5 mg/5 mL) showed favorable results in a recent trial.[84] Opportunistic infections such as candidiasis should always be considered in immunosuppressed patients. The development of secondary malignancies has been recognized as a potentially serious complication of GVHD. Patients with a history of oral GVHD should therefore be examined for oral malignancies as part of the medical follow-up procedure.

Lupus Erythematosus

Etiology and Pathogenesis

LE represents the classic prototype of an autoimmune disease involving immune complexes. Both the natural and the adaptive parts of the immune system participate, with the latter involving both B and T lymphocytes.[85,86] Environmental factors are of importance such as sun exposure, drugs, chemical substances, and hormones, which all have been reported to aggravate the disease. A genetic predisposition is supported by an elevated risk for siblings to develop LE and by an increased disease concordance in monozygotic twins. More than 80 different drugs have been associated with the onset of SLE, including hydralazine, methyldopa, chlorpromazine, isoniazid, quinidine, and procainamide.[87]

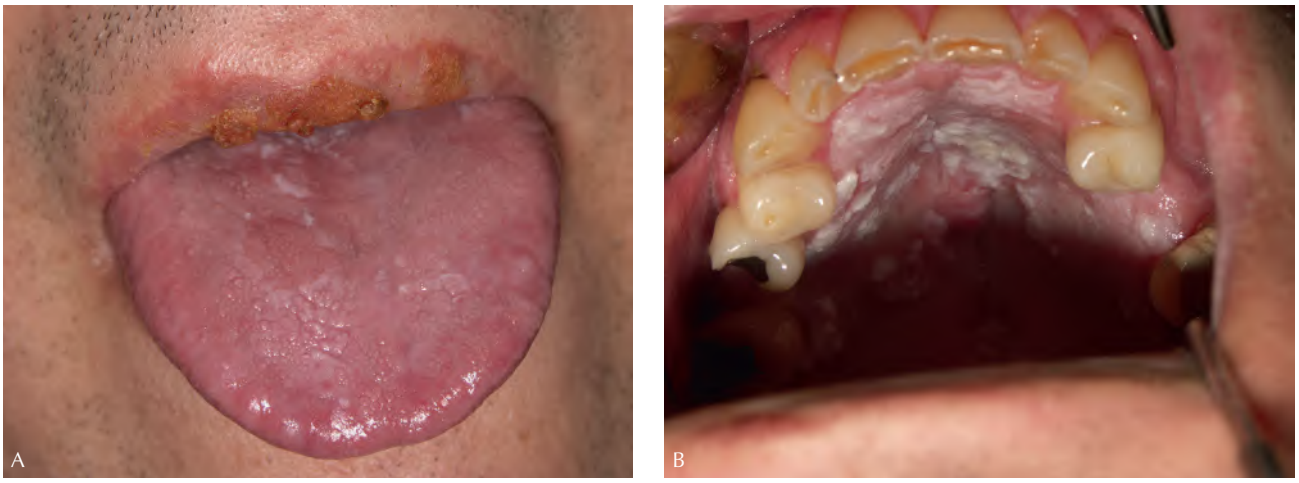

Figure 4-46 Oral manifestations of graft-versus-host disease. (A) Irregular depapillation of the dorsusm of the tongue with apparently keratotic patches; and (B) nonremovable white patches of the hard and soft palate in the same patient.

Epidemiology

SLE predominantly affects women of reproductive age, and the prevalence decreases during the menopause. In the interval of 20–40 years, as much as 80% of cases have been reported to be women.[88] This predominance has lent support to the involvement of hormones in the pathogenesis of LE, as well as the fact that the disease can be precipitated by hormonal drugs. There are large variations in the distribution of the disease between different ethnic groups. In the United Kingdom, the prevalence of SLE among Asian individuals is 40 per 100,000; for Caucasians, it is 20 per 100,000 individuals.

Clinical Findings

The oral lesions observed in SLE and DLE are similar in their characteristics, both clinically and histopathologically.[89] The typical clinical lesion comprises white striae with a distinctive radiating orientation, and these may sharply terminate toward the center of the lesion, which has a more erythematous appearance (see Figure 4-39). However, several clinical manifestations of oral LE exist. The most affected sites are the hard palate (Figure 4-47A), buccal mucosa (Figure 4-47B), and gingiva. The tongue also can be involved. Lesions in the palatal mucosa can be dominated by erythematous lesions, and white structures may not be observed (Figure 4-48). Oral mucosa lesions compatible with LE may be the first sign of the disease. Approximately 20% of patients with LE have been reported to display oral lesions, although the figures vary from 9% to 45%.

Clinical Manifestations

The classic categorization of LE into SLE and DLE has during recent years been supplemented with acute cutaneous LE and subacute cutaneous LE.[90] SLE may also occur in concert with other rheumatologic diseases such as secondary Sjögren's syndrome and mixed connective tissue disease. An SLE diagnosis requires that four or more of the diagnostic criteria displayed in Table 4-12 should be present at each time point of the disease. The typical DLE diagnosis comprises well-demarcated cutaneous lesions with round or oval erythematous plaques with scales and follicular plugging. These lesions may form butterfly-like rashes over the cheeks and nose, known as a malar rash. The typical oral DLE lesion is a well-demarcated lesion with a mixed center and with a brush border of fine striae around the lesion (Figure 4-39). They are usually asymmetric or scattered, in contrast to OLP.

Laboratory Findings

Antinuclear antibodies are frequently found in patients with SLE and can be used to indicate a systemic involvement, but patients with other rheumatologic diseases, such as Sjögren's syndrome and rheumatoid arthritis, may be positive as well. Moderate to high titers of anti-DNA and anti-Smith antibodies are almost pathognomonic of SLE.

Pathology

The clinical picture of LE varies, which also is reflected in the histopathology. Variable histopathology is depending on the duration and mucosal site, but the pattern overlaps with OLP and other lichenoid lesions, causing it to be very challenging to differentiate between them. Some distinction may be represented by more common histopathologic features of LE: (1) hyperkeratosis with keratotic plugs; (2) atrophy of the rete processes; (3) deep inflammatory infiltrate; (4) edema in the lamina propria; and (5) thickening of basement membrane, which may show patchy or continuous periodic acid–Schiff (PAS)-positive deposits. Perivascular infiltrate may be present.

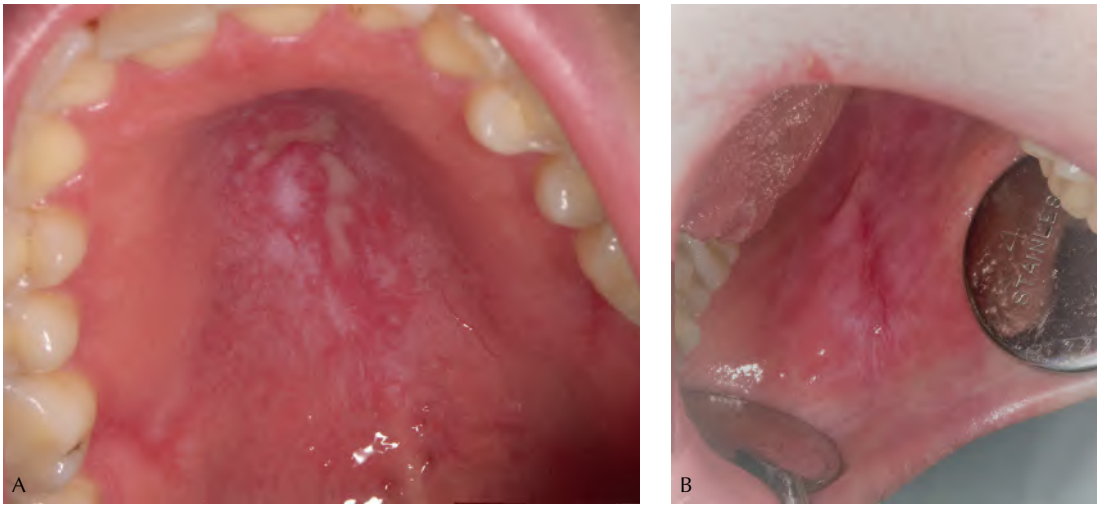

Figure 4-47 Discoid lupus erythematosus lesions in (A) the palate and (B) the left buccal mucosa in the same 47-year-old female. The pale lesions are a mixture of irregular ulcers and white patches with a keratotic appearance.

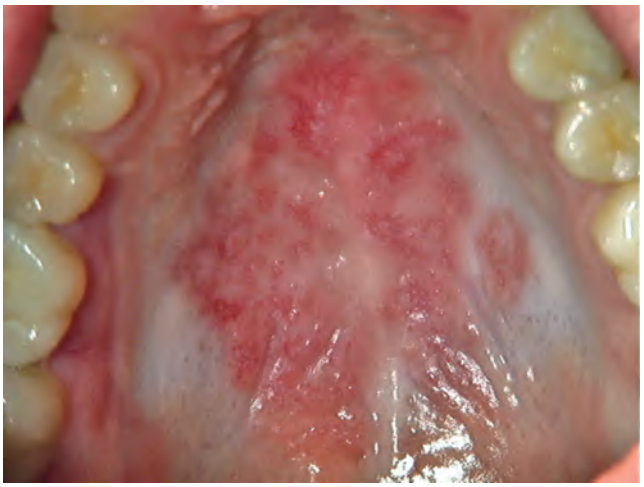

Figure 4-48 Systemic lupus erythematosus oral lesions on the hard palate showing irregular erythematous patches.

Table 4-12 American college of rheumatology criteria for systemic lupus erythematosus.*

1	Malar rash
2	Discoid lesions
3	Photosensitivity
4	Presence of oral ulcers
5	Nonerosive arthritis of two joints or more
6	Serositis
7	Renal disorder
8	Neurologic disorder (seizures or psychosis)
9	Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia)
10	Immunologic disorder (anti-DNA, anti-Smith, or antiphospholipid antibodies)

*Systemic lupus erythematosus diagnosis with 4 or more of 10 criteria present at any time.

Diagnosis

Oral mucosal lesions seen in conjunction with different types of LE are clinically and histopathologically indistinguishable. Liquefaction degeneration may also be present, which may result in diagnostic problems in relation to OLP. The criteria mentioned earlier were tested among clinically atypical cases of DLE and the other groups of mucosal lesions, with a sensitivity of 92% and a specificity of 96% against both OLP and leukoplakia for the presence of two or more of the five criteria. DIF of the lesion is conducted to reveal granular, homogeneous, shaggy, lumpy, linear, or fibrillar deposition of IgG, IgA, IgM, and c3 in the BMZ (in all SLE and 70% of DLE cases), unlike in OLP where fibrinogen may be seen there.

Oral LE lesions would respond less rapidly than OLP to the usual topical steroid treatment. This also may be helpful in distinguishing between LE and OLP. If we are having doubts about differential diagnosis between the two and if we do not get a steady improvement following steroid treatment, we should consider LE "ex iuvantibus" (see the "Treatment" section).

A lupus band test is DIF performed on uninvolved skin or mucosa in order to differentiate between SLE and DLE. The extralesional oral mucosa in SLE patients has a positive reaction to IgM in 45% of cases in combination with variable deposits of IgG, IgA, and c3. DLE is accompanied by a positive antibody reaction in as few as 3% of patients.

Management

No randomized clinical trials with acceptable quality considering outcome measures have been conducted in regard to the treatment of oral mucosal LE lesions.[91] The oral lesions may respond to systematic treatment used to alleviate the systemic disease in SLE. Not all lesions are symptomatic, and many do not therefore require topical therapy. When symptomatic intraoral lesions are present, topical steroids may be considered (Table 4-13). It takes much longer and more frequent applications of topical steroids to show improvement of oral LE lesions compared to OLP. Prolonged use over several months is necessary to obtain observable effects. To obtain relief of symptoms, potent topical steroids such as clobetasol propionate gel 0.05% should be used, but also other steroids, such as betamethasone dipropionate 0.05%, fluticasone propionate spray 50 µg aqueous solution,

Table 4-13 Topical therapy for oral lesions of lupus erythematosus.

Topical Steroid Therapy*	Directions for Use†
0.05% fluocinonide gel	Place on affected area(s) 2 times/day for 2 weeks
0.05% clobetasol gel	Place on affected area(s) 2 times/day for 2 weeks
Dexamethasone elixir (0.5 mg/mL)	Swish and spit 10 mL 4 times/day for 2 weeks
Triamcinolone acetonide (5 mg/mL)	Intralesional injection
Topical antifungal therapy (10 mg clotrimazole troches)	Dissolve in mouth 5 times/day for 10 days
Nystatin suspension (100,000 U/mL)	Swish and spit 5 mL 4 times/day for 10 days
Chlorhexidine rinse (0.12%)	Swish and spit 10 mL 2 times/day until lesions resolve

* Fungal infections are a side effect of topical steroids.
† If lesions do not respond appropriately to topical steroids in 2 weeks, consider systemic therapy such as antimalarials, steroids, thalidomide, clofazimine, and methotrexate.
Source: Adapted from Brennan MT, Valerin MA, Napenas JJ, et al. Oral manifestations of patients with lupus erythematosus. *Dent Clin North Am.* 2005;49:127–141.

betamethasone valerate 0.1% cream, or triamcinolone acetonide 0.1% ointment may be used. Calcineurin inhibitors, such as tacrolimus 0.03–0.1% ointment or pimecrolimus 1% cream, showed some efficacy as well.[92] The treatment may begin with applications two to three times a day followed by tapering during the next six to nine weeks. When topical steroids are ineffective, antimalarial drugs are the treatment of choice (hydroxychloroquine has a success rate of 85%). Other immunosuppressive drugs (and their success rates) include azathioprine (59%), dapsone (41%), thalidomide (35%), and pulse steroids (27%).[93] Immunosuppressive drugs used to treat LE may precipitate opportunistic fungal and viral infections. Opportunistic oral infections can also originate from the immunologic defects that are part of the pathogenesis. In SLE, oral mucosal lesions often mirror the disease activity. They may regress spontaneously, but can also persist for months or even years.

ALLERGIC REACTIONS

Oral Lichenoid Contact Reactions

OLCR is considered to be due to a delayed (contact) hypersensitivity reaction to constituents derived from dental materials. The majority of patients, but not all, are patch test positive to mercury (Hg), which lends support to OLCR being allergic in nature. Although Hg is usually considered the primary etiologic factor, other amalgam constituents may also initiate OLCR, and other filling materials such as gold, composites, and glass ionomers may also generate reactions.

Etiology and Pathogenesis

The pathogenesis of OLCR is considered to be a type of delayed hypersensitivity reaction to constituents derived from dental materials, predominantly amalgam fillings. The pathogenesis of OLCR is not fully elucidated, but based on the knowledge of delayed hypersensitivity, the following probably occurs (Figure 4-49). Hg is a hapten and cannot be recognized by T lymphocytes, as the T-cell receptor (TCR) is primarily limited to the identification of peptides. However, Hg ions are highly reactive and may bind to self-proteins of the oral epithelium, which will induce transformation changes of the protein. This assembly between Hg and protein will be perceived as non-self and, following pinocytosis by APCs, such as the Langerhans cells of the oral epithelium, these cells will degrade the protein complex to oligopeptides. The activated APCs will mature through migration to regional lymph nodes and start to express Hg-containing peptides together with class II molecules on the cell surface. Class II molecules represent a subset of glycoproteins derived from the MHC, which is critical for the APC–T lymphocyte interaction. The process of antigen presentation is therefore considered to be class II molecule restricted.

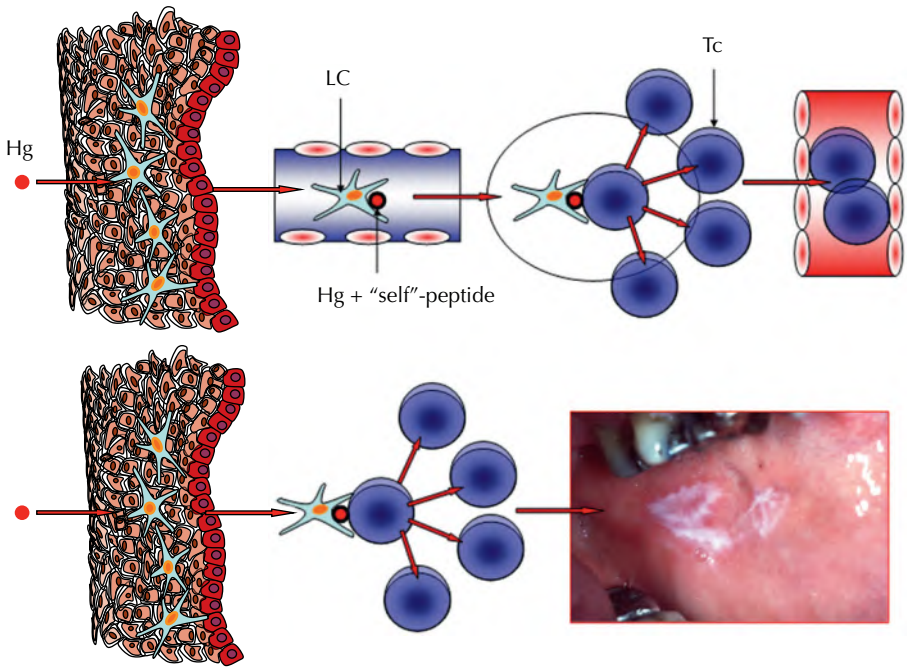

Figure 4-49 Diagrammatic representation of the mechanisms of sensitivity to dental materials leading to lichenoid contact reactions. Mercury ions (Hg) combined with host peptides are presented by Langerhans cells (LC) to cytolytic T cells (Tc). Sensitized Tc cells amplify and in the presence of further Hg^{+} self-peptide cause a localized lesion.

Within the lymph node, an interaction between the assembly of class II molecule–Hg-containing peptide on the APC and the TCR expressed on the antigen-specific T lymphocyte will occur. This interaction is known as the first signal in the antigen-presenting process. The second signal comprises further cellular interactions, which are decisive for the clonal expansion of the Hg peptide-specific T lymphocytes to take place. These cells will migrate into the bloodstream to reach and patrol all peripheral tissues of the body. At this stage, the patient is considered to be sensitized against Hg.

Once the oral mucosa of a sensitized individual is re-exposed to Hg, the Langerhans cells in the oral epithelium are able to present peptide-conjugated Hg to peripheral T lymphocytes with an appropriate TCR. Thus, in a sensitized individual, the Langerhans cells are able to fulfill their mission in situ and do not have to migrate to the regional lymph node to encounter an appropriate T lymphocyte. The interaction between the cells instigates cytokine production, which will lead to the attraction of inflammatory cells necessary to mount a local immune response in the Hg-exposed oral mucosa, and eventually also lead to healing once Hg exposure is eliminated. The cytokine profile produced is most likely responsible for the stimulation of inherent cells of the oral mucosa, which gives rise to the clinical reaction pattern of OLCR.

Epidemiology

No prevalence figures for OLCR have been reported in the literature. The sex distribution seems to be different from OLP, with a higher proportion of women among patients affected by OLCR. No significant differences regarding general diseases, drugs, or history of allergy between OLCR and OLP have been reported.

Clinical Findings

Clinically, OLCR displays the same reaction patterns as seen in OLP; that is, reticulum, papules, plaque, erythema, and ulcers (Figure 4-50). The most apparent clinical difference between OLP and OLCR is the extension of the lesions and proximity to restorations, and the fact that OLCR are asymmetric and usually unilateral, making this a dominant differential distinction.[94] In a case when a patient has silver amalgam fillings bilaterally, and if symmetrically distributed lichenoid reactions develop, it will not be possible to easily discriminate between a lichenoid reaction and idiopathic OLP. Unfortunately, histopathology findings of lichenoid reactions are very similar to those of OLP, and thus performing biopsy for that reason is usually not helpful. The majority of OLCRs are confined to sites that are regularly in contact with dental materials, such as the buccal mucosa and the border of the tongue. Lesions are hardly ever observed in sites as the gingiva, palatal mucosa, floor of the mouth, or dorsum of the tongue. Most OLCRs are asymptomatic, but when erythematous or ulcerative lesions are present, the patient may experience discomfort from spicy and warm food constituents. The duration with which the material is in contact with the oral mucosa has a decisive influence on the development of OLCR. The clinical implication of this is that some lesions, especially those on the lateral border of the tongue, may extend somewhat beyond the direct contact of dental material.

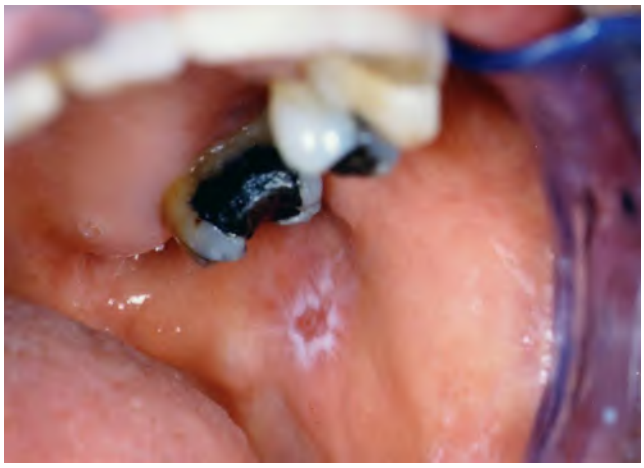

Figure 4-50 Oral lichenoid contact reaction. This lesion in the left buccal mucosa is immediately adjacent to a large amalgam restoration. No other lesions were present and it regressed on replacement of the amalgam.

Lichenoid reactions in contact with composites have been observed on the mucosal side of both the upper and lower lips.[95] The majority of this type of OLCR improve following treatment with chlorhexidine, possibly indicating a role for plaque in exacerbating symptoms. Further studies have to be conducted to substantiate a true lichenoid nature of these lesions.

Diagnosis

There are no dependable investigations that could help discriminate between idiopathic OLP and OLCR. The diagnosis is primarily based on the topographic relationship to dental materials. OLP may display similar characteristics, and clinical improvement after replacement of the culprit dental material may assist to discriminate between OLCR and OLP (Figure 4-51). However, OLP lesions in close contact with amalgam may also improve following the replacement, but to a lesser extent compared to OLCR. Cutaneous patch tests (CPTs), if well done, may be helpful.[96,97] It should be noted that many patients with OLCR may test negative to relevant test compounds, although the lesions may resolve following replacement of the dental material. A CPT may not relate directly to mucosal sensitization, since the concentration of antigen to elicit a positive reaction in the oral mucosa needs

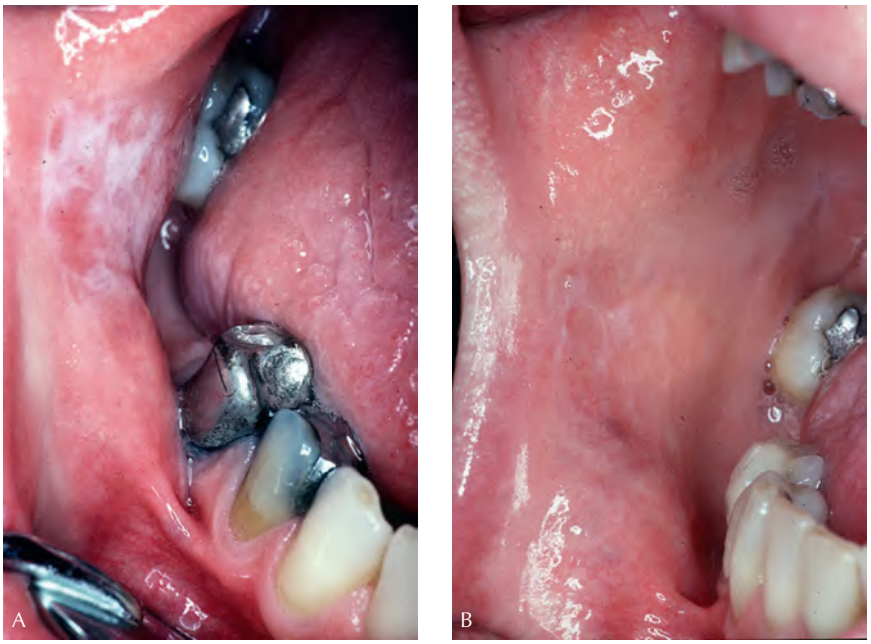

Figure 4-51 (A) Widespread lichenoid reactions in the buccal mucosa and tongue in relation to extensive amalgam restorations. (B) Removal and replacement of the amalgams resulted in almost complete remission of the lesions within three months.

to be 5–12 times higher than in skin.[98] Thus, CPT results, though more sensitive, may not reliably identify patients in whom amalgam replacement will achieve healing of the lesion.[99,100] There are also reported OLCRs to gold and composites, with resolution on their replacement, and to most restorative materials except palladium, titanium, and zirconium. Histopathology will not normally be of much assistance in discrimination between OLP and OLCR, but may be useful in identifying dysplasia and any risk of malignant transformation.

Management

Replacement of dental materials in direct contact with OLCR will result in cure or considerable improvement in at least 90% of cases (Figure 4-51B).[99] Most lesions should be expected to heal within one to two months. There is no need for replacement of restorative materials that are not in direct contact with the OLCR. Healing does not seem to depend on what type of dental material is used for replacement. A malignant potential of OLCR has been suggested in some large case series, but no prospective studies have been conducted to support this hypothesis.[101]

Reactions to Dentifrice and Chlorhexidine

Delayed hypersensitivity reactions to toothpastes (Figure 4-52) and mouthwashes have been reported, but such reactions are rare.[102] The compounds responsible for the allergic reactions may include flavor additives such as carvone and cinnamon aldehyde, eugenol, menthol, or preservatives. These flavoring constituents may also be used in chewing gum and produce similar forms of plasma-cell gingivitis. The clinical manifestations include fiery red edematous gingiva, which may include both erosions and white lesions. Similar lesions may involve other sites, such as the labial, buccal, and tongue mucosae. The clinical manifestations are characteristic and form the basis of the diagnosis, which is supported by healing of the lesions after withdrawal of the allergen-containing agent.[102] Dentifrice may also cause a disturbed desquamation, which clinically can be observed as thin veils of scaling keratin (Figure 4-53).

TOXIC REACTIONS

Reactions to Smokeless Tobacco

Smokeless tobacco represents a nonhomogeneous group of compounds used with different intraoral application methods. Three different geographic areas are of special interest: South Asia, the United States, and Scandinavia. In India, tobacco is often used in combination with betel leaf, sliced areca nut, and powdered slaked lime, which increases the toxicity of the compound. There is a definitive association between this form of smokeless tobacco and oral cancer (see the earlier section "Oral Submucous Fibrosis").

Smokeless tobacco in the United States and Scandinavia can be divided into three different groups: chewing tobacco,

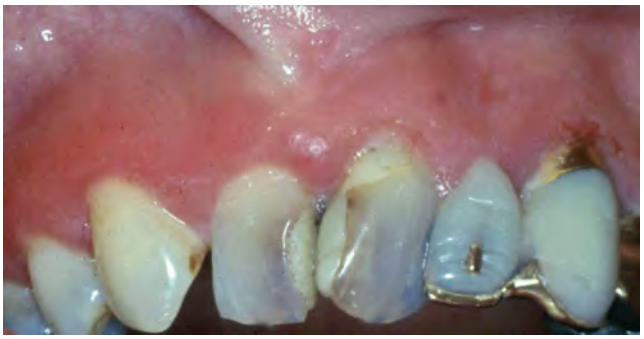

Figure 4-52 Immune delayed hypersensitivity response (allergy) to components of dentifrice resulting in gingival erythema, particularly the attached gingivae in the upper right anterior region.

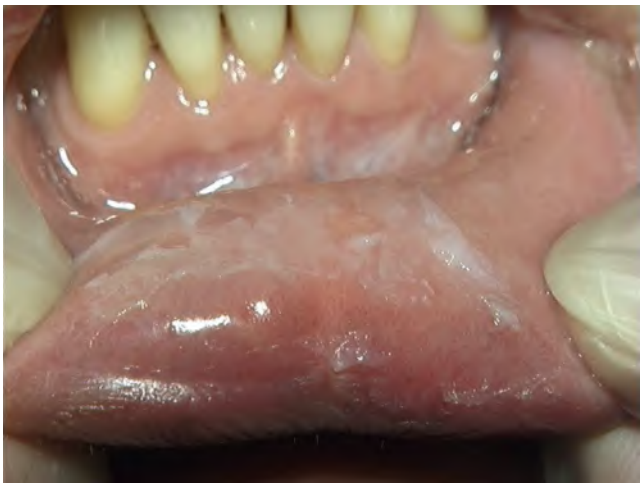

Figure 4-53 Hypersensitivity reaction to dentifrice resulting in desquamation of the superficial epithelial layers.

moist snuff, and dry snuff.[103] All three are different regarding composition, manufacturing procedures, and type of consumers. In Scandinavia, moist snuff is the most popular compound, but is different in the manufacturing process from the moist snuff used in the United States.[104] The latter contains higher concentrations of tobacco-specific nitrosamines and nitrite.

The clinical picture varies in relation to the type, brand, frequency, and duration of use of moist snuff.[105] In its mildest form, the lesion may just be noted as wrinkles at the site of application, whereas high consumers may display a white and leathery lesion (Figure 4-54), which sometimes contains ulcerations. Hyperkeratinization, acanthosis, and epithelial vacuolizations are common histopathologic features together with different degrees of subepithelial inflammation. Gingival retraction is the most common adverse reaction seen in conjunction with a smokeless tobacco habit. These retractions are irreversible, whereas the mucosal lesion usually regresses within a couple of months. Oral mucosal lesions are less

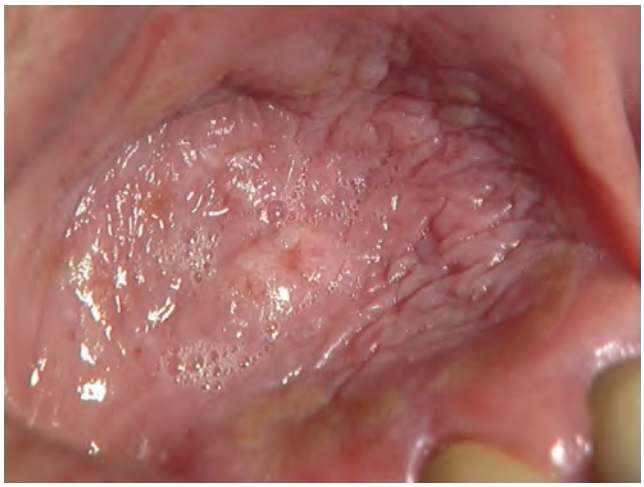

Figure 4-54 Oral mucosal reaction to moist snuff held in contact in the central part of the maxillary vestibulum, displaying both wrinkles at the site of application and a white and leathery lesion. Generalized hyperkeratinization overlies apparent edema of the mucosa.

frequently observed in association with chewing tobacco compared with moist snuff.

There is a distinct difference between lesions caused by smokeless tobacco and oral leukoplakia with respect to the presence of epithelial dysplasia, which is more frequently found in the latter. Furthermore, the degree of dysplasia is also milder. The carcinogenic potential of smokeless tobacco has been a subject of considerable debate, and no global consensus has been reached. However, it is undisputable that smokeless tobacco products contain nitrosamines, polycyclic hydrocarbons, aldehydes, heavy metals, and polonium 210, which all have the potential to cause harm.[106,107] Some studies conclude that there is a higher risk of oral cancer and pancreatic cancer, results that have not been confirmed by others. The World Health Organization International Agency for Research on Cancer established in its report from 2004 that "overall, there is sufficient evidence that smokeless tobacco causes oral cancer and pancreatic cancer in humans, and sufficient evidence of carcinogenicity from animal studies." In a recent comprehensive review, it was concluded that the use of moist snuff (Figure 4-54) and chewing tobacco imposes minimal risks for cancers of the oral cavity and other upper respiratory sites, with relative risks ranging from 0.6 to 1.7. The use of dry snuff imposes higher risks, ranging from 4 to 13, and the risks from smokeless tobacco, unspecified as to type, are intermediate, from 1.5 to 2.8.[106]

Smoker's Keratosis

Moderate to heavy tobacco smoking, especially cigarettes but also cannabis, can give rise to reactive keratosis anywhere in

the oral cavity, but especially in the palate (see later) and sublingually (Figure 4-20). Sublingual keratosis can be clinically indistinguishable from sublingual leucoplakia, except that cessation of the habit and removal of the irritant may lead to regression of the lesion(s). Persistence of the lesion after cessation of smoking confirms a sublingual leucoplakia, which must be biopsied due to the high risk of malignant transformation.

Smoker's Palate

The most common effects of smoking are presented clinically as dark brown pigmentations of the oral mucosa (smoker's melanosis) and as white leathered lesions of the palate, usually referred to as nicotine stomatitis or smoker's palate. In smoker's palate, an erythematous irritation is initially seen, and this lesion is followed by a whitish palatal mucosa reflecting a hyperkeratosis (Figure 4-55). As part of this lesion, red dots can be observed representing orifices of accessory salivary glands, which can be enlarged and display metaplasia. Histopathologically, smoker's palate is characterized by hyperkeratosis, acanthosis, and a mild subepithelial inflammation.[108]

The prevalence of smoker's palate has been reported in the range of 0.1–2.5%. Smoker's palate is more prevalent in men and is a common clinical feature in high consumers of pipe tobacco and cigarettes and among individuals who practice inverse smoking. The etiology is probably more related to the high temperature rather than the chemical composition of the smoke, although there is a synergistic effect of the two.[109]

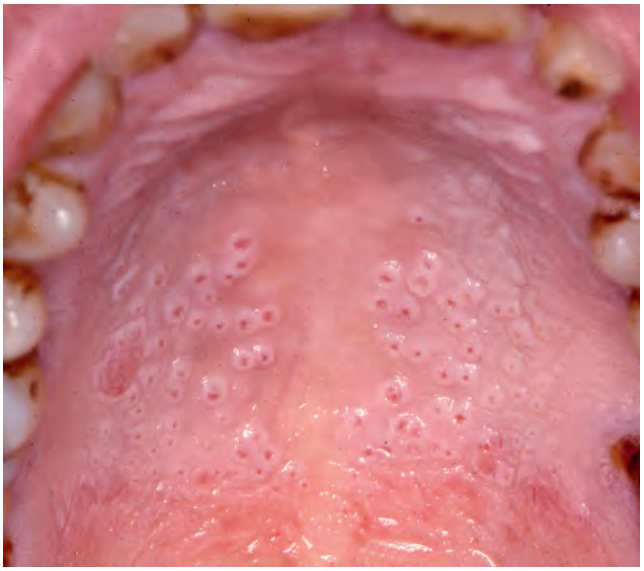

Figure 4-55 Classic appearance of smoker's palate showing widespread reactive keratosis, and enlarged, inflamed minor salivary glands with obvious ductal orifices.

REACTIONS TO MECHANICAL TRAUMA

Morsicatio (Mucosal Nibbling)

Morsicatio is instigated by habitual chewing (Figure 5-56). This parafunctional behavior is done unconsciously and is therefore difficult to bring to an end. Morsicatio is most frequently seen in the buccal and lip mucosa and is never encountered in areas that it is not possible to traumatize by habitual chewing.[110,111] Typically, morsicatio does not entail ulcerations, but encompasses an asymptomatic shredded area. In cases of more extensive destruction of oral tissues by habitual chewing, a psychiatric disorder should be suspected. The prevalence has been reported to be in the range of 0.5–1.0%. Morsicatio is three times more common among women.

Morsicatio has a very typical clinical appearance, and the diagnosis is relatively easy to establish, with one exception. If the lesion affects the borders of the tongue, it may mimic hairy leukoplakia. This also has bearing for the histopathologic picture, which is characterized by hyperkeratosis and acanthosis. A careful disease history will assist in the discrimination between the two conditions. The management is limited to reassurance, and the patient should be informed about the parafunctional behavior. There is no malignant potential.

Frictional Hyperkeratosis

Oral frictional hyperkeratosis is typically clinically characterized by a white lesion without any red elements. The lesion is observed in areas of the oral mucosa subjected to increased friction caused by, for example, food intake (Figure 4-57).

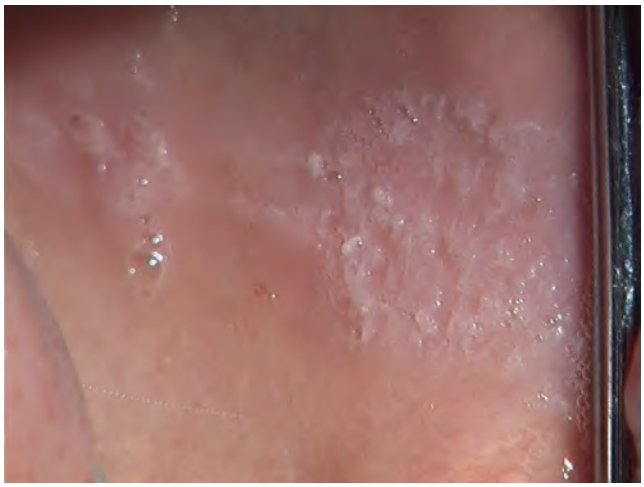

Figure 4-56 Morsicatio lesions in the left buccal mucosa in a 33-year-old female, caused by habitual chewing of the cheek. Chewing has resulted in shredding of the mucosa and reactive keratosis.

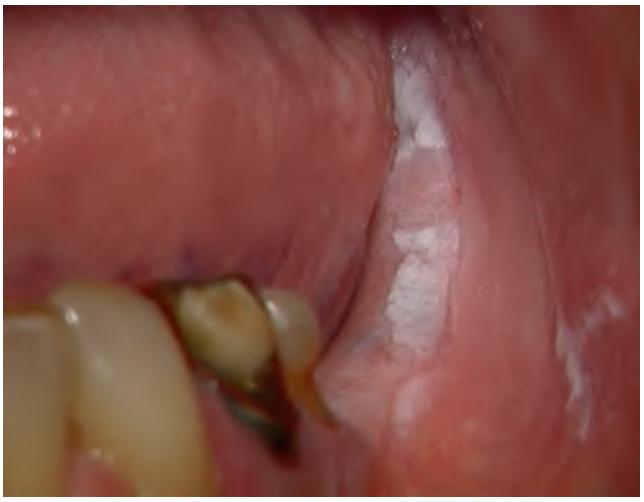

Figure 4-57 Frictional keratosis of the lower left alveolar ridge, caused by chewing solid foods directly on the ridge in the absence of a denture.

Etiology and Pathogenesis

Frictional hyperkeratosis is observed in areas subjected to increased abrasion, which stimulates the epithelium to respond with increased production of keratin. The reaction can be regarded as a physiologic response to minor trauma. Smoking and alcohol consumption have been reported as predisposing factors.[112] Thus, the development of frictional hyperkeratosis is facilitated when the oral mucosa is exposed to these factors.

Epidemiology

In population studies, the prevalence has been reported to be in the range of 2–7%. Predisposing factors such as smoking and alcohol will increase the prevalence of frictional hyperkeratosis, and it is the most common mucosal lesion in individuals with these habits.

Clinical Findings

Frictional hyperkeratosis is often seen in edentulous areas of the alveolar ridge, but may also be observed in other parts of the oral mucosa exposed to increased friction or trauma. The lesions are asymptomatic, although they can cause anxiety to the patient as they can be perceived as malignant or premalignant.

Diagnosis

For most lesions, the diagnosis can be established based on clinical features. As frictional hyperkeratosis does not carry any symptoms and is caused by comparatively common habits, it may be difficult to relate the lesions to increased friction. If the diagnosis is doubtful, biopsy is mandatory to exclude premalignant lesions. The histopathologic picture is characterized by hyperkeratosis without dysplasia and no or mild subepithelial inflammation. Differential diagnosis against homogeneous leukoplakia is clinically based on a combination of features such as the affected site and a more diffuse demarcation. The ultimate way to differentiate between the two is to reduce or eliminate predisposing factors and await a remedy.

Management

No surgical intervention is indicated. Information about the nonmalignant nature of the lesions and attempts to reduce predisposing factors are sufficient.

OTHER RED AND WHITE LESIONS

Benign Migratory Glossitis (Geographic Tongue)

Geographic tongue is an annular lesion affecting the dorsum and margin of the tongue. The lesion is also known as erythema migrans or benign migratory glossitis. The typical clinical presentation comprises a white, yellow, or gray, slightly elevated peripheral zone (Figure 4-58) surrounding an erythematous patch. Since several layers of tongue epithelium can be desquamated per day, the clinical appearance can alter from day to day.

The occurrence of geographic tongue makes people worried and prone to self-observation of the tongue. It creates a disproportional level of stress. Additionally, it may cause symptoms while eating certain types of food. Sometimes people discover it during self-examination of the tongue if they have burning mouth syndrome.

Etiology and Pathogenesis

Although geographic tongue is one of the most prevalent oral mucosal lesions, there are virtually no studies available with the objective of elucidating the etiology behind this disorder. Heredity has been reported, suggesting the involvement of genetic factors in the etiology.

Epidemiology

The prevalence of geographic tongue varies considerably between different investigations, which may reflect not only geographic differences but also patient selection procedures and diagnostic criteria. The most frequently reported prevalence is in the range of 1.5–2.5%.[113] The sex distribution appears to be equal.

Clinical Findings

Geographic tongue is circumferentially migrating and leaves an erythematous area behind, reflecting atrophy of the filiform papillae. The peripheral zone disappears after some time, and healing of the depapillated and erythematous area starts. The lesion may commence at different starting points,

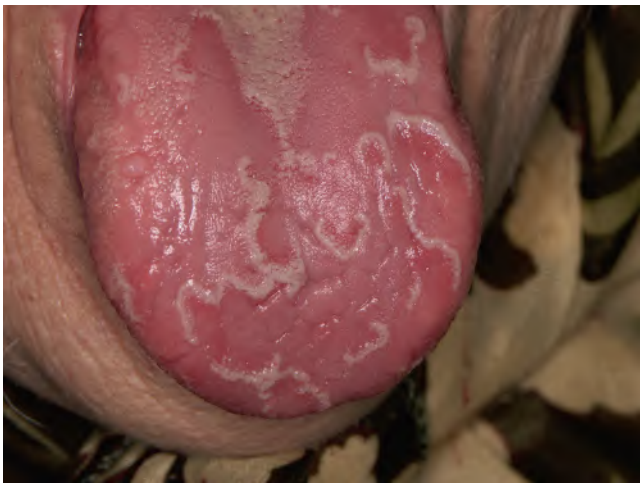

Figure 4-58 Benign migratory glossitis showing typical appearance of apparently atrophic areas of the dorsum of the tongue surrounded by gray-white keratotic margins.

the peripheral zones fuse, and the typical clinical features of a geographic tongue emerge. Depending on the activity of the lesion, the clinical appearance may vary from single areas to multiple lesions occupying the entire dorsum of the tongue.[114] Disappearance of the peripheral zone may indicate that the mucosa is recovering. Geographic tongue is characterized by periods of exacerbation and remission, with different durations over time. The disorder is usually nonsymptomatic, but some patients experience a smarting sensation. Typical of this condition is that patients experience symptoms only upon eating certain foods. These include walnuts and other nuts, as well as kiwi fruit, citric flavors, and tomatoes. In these cases, a parafunctional habit, revealed by indentations at the lateral border of the tongue, may be a contributing factor to the symptoms. Patients often report that their lesions are aggravated during periods of stress.[114,115] Geographic tongue may be followed by a fissured tongue and sometimes the two lesions are observed simultaneously (Figure 4-59).

The appearance of the tongue dorsum may vary greatly, from a mild presentation to a very dramatic one. A geographic appearance can be observed at sites of the oral mucosa other than on the dorsum of the tongue, and is then denoted geographic stomatitis (sometimes called "ectopic geographic tongue"). The information about geographic stomatitis is sparse and relies on case reports. A similar clinical presentation as for geographic stomatitis may be seen as part of Reiter's disease. This disease is characterized by arthritis, uveitis or conjunctivitis, and urethritis. Reiter's disease is considered to be a reaction that originates from a gastroenteral or urogenital infection.[116,117]

An increased prevalence of geographic tongue has been observed in patients with generalized pustular psoriasis. In psoriasis in general, no such association has been revealed. No

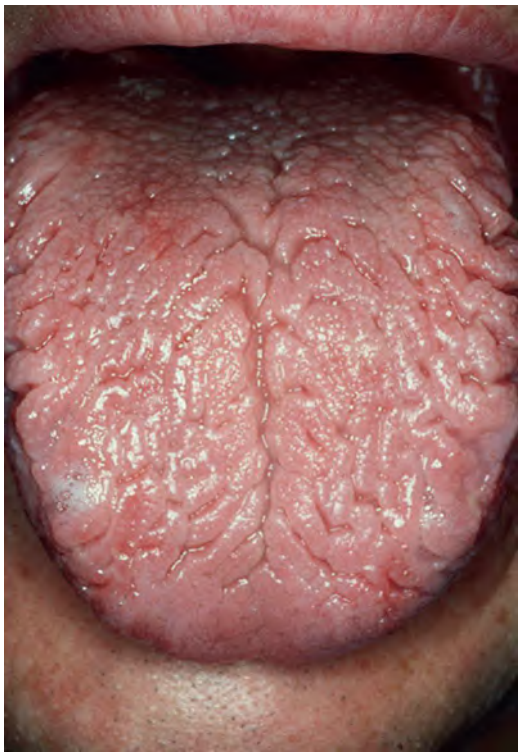

Figure 4-59 Fissured tongue associated with concurrent benign migratory glossitis (BMG). Fissures can appear in the apparent absence of BMG.

studies have demonstrated that patients with geographic tongue are at increased risk of acquiring psoriasis. Atopy has also been associated with geographic tongue, but this was not confirmed by a recently conducted study in the United States.

Diagnosis

The clinical features of this mucosal disorder are quite characteristic, and histopathologic confirmation is not needed. If biopsy is considered, it should involve the peripheral zone to capture the lesion's typical histopathologic features. These include parakeratosis, acanthosis, subepithelial inflammation of T lymphocytes, and transepithelial migrating neutrophilic granulocytes. These cells may be a part of microabscesses formed near the surface, similar to those found in pustular psoriasis (Monro's microabscesses).

Management

Since the etiology is unknown, no causal treatment strategy is available.[114] Symptoms are rarely present, and management is confined to reassurance and proper information about the disorder's benign character. It is important to emphasize that it is not a pathologic lesion, but rather a morphologic variation of generally health mucosa, as well as that patients may eat anything except walnuts, kiwi fruit, tomatoes, and citric foods. It is helpful to have an information

sheet ready for patients to read about the benign nature of the condition. No special treatment is required, although many approaches have been tried. If symptoms are reported, topical anesthetics may be used to obtain temporary relief. Other suggested treatment strategies include antihistamines, anxiolytic drugs, or steroids, but none of these has been systematically evaluated.

Geographic tongue may regress, but it is not possible to predict when and to which patient this may happen. The prevalence of the disease seems to decrease with age, which supports spontaneous regression over time.

Leukoedema

Leukoedema is defined as edematous mucosa with a whiteish, often apparently translucent appearance.

Etiology and Pathogenesis

The etiology of leukoedema is not clear.

Epidemiology

The prevalence of areas of leukoedema in Caucasians has been estimated at 50%. The lesion is even more prevalent in the black population. The distribution between sexes has been found to be equal.[112]

Clinical Findings

Leukoedema is a white and veil-like alteration of the oral mucosa that is merely considered a normal variant. The condition is often encountered bilaterally in the buccal mucosa (Figure 4-60) and sometimes at the borders of the tongue. Leukoedema is less clinically evident after stretching the mucosa, but reappears after this manipulation is discontinued.

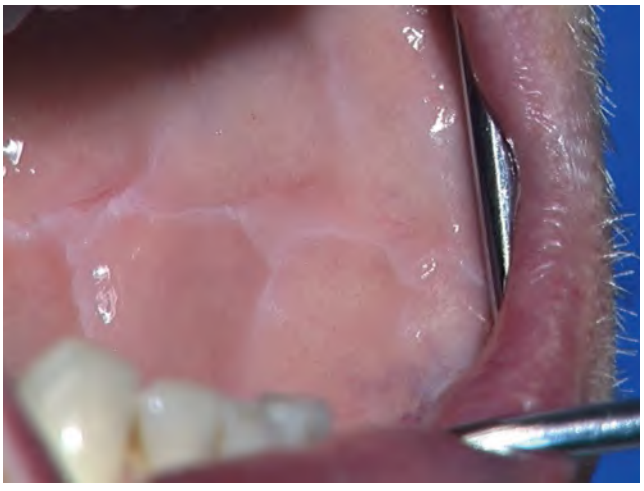

Figure 4-60 Leukodema in the left buccal mucosa showing an apparent edematous mucosa with a whiteish, translucent appearance associated with parafunctional behavior.

In more pronounced cases, leukoedema is accompanied by mucosal folds. The condition is asymptomatic and has no malignant potential.

Diagnosis

The clinical features of leukoedema are quite different from oral keratosis, such as leukoplakia, as the demarcation is diffuse and gentle stretching results in a temporary disappearance. The histopathology is characterized by parakeratosis and acanthosis together with intracellular edema in epithelial cells of stratum spinosum.

Management

There is no demand for treatment as the condition is asymptomatic and has no complications, including premalignant features.

White Sponge Nevus

Etiology and Pathogenesis

White sponge nevus is initiated following mutations in those genes that are coding for epithelial keratin of types K4 and K13. In K4-deficient mice, epithelial disturbances have been reported that are compatible with white sponge nevus.[118]

Epidemiology

White sponge nevus has been listed as a rare disorder by the US National Institutes of Health, which implicates a prevalence below 1 in 200,000. In a population study of 181,338 males between 18 and 22 years of age, two cases of white sponge nevus were identified. The clinical appearance usually commences during adolescence, and the sex distribution has been reported to be equal.

Clinical Findings

White sponge nevus is an autosomal dominant disorder with high penetrance. The typical clinical appearance is a white lesion with an elevated and irregular surface comprising fissures or plaque formations (Figure 4-61). The most affected sites are the buccal mucosa, but the lesion may be encountered in other areas of the oral cavity covered by parakeratinized or nonkeratinized epithelium. The disorder may also involve extraoral sites, such as the esophagus and anogenital mucosa. Although the lesion does not entail any symptoms, it may cause dysphagia when the esophagus is involved.

Diagnosis

White sponge nevus may constitute a differential diagnostic problem, as this disorder may be taken for other oral dyskeratoses, for example oral leukoplakia and plaque type candidiasis. The hallmark microscopic feature of this disorder is pronounced intracellular edema of the superficial epithelial

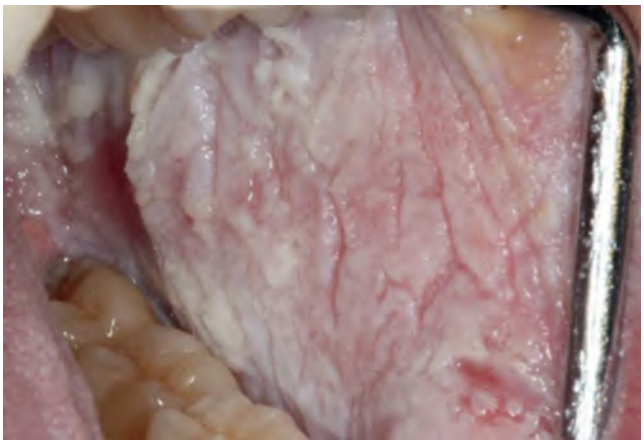

Figure 4-61 White sponge nevus in the left buccal mucosa.

cells, predominantly located within the stratus spinosum. Cells with pyknotic nuclei are present, and these cells may imitate the koilocytosis observed in viral infections. Deep fissures in the nondysplastic epithelium may reach just above the basal layer, but the lower portions of the epithelium are not involved. No or only mild infiltrations may be seen in the subepithelial tissue.

Management

White sponge nevus does not entail any symptoms, and no treatment is therefore required. Systemic antibiotics have been used in an attempt to resolve the disorder, but with inconsistent results. When a positive effect is obtained, the recurrence rate is considerable. White sponge nevus is a totally benign condition.

Hairy Tongue

Hairy tongue is characterized by an impaired desquamation of the filiform papillae, which leads to the hairy-like clinical appearance.[119,120] The tongue frequently becomes stained through tea or coffee drinking, smoking, or resident bacteria, and is then designated *black hairy tongue*.

Etiology and Pathogenesis

The etiology of hairy tongue is unknown in most cases. A number of predisposing factors have been related to this disorder, including decreased tongue motility and subsequent lack of physiologic exfoliation of filiform papillae (oral inactivity), neglected oral hygiene, a shift in the microflora, antibiotics and immunosuppressive drugs, oral candidiasis, excessive alcohol consumption, and prolonged use of chlorhexidine. The impact of oral inactivity and ignored oral hygiene is supported by the high prevalence of hairy tongue in hospitalized patients, who are not able to carry out their own oral hygiene. An example of this is a patient thrusting the tongue against an unstable upper denture, causing a lack of exfoliation of papillae. Hairy tongue is also associated with smoking habits.

Epidemiology

The reported prevalence varies between different geographic areas, diagnostic criteria, and frequencies of predisposing factors. In studies from the United States and Scandinavia, the prevalence of hairy tongue is reported at below 1%.

Clinical Findings

The elongation of the filiform papillae has to reach lengths in excess of 3 mm to be classified as "hairy," although lengths of more than 15 mm have been reported in hairy tongue. The lesion is commonly found in the posterior third of the tongue, but may involve the entire dorsum (Figure 4-62).

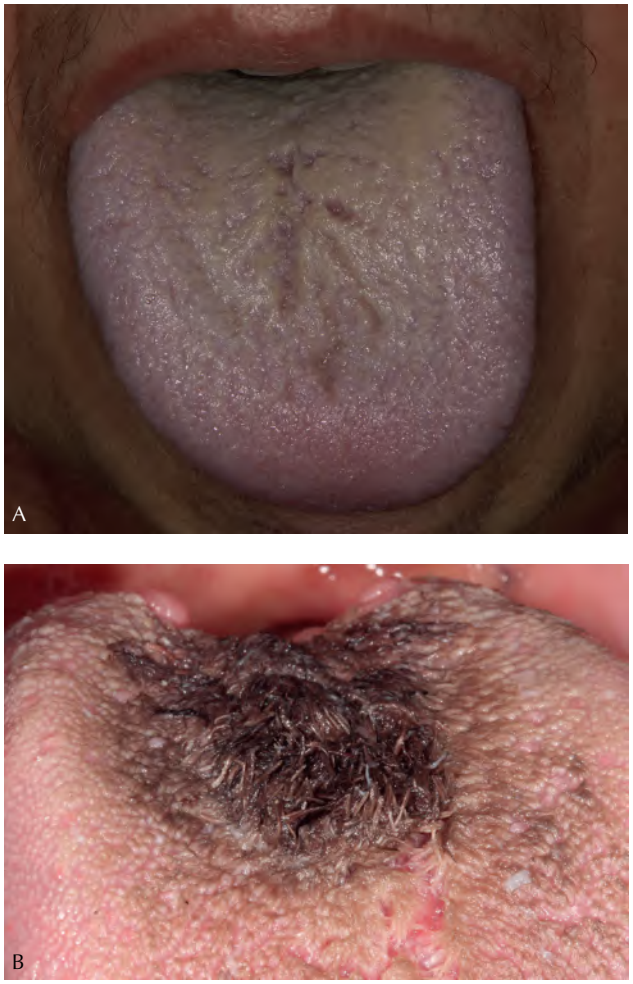

Figure 4-62 Clinical appearances of "hairy" tongue. (A) Central yellow-white appearance of the dorsum of the tongue caused by elongation of the filiform papillae. (B) Black hairy tongue caused by bacterial and food staining on the greatly elongated filiform papillae.

Hairy tongue may adopt colors from white to black depending on food constituents and the composition of the oral microflora. Patients with this disorder may experience both physical discomfort and esthetic embarrassment related to the lengths of the filiform papillae.

Diagnosis

The diagnosis is based on clinical appearance, and microbiologic examinations do not give any further guidance.

Management

The treatment of hairy tongue is focused on reduction or elimination of predisposing factors and removal of the elongated filiform papillae. Patients should be instructed on how to use devices developed to scrape the tongue. Food constituents with an abrasive effect may also be used to prevent recurrences. Attempts have been made with tretinoin, but this treatment has not reached any widespread acceptance. Patients should be informed about the benign and noncontagious nature of hairy tongue.

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5

Pigmented Lesions of the Oral Mucosa

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Healthy oral soft tissue presents a typical pink to red hue that reflects the degree of keratinization, quantity and activity of melanocytes, vascularization, and type of submucosal tissue of distinct topographic areas.[1] Although oral and perioral pigmentation may be physiologic in nature, particularly in individuals with a darker complexion, throughout the course of disease it is possible for the oral mucosa and perioral tissues to assume a variety of discolorations, including brown, blue, gray, and black. Such color changes are often attributed to the deposition, production, or increased accumulation of various endogenous or exogenous pigmented substances. However, although an area may appear pigmented, the discoloration may not be related to actual pigment, but rather to the deposition or accumulation of organic or inorganic substances, including various metals and drug metabolites.[2]

Hemoglobin, hemosiderin, and melanin represent the most common endogenous sources of mucosal color change (Table 5-1). A submucosal collection of hemoglobin or hemosiderin, produced by extravasation and/or lysis of red blood

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

Table 5-1 Common causes of endogenous oral and perioral discoloration.

Source	Etiology	Examples of Associated Lesion, Condition, or Disease
Vascular	Developmental	Varix
	Hamartomatous	Hemangioma
	Neoplastic	Lymphangioma
	Genetic	Angiosarcoma
	Autoimmune	Kaposi's sarcoma
		Hereditary hemorrhagic telangiectasia
		CREST syndrome
Extravasated hemorrhage, hemosiderin	Trauma	Hematoma
	Idiopathic	Ecchymosis
	Genetic	Purpura
	Inflammatory	Petechiae
	Autoimmune	Vasculitis
		Hemochromatosis
Melanin	Physiologic	Melanotic macule
	Developmental	Ephelis
	Idiopathic	Actinic lentigo
	Neoplastic	Melanocytic nevus
	Reactive	Malignant melanoma
	Drugs	Physiologic pigmentation
	Hormones	Chloroquine-induced pigmentation
	Genetic	
	Autoimmune	Imatinib-induced pigmentation
	Infectious	Lichen planus pigmentosus
		Laugier–Hunziker syndrome
		Smoker's melanosis
		Oral submucous fibrosis
		Peutz–Jeghers syndrome
		Adrenal insufficiency
		Cushing's syndrome
		HIV/AIDS
Bilirubin	Trauma	Jaundice
	Alcohol	
	Infection	
	Neoplasia	
	Genetic	
	Autoimmune	

cells, may impart a red, blue, or brown ephemeral appearance to the oral mucosa. Melanin, which is synthesized by melanocytes and nevus cells, may appear as brown, blue, or black, depending on the amount of melanin and its spatial location within the tissue (i.e., superficial vs. deep).

Exogenous pigmentations are usually associated with traumatic or iatrogenic events resulting in the deposition of foreign material directly into the mucosal tissues (Table 5-2).[3] In some cases, the substances may be ingested, absorbed, and distributed hematogenously into connective tissues, particularly in areas subject to chronic inflammation, such as the gingiva. In other instances, these ingested substances can stimulate melanin production, thus precipitating a color change. Chromogenic bacteria can produce discoloration of the dorsal tongue. Certain foods, drinks, and confectionery can also result in exogenous pigmentation that, in most cases, is reversible.

Clinically, oral pigmentations can range from a solitary macule to large patches and broad, diffuse tumefactions. The specific hue, duration, location, number, distribution, size, and shape of the pigmented lesion(s) may be of diagnostic importance. In addition, recording extensive social, family, medical, and dental histories, various diagnostic procedures (e.g., colonoscopy), and laboratory tests (including biopsy) may be necessary. Thus, an understanding of the various disorders and substances that can contribute to oral and perioral pigmentation is essential for the appropriate evaluation, diagnosis, and management of the patient.

Table 5-3 lists additional lesions that may be associated with oral mucosal discoloration. Each of these lesions is discussed in more detail elsewhere in this textbook. Similarly, vascular lesions such as hemangioma, lymphangioma, angiosarcoma, and Kaposi's sarcoma, which are frequently considered in the differential diagnosis of macular and mass-forming pigmented lesions, are shown in Table 5.1, but otherwise excluded from this chapter.

ENDOGENOUS PIGMENTATION

Melanin is the pigment derivative of tyrosine and is synthesized by melanocytes, which typically reside in the basal cell layer of the epithelium.[4] Investigations into normal melanocyte homeostasis led to the discovery that keratinocytes control melanocytic growth.[5] Yet the mechanisms by which melanocytes are stimulated to undergo cell division remain poorly understood. Their presence in the skin is thought to protect against the damaging effects of actinic irradiation. They also act as scavengers, protecting against cytotoxic intermediates.[6] However, the role of melanocytes in oral epithelium is unclear.

Melanin is not commonly observed in routine biopsies of the oral mucosa, unless the tissues were obtained from non-Caucasoid individuals. Oral melanocytic pigmentation in Caucasians is almost always considered pathologic in origin, although the pathology or pigment itself may be of no clinical significance.

Melanin is synthesized within specialized structures known as melanosomes. It is composed of eumelanin, a

Table 5-2 Sources of exogenous oral and perioral pigmentation.

Source	Etiology	Examples of Associated Lesion, Condition, or Disease
Metal	Iatrogenic Medications Environment	Amalgam tattoo Chrysiasis Black tongue Heavy metal pigmentation
Graphite/ink	Trauma Factitious Tribal customs	Graphite tattoo
Bacteria	Poor oral hygiene Antibiotics	Hairy tongue
Drug complexes	Medications	Minocycline-induced pigmentation
Plant derivatives	Factitious Tribal customs	Ornamental tattoo Orange mouth

Source: Based on Muller S. Melanin-associated pigmented lesions of the oral mucosa: presentation, differential diagnosis, and treatment. Dermatol Ther. 2010(3);23:220–9.

Table 5-3 Miscellaneous lesions that may be associated with oral mucosal discoloration.

Lesion	Color
Pyogenic granuloma	Red, blue
Peripheral ossifying fibroma	Red, blue
Peripheral giant cell granuloma	Red, blue
Mucocele	Blue
Mucoepidermoid carcinoma	Blue
Acinic cell carcinoma	Blue
Lymphoma	Blue, purple
Vascular leiomyoma	Red, blue
Metastatic cancer	Red, blue
Fordyce granule	Yellow
Lipoma	Yellow
Granular cell tumor	Yellow

brown-black pigment, and pheomelanin, a pigment of red-yellow color.[4] The term *melanosis* is used to describe diffuse hyperpigmentation. Cutaneous overproduction of melanin may be associated with a variety of mechanisms, but most commonly with increased sun exposure. However, intraorally, hyperpigmentation is more typically a consequence of physiologic, idiopathic sources, neoplasia, medications, high serum concentrations of pituitary adrenocorticotropic hormone (ACTH), postinflammatory changes, and genetic or autoimmune disorders. Therefore, the presence or absence of systemic signs and symptoms, including cutaneous hyperpigmentation, is of great importance to elucidate the genesis of oral pigmentations. If the etiology of the oral pigmentation cannot be clinically established, a tissue biopsy is warranted for definitive diagnosis. This is critical, because malignant melanoma may present with a deceptively benign clinical appearance.

In addition to biopsy and histologic study, various laboratory and clinical tests, including diascopy, radiography, and blood tests, may be necessary for the definitive diagnosis of oral pigmentations. Recently, two noninvasive tests, which were originally developed to study cutaneous pigmentation, have been applied to evaluate oral melanosis. The first, dermoscopy (also known as epiluminescence microscopy), uses a handheld surface microscope, incident light, and oil immersion. This technique has been successfully used for the evaluation of selected oral pigmented lesions.[7] The second, reflectance confocal microscopy (RCM), allows the in vivo microscopic visualization of the skin and mucosa, which provides high-resolution horizontal views with an approximate depth of 200–300 μm.[8] This procedure can assist in the diagnosis and management of benign and malignant pigmented lesions of the lips.[9] Because prospective and controlled studies detailing the predictive value and efficacy of dermoscopy and RCM for the diagnosis of oral pigmented lesions have not been performed, the practitioner should be wary of their use in common clinical dental practice.

In summary, melanin pigmentation may be physiologic or pathologic, and may clinically present with focal, multifocal, or diffuse patterns. Figures 5-1 and 5-2 show algorithms that can assist the clinician in associating these patterns with selected pigmented conditions.

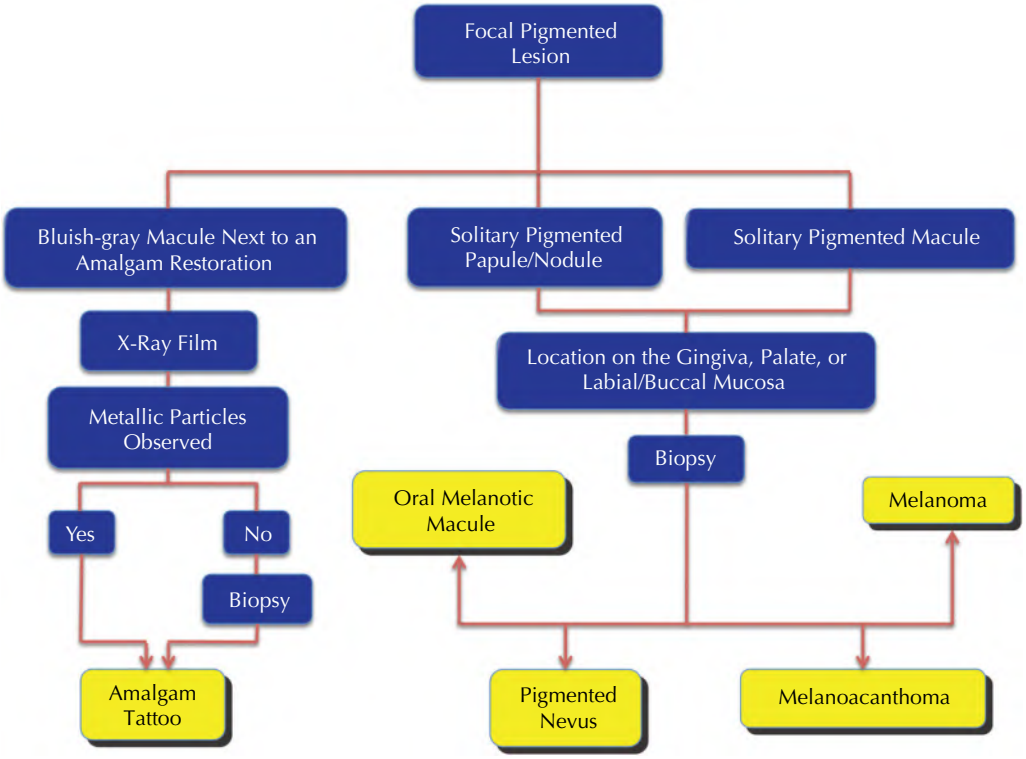

Figure 5-1 Focal pigmented lesions. Algorithm illustrating clinical procedures needed to segregate and diagnose common focal pigmented lesions.

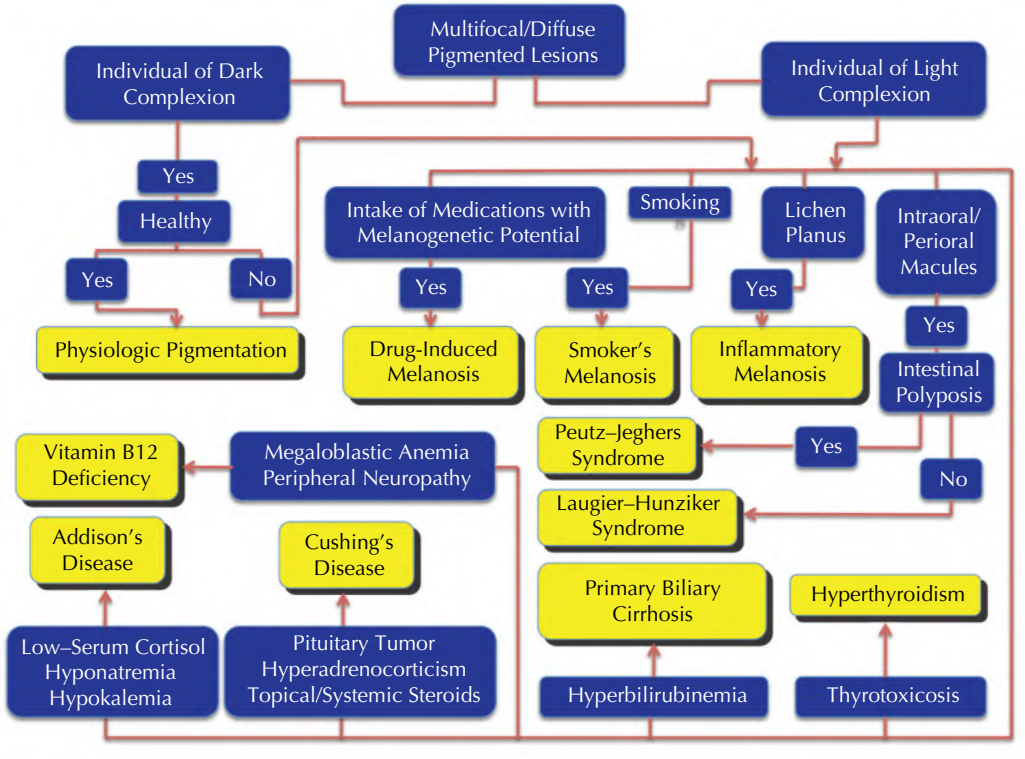

Figure 5-2 Multifocal and diffuse pigmented lesions. Algorithm illustrating the clinical presentation of pigmented lesions with accompanying habits, endoscopic features, and systemic/laboratory findings that allow their segregation.

FOCAL MELANOCYTIC PIGMENTATION

Freckles/Ephelis

Freckles is the lay term for ephelis and lentigines, which are commonly occurring, asymptomatic, well-circumscribed, tan- or brown-colored macules often seen on sun-exposed regions of the skin (Figure 5-3). Ephelides are most commonly observed in light-skinned individuals and are quite prevalent in red- or light blond-haired individuals. Freckles are thought to be developmental in origin. A number of genes have been shown to participate in their formation.[10]

Ephelides are usually more abundant in number and darker in intensity during childhood and adolescence. They tend to become darker during periods of prolonged sun exposure (e.g., spring, summer) and fade during the autumn and winter months. However, the increase in pigmentation is solely related to an increase in melanin production without a concomitant increase in the number of melanocytes. With increasing age, the number of ephelides and color intensity tend to diminish. In contrast, the number of lentigines tends to increase. In general, no therapeutic intervention is required.

Oral/Labial Melanotic Macule

Etiology and Pathogenesis

The melanotic macule is a unique, benign, pigmented lesion that has no known dermal counterpart. Melanotic macules are the most common oral lesion of melanocytic origin. In one large-scale retrospective study, melanotic macules made up over 85% of all solitary melanocytic lesions.[11] Although the etiology remains elusive, trauma has been postulated to play a role. Sun exposure is not a precipitating factor.

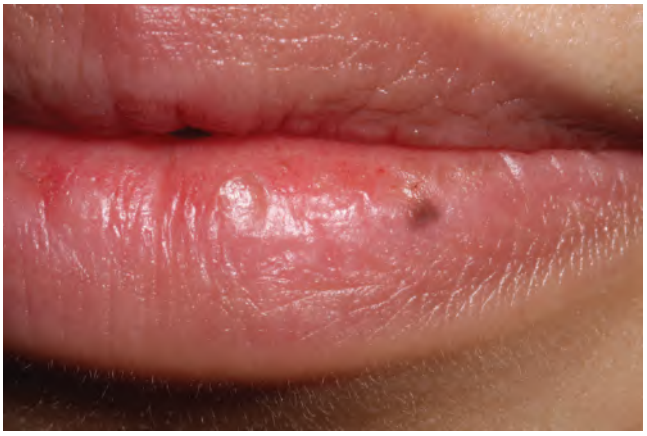

Figure 5-3 Ephelis of the lower vermilion border. Brown pigmented macule with circumscribed borders on the left lower vermilion border.

Clinical Features

Melanotic macules develop more frequently in females, usually in the lower lip (labial melanotic macule) and gingiva. However, any mucosal site may be affected. Although the lesion may develop at any age, it generally tends to present in adulthood. Congenital melanotic macules have been described, occurring primarily in the tongue.[12] Overall, melanotic macules tend to be small (<1 cm), well-circumscribed, oval or irregular in outline, and often uniformly pigmented (Figure 5-4). Once the lesion reaches a certain size, it does not tend to enlarge further. Unlike an ephelis, a melanotic macule does not become darker with continued sun exposure. Overall, the oral melanotic macule is a relatively innocuous lesion, and in general will not recur following surgical removal. However, an apparent association between oral melanotic macule and melanoma has been documented.[13]

Pathology

Microscopically, melanotic macules are characterized by the presence of abundant melanin pigment in the basal cell layer without an associated increase in the number of melanocytes (Figure 5-5). Pigmentation is often accentuated at the tips of the rete pegs, and melanin incontinence into the subjacent lamina propria is commonly encountered. Melanocytic hyperplasia is an ominous microscopic finding that may herald the development of malignant melanoma.

Differential Diagnosis

The differential diagnosis includes melanocytic nevus, malignant melanoma, amalgam tattoo, and focal ecchymosis. If such pigmented lesions are present after a two-week period, ecchymosis can usually be ruled out.

Figure 5-4 Melanotic macule of the lower labial mucosa. *Source:* Courtesy of Dr. John Fantasia, North Shore-LIJ Health System, LIJMC, New Hyde Park, NY, USA.

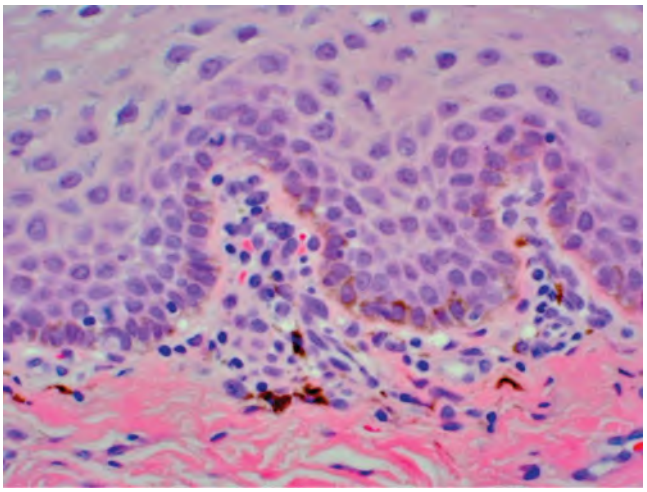

Figure 5-5 Melanotic macule exhibiting increased melanin pigmentation within the basal cell layer and melanin incontinence (hematoxylin and eosin, ×400). *Source:* Courtesy of Dr. John Fantasia, North Shore-LIJ Health System, LIJMC, New Hyde Park, NY, USA.

Management

A biopsy specimen should be obtained to secure a definitive diagnosis. Once the microscopic diagnosis is obtained, no further treatment is necessary. Since oral mucosal malignant melanomas have no defining clinical characteristics, a biopsy of any persistent solitary pigmented lesion is always warranted.

Oral Melanoacanthoma

Etiology and Pathogenesis

Oral melanoacanthoma is an innocuous melanocytic lesion that may spontaneously resolve, with or without surgical intervention.[14] Although the term *melanoacanthoma* may imply a neoplastic process, the oral lesion is actually reactive in nature. Most patients report a rapid onset, with acute trauma or a history of chronic irritation preceding the development of the lesion. A biopsy is always warranted to confirm the diagnosis, but once rendered, no further treatment is required. The biopsy procedure itself may lead to spontaneous regression of the lesion. If it has been identified, the underlying source of the irritation should be eliminated in order to minimize recurrence.

Clinical Features

Oral melanoacanthoma usually presents as a rapidly enlarging, ill-defined, darkly pigmented flat or slightly elevated lesion with a predilection for black females. Although lesions may present over a wide age range, the majority occur between the third and fourth decades of life. Typically, melanoacanthoma presents as a solitary lesion; nevertheless, bilateral and multifocal lesions have been reported.[15]

Oral melanoacanthomas are generally asymptomatic; however, pain may be present.[14] Although any mucosal surface may be involved, close to 50% of melanoacanthomas arise on the buccal mucosa.[15] The size of the lesion is variable, ranging from small and localized to large, diffuse areas of involvement, measuring several centimeters in diameter. The borders are typically irregular in appearance, and the pigmentation may be uneven (Figure 5-6).

Although there is a recognized cutaneous melanoacanthoma,[16] it is clear that the similarities with oral melanoacanthoma lie solely in the nomenclature. Cutaneous melanoacanthoma represents a pigmented variant of seborrheic keratosis and typically occurs in older Caucasian patients. Dermatosis papulosa nigra is a relatively common facial condition that typically manifests in older black patients, often female, and represents multiple pigmented seborrheic keratoses.[17] These small papules are often identified in the malar and preauricular regions of the face.

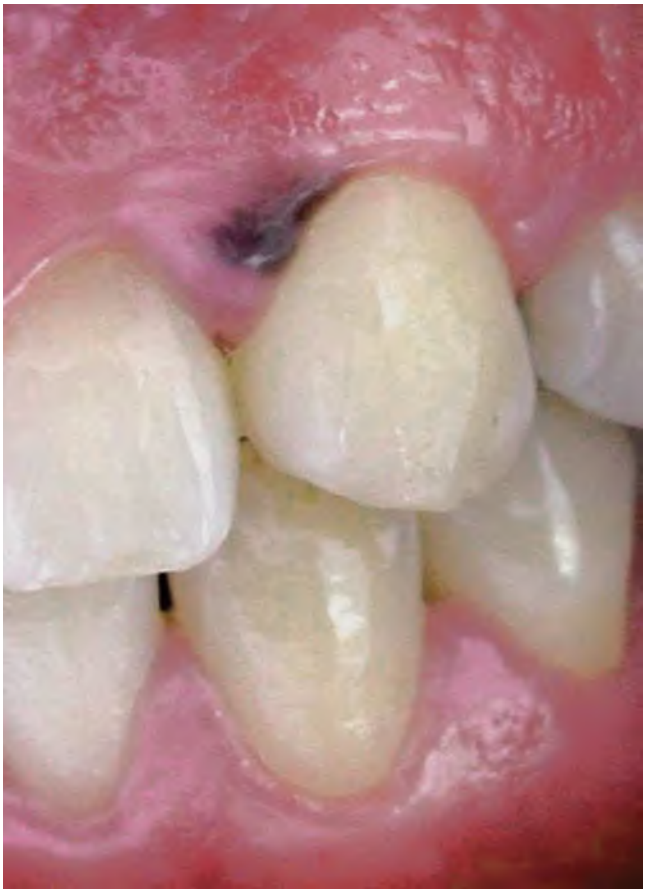

Figure 5-6 Melanoacanthoma. Pigmented macule on the attached and marginal gingiva displaying irregular borders. *Source:* Reproduced from Tapia JL, Quezada D, Gaitan L, et al. Gingival melanoacanthoma: case report and discussion of its clinical relevance. *Quintessence Int.* 2011;42(3):253–258, with permission from Quintessence International.

Pathology

Microscopically, oral melanoacanthomas are characterized by a proliferation of benign, dendritic melanocytes throughout the full thickness of an acanthotic and spongiotic epithelium (Figure 5-7).[14] A mild lymphocytic infiltrate with exocytosis is also characteristic. Occasional eosinophils may be observed.

Differential Diagnosis

Pigmented nevus, melanotic macule, and melanoma should be included in the differential diagnosis.

Management

A biopsy is warranted to obtain a definitive diagnosis. No further treatment is indicated.

Melanocytic Nevus

Etiology and Pathogenesis

Melanocytic nevi include a diverse group of clinically and/or microscopically distinct lesions.[18] Unlike ephelides and melanotic macules, which result from an increase in melanin pigment synthesis, nevi arise as a consequence of melanocytic growth and proliferation.[11] In the oral cavity, the intramucosal nevus is most frequently observed, followed by the common blue nevus.[19] Compound nevi are less common, and the junctional nevus and combined nevus (a nevus composed of two different cell types) are infrequently identified. Rare reports of congenital nevus, Spitz nevus, balloon cell nevus, and the cellular, epithelioid, and plaque type variants of blue nevus have also been described. However, the list of morphologically distinct nevi continues to expand.

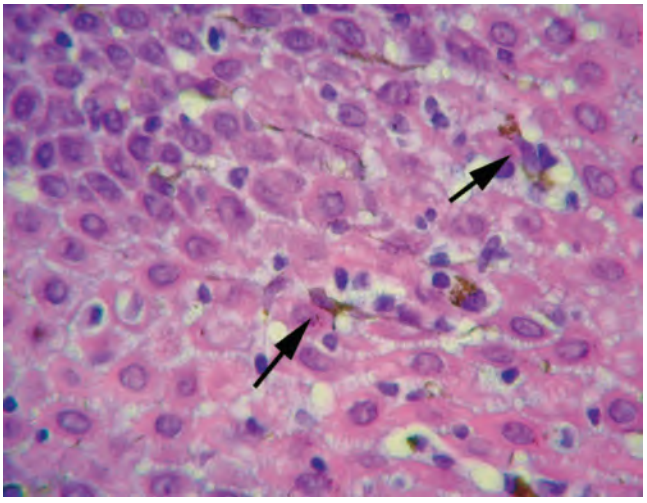

Figure 5-7 Melanoacanthoma. Dendritic-shaped, pigmented melanocytes (arrows) are noted throughout the full thickness of a spongiotic and acanthotic epithelium (hematoxylin-eosin stain; ×400 original magnification).

Relatively little is known about the pathogenesis of the various melanocytic nevi. In fact, there is still debate as to whether "nevus cells" are a distinct cell type derived from the neural crest or if they are simply a unique or immature form of melanocyte.[4] Nonetheless, the lesional nevus cells are cytologically and biologically distinct from the melanocytes that colonize the basal cell layer of the epidermis and oral epithelium. Whereas native melanocytes tend to have a dendritic morphology, most nevic cells tend to be round, ovoid, or spindle shaped.[20] Additional differences include the tendency for nevus cells to closely approximate one another, if not aggregate in clusters, and their ability to migrate into and/or within the submucosal tissues.

In general, both genetic and environmental factors are thought to play a role in nevogenesis. The effect of sun exposure on the development of cutaneous nevi is well recognized. However, there are also age- and location-dependent differences in the presentation, number, and distribution of nevi. Although most melanocytic nevi are acquired, some may present as congenital lesions (including those in the oral cavity). Moreover, there are several examples of increased nevus susceptibility in various inherited diseases, thus confirming the role of genetics. To illustrate: familial atypical multiple mole and melanoma syndrome is characterized by the formation of histologically atypical nevi,[21] blue nevus may be associated with the Carney complex,[22] markedly increased numbers of common nevi are characteristic in patients with Turner's syndrome[23] and Noonan's syndrome,[24] and congenital nevi are typical of neurocutaneous melanosis.[25] Thus, these findings also bring into question whether nevi are true benign neoplasms or hamartomatous or developmental in nature, as they have been historically characterized. A study by Pollock and colleagues demonstrated that up to 90% of dermal melanocytic nevi exhibit somatic, activating mutations in the *BRAF* oncogene.[26] Mutations in the *HRAS* and *NRAS* oncogenes have also been identified.[27,28] This lends further credence to the notion that cutaneous melanocytic nevi are neoplastic. It is currently unknown whether oral melanocytic nevi also harbor any of these same mutations.

Clinical Features

Cutaneous nevi are common. The average Caucasian adult may have several nevi; some individuals may have dozens. The total number of nevi occurring in males tends to be higher than that seen in females. In contrast, oral melanocytic nevi are rare solitary lesions that are more common in females.[6]

Oral melanocytic nevi have no distinguishing clinical characteristics. Lesions are usually asymptomatic and often present as a small (<1 cm), solitary, brown or blue, well-circumscribed nodule or macule (Figure 5-8). Up to 15% of

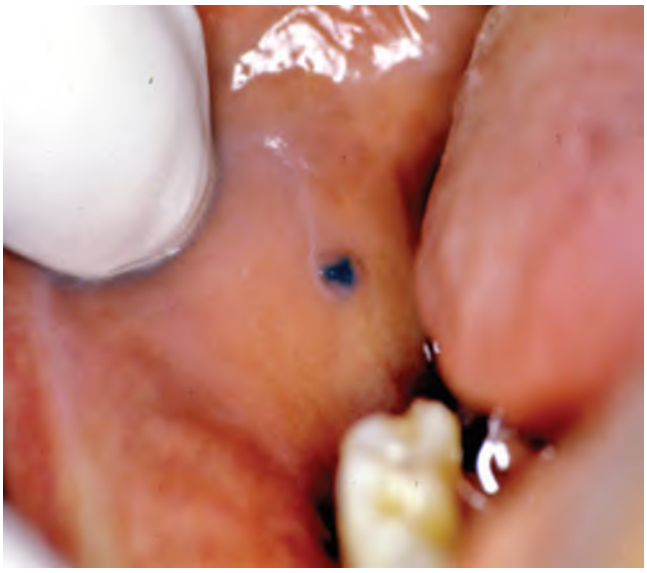

Figure 5-8 Intramucosal nevus of the right buccal mucosa.

oral nevi may be amelanotic. Once the lesion reaches a given size, its growth tends to cease and may remain static indefinitely. In rare cases, multifocal lesions have been described.[29] Whereas some studies suggest a greater prevalence of oral nevi in black patients, other studies have not identified any significant racial predilection. Oral nevi may develop at any age; however, most are identified in patients over the age of 30. The hard palate represents the most common site, followed by the buccal and labial mucosae and gingiva.

Pathology

Nevus cells initially maintain their residency at the basal layer, as cellular clusters at the junction of the epithelium and the underlying connective tissue (Figure 5-9). These junctional nevi are usually small (<5 mm), macular, and tan to brown in color. Over time, the clustered melanocytes are thought to proliferate down into the connective tissue, often in the form of variably sized nests of relatively small, rounded cells. Nonetheless, some nevus cells may still be seen at the epithelial–connective tissue interface. Such nevi often assume a dome-shaped appearance and are referred to as compound nevi. As the lesion further matures, the nevus cells completely lose their association with the epithelial layer and become confined to the lamina propria, often with an associated decrease in the amount of pigmentation. At this point, the lesion is given the designation of intramucosal nevus and, clinically, may appear brown, tan, or may even resemble the color of the surrounding mucosa.

Blue nevi are characterized by a variety of microscopic features. The "common" blue nevus, which is the most frequent histologic variant seen in the oral cavity, is characterized by a stromal proliferation of pigment-laden, spindle-shaped melanocytes. The blue nevus is described as such because the melanocytes that reside deep in the connective tissue and the overlying fibrous connective tissue often conceal the brown color of melanin, resulting in a blue tint. The less frequently occurring cellular blue nevus is characterized by a stromal proliferation of both spindle-shaped and larger round or ovoid-shaped melanocytes. It should be noted that histologic differentiation of the two forms is not merely academic. Whereas the common blue nevus usually has an innocuous

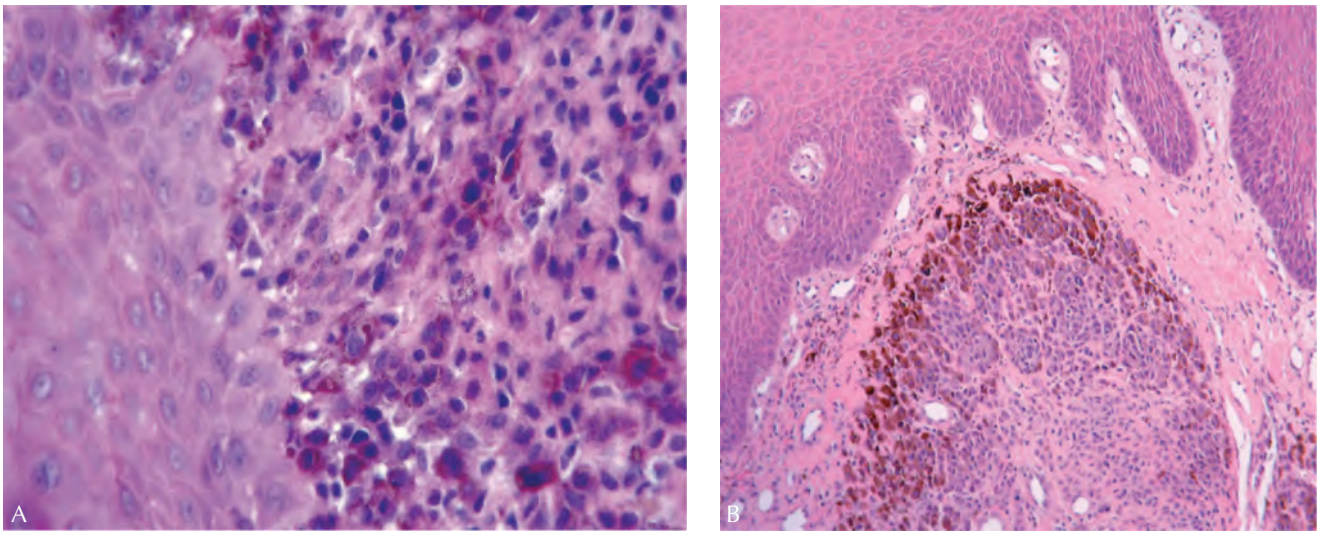

Figure 5-9 (A) Compound nevus: nevus cells are located at the junction of the epithelium and connective tissue and within the submucosal tissue. The cells are variably pigmented (hematoxylin-eosin stain; ×400 original magnification). (B) Intramucosal nevus: the nevus cells are located within the lamina propria, with no evidence of any junctional component. The superficial melanocytes are heavily pigmented. Melanin is less evident in the remaining cells (hematoxylin-eosin stain; ×100 original magnification).

clinical course, the cellular blue nevus may behave more aggressively and exhibit a greater rate of recurrence.[30] Rare reports of malignant transformation have also been associated with the cellular cutaneous variant.

While cutaneous acquired nevi and dysplastic nevi may represent precursors of malignant melanoma, there is no evidence of an increased malignant transformation rate for melanocytic nevi of the mouth. Nonetheless, it is advised that all oral nevi, regardless of histologic type, should be completely removed.[31]

Differential Diagnosis

The differential diagnosis includes a variety of other focally pigmented lesions, including malignant melanoma. Various vascular lesions and exogenous pigmentations may also be considered in the differential diagnosis.

Management

Biopsy is necessary for diagnostic confirmation of an oral melanocytic nevus. Complete but conservative surgical excision is the treatment of choice for oral lesions. Recurrence has only rarely been reported. Laser and intense pulse light therapies have been used successfully for the treatment of cutaneous nevi.[32] However, their value in the treatment of oral nevi is unknown.

Malignant Melanoma

Etiology and Pathogenesis

Malignant melanoma is the least common but most deadly of all primary skin cancers. Similar to other malignancies, extrinsic and intrinsic factors play a role in its pathogenesis. A history of multiple episodes of acute sun exposure, especially at a young age; immunosuppression; the presence of multiple cutaneous nevi; and a family history of melanoma are all known risk factors for the development of cutaneous melanoma.[33] Melanoma-prone families have a high incidence of germline mutations in the tumor suppressor genes, *CDKNA2/p16*^{INK4a} or, less commonly, *CDK4*.[34] Similar to melanocytic nevi, melanomas also frequently exhibit mutations in the *BRAF*, *HRAS*, and *NRAS* proto-oncogenes.[27,35] Other recurrent molecular findings, including *MC1R* polymorphisms and alterations or loss of PTEN function, have also been described.[36,37] This suggests that several distinct genetic changes are required for the molecular evolution of melanoma.

Clinical Features

Cutaneous melanoma is most common in white people living in sunbelt regions of the world. However, mortality rates are higher in black and Hispanic people. Epidemiologic studies suggest that its incidence is increasing in patients, especially males, over the age of 45.[38] In contrast, the incidence is decreasing in patients under the age of 40. Despite an overall predilection for males, melanoma is one of the most commonly occurring cancers in women of child-bearing age.[39]

Melanomas may develop either de novo or, less commonly, from an existing melanocytic nevus.[33] The malar region is a common site for melanoma because this area is subject to significant solar exposure. In general, the clinical characteristics of cutaneous melanoma are best described by the ABCDE criteria: asymmetry, irregular borders, color variegation, diameter greater than 6 mm, and evolution or surface elevation. These criteria are very useful (although not absolute) in differentiating cutaneous melanoma from other focal, pigmented melanocytic lesions.[40]

There are four main clinicopathologic subtypes of cutaneous melanoma: superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanoma, and nodular melanoma (Figures 5-10 and 5-11).[33] In the first three subtypes, the initial growth is radial, where the melanocytic tumor cells spread laterally and therefore superficially. These lesions have a good prognosis if they are detected early and treated before the onset of nodular lesions, which would indicate invasion into the deeper connective tissue (i.e., a vertical growth phase). The development of nodularity in a previously macular lesion is an ominous sign.

The prognosis of melanoma can be ascertained by Breslow's tumor thickness criteria, or Clark's level of invasion. Microscopic findings such as surface ulceration, vascular or lymphatic invasion, neurotropism, high mitotic index, and absence of lymphocytes infiltrating the tumor are all associated with a poor prognosis.[6] Additionally, various clinical parameters, including tumor site, age of the

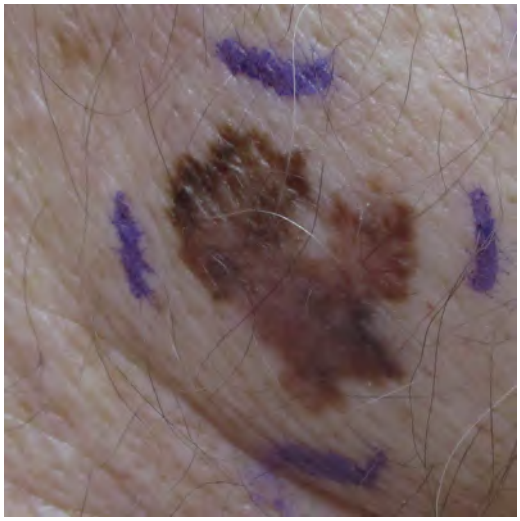

Figure 5-10 Cutaneous macular melanoma fulfilling the ABCDE criteria. *Source:* Courtesy of Dr. Gyorgi Paragh, Department of Dermatology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA.

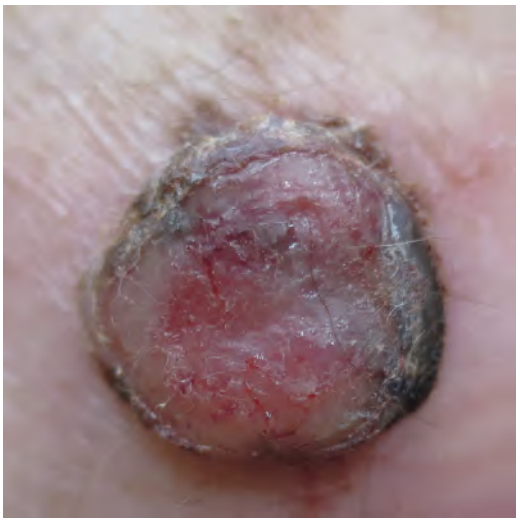

Figure 5-11 Ulcerated cutaneous nodular melanoma. *Source:* Courtesy of Dr. Gyorgi Paragh, Department of Dermatology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA.

patient (>60 years), sex (male), and regional or distant metastasis, also are predictive of poor prognosis. The 5-year survival rate of patients with metastatic melanoma is less than 15%.[33]

Awareness of the epidemiologic and biologic properties of cutaneous melanoma is necessary for the clinical practitioner. However, these factors have little bearing on the clinical, histologic, demographic, and biologic profiles associated with primary mucosal malignant melanoma. In brief, mucosal melanomas are very distinct neoplasms.[41,42]

Primary mucosal melanomas comprise less than 1% of all melanomas.[41,43] The majority develop in the head and neck, mainly in the sinonasal tract and oral cavity. The prevalence of oral melanoma appears to be higher among black and Japanese people than in other populations.[41,44] The tumor presents more frequently in males than in females. Unlike the cutaneous variant, which has distinct and well-recognized risk factors associated with its development, the etiology of oral melanoma remains unknown. *BRAF* mutations are rarely observed in mucosal melanomas.[42]

Oral melanoma may develop at any age, but is most prevalent over the age of 50.[44,45] Any mucosal site may be affected; however, the palate represents the most common site of involvement, followed by the maxillary gingiva/alveolar crest.[46] Oral melanomas have no distinctive clinical features. They may present as macular, plaque like, or as a mass, well-circumscribed or irregular, and may exhibit focal or diffuse areas of brown, blue, or black pigmentation (Figure 5-12). Up to one-third of oral melanomas exhibit little or no clinical evidence of pigmentation (amelanosis).[47] In some cases, oral melanomas may display multifocal areas of pigmentation. This phenomenon most likely represents both melanotic and amelanotic areas.[44,47]

Additional signs and symptoms that may be associated with oral melanoma are nonspecific and similar to those observed with other malignancies. Ulceration, pain, tooth mobility or spontaneous exfoliation, root resorption, bone loss, and paresthesia/anesthesia may be evident. However, in some patients the tumors may be completely asymptomatic.[43] Thus, the clinical differential diagnosis may be quite extensive and could include melanocytic nevus, oral melanotic macule, and amalgam tattoo, as well as various vascular lesions and other soft tissue neoplasms. It is for this reason that a biopsy of any persistent solitary pigmented lesion is always warranted.[48]

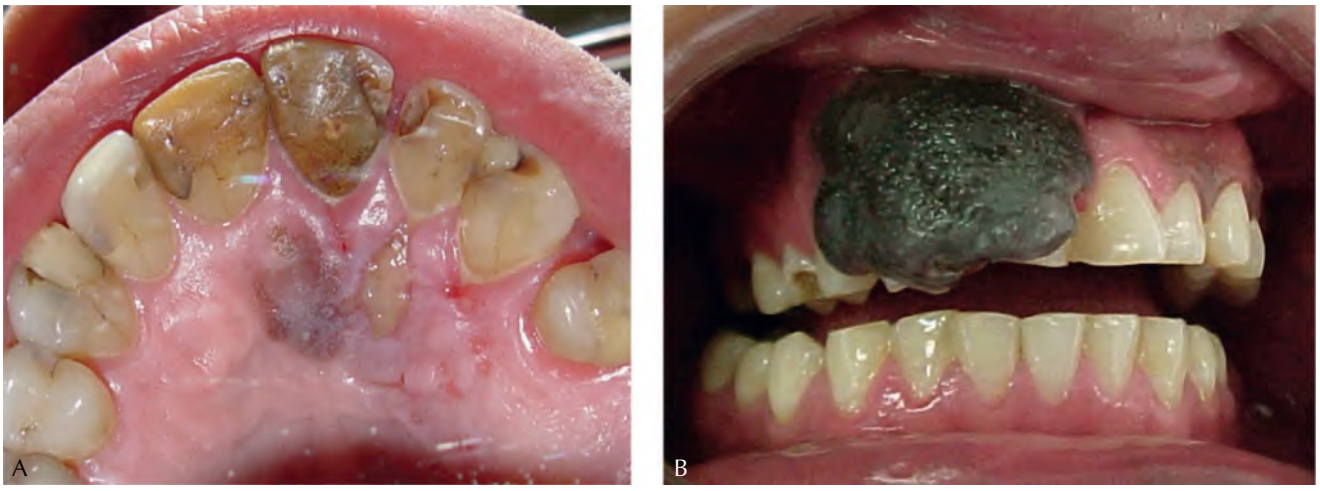

Figure 5-12 (A) Malignant melanoma exhibiting macular involvement of the anterior hard palate. *Source:* Courtesy of Dr. Guy DiTursi, VA Medical Center-Buffalo, Buffalo, NY, USA. (B) Malignant melanoma presenting as a mass on the maxillary gingiva. Courtesy of Dr. Rocio Fernandez, National Autonomous University of Mexico, Mexico City, Mexico.

Oral mucosal malignant melanoma is associated with a very poor prognosis. Studies have demonstrated 5-year survival rates of 15–40%.[43,44] Involvement of the palate is predictive of the worst prognosis compared to other intraoral sites.[49] Regional lymphatic metastases are frequently identified and contribute to the poor survival rate.[50] Less than 10% of patients with distant metastases survive after 5 years.[44] The 10-year survival rate is 0%.[51]

Pathology

Microscopically, oral mucosal melanomas (like cutaneous melanomas) may exhibit radial or vertical growth patterns. The radial or superficial spreading pattern is often seen in macular lesions, where clusters of pleomorphic melanocytes exhibiting nuclear atypia and hyperchromatism proliferate within the basal cell region of the epithelium. Upward spreading of abnormal melanocytes (pagetoid spread) and superficial invasion of the papillary lamina propria are evident (Figure 5-13).[3] Once vertical growth into the connective tissue is established, the lesions become clinically tumefactive.

Owing to its rare occurrence, even the most renowned clinical cancer centers do not have a large enough cohort of oral melanoma cases to reliably and significantly correlate the histologic findings with prognosis.[44] Thus, apart from tumor thickness greater than 5 mm and the presence of lymphovascular invasion, many of the histologic prognostic parameters of cutaneous melanoma (i.e., Breslow's classification and Clark's level of invasion) do not apply to oral melanoma.[3,6,47]

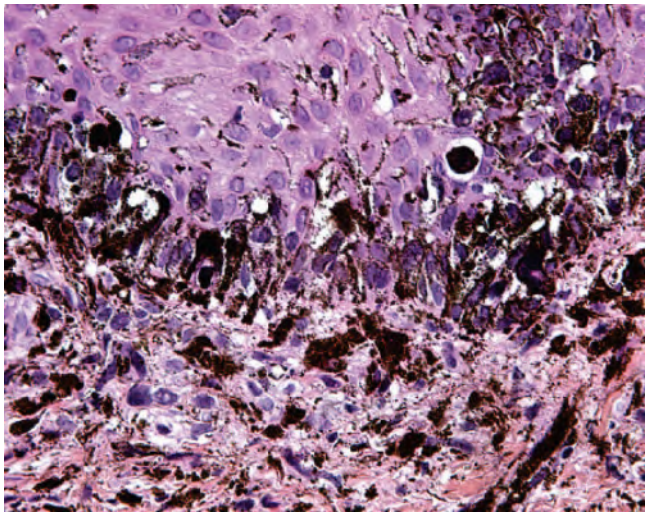

Figure 5-13 Heavily pigmented malignant melanoma exhibiting a primarily radial growth phase with pagetoid spread of tumor cells (hematoxylin and eosin stain; ×400 original magnification). *Source:* Photomicrograph courtesy of Dr. Julien Ghannoum.

Diagnosis

One of the main clinical and microscopic challenges in diagnosing oral melanoma is determining whether the lesion is a primary neoplasm or a metastasis from a distant site. This is not a semantic distinction, since confirming the primary site will dictate the patient's clinical stage and the type of therapy they will undergo. A history of a previous melanoma, sparing of the palate and gingiva, amelanosis, and microscopic features such as a lack of junctional activity and pagetoid spread are findings that may be more suggestive of a metastatic tumor.[6]

Management

For primary oral melanomas, ablative surgery with wide margins remains the treatment of choice.[3,44] Adjuvant radiation therapy may also be necessary.[52] However, it remains unclear whether radiation therapy alone is beneficial for the treatment of oral mucosal melanoma.[53] Computed tomography and magnetic resonance imaging studies should be undertaken to explore metastases to the regional lymph nodes. A variety of chemo- and immunotherapeutic strategies are often used if metastases are identified or for palliation.[3]

Melanoma is one of the most immunogenic cancers, and there are several clinical immunotherapeutic trials currently being conducted to test the effects of various antitumor vaccines. Adjuvant interferon-α-2B therapy has already been approved for the treatment of primary cutaneous melanomas more than 4 mm in thickness.[54] Unusual side effects of chemo- and immunotherapy may include the onset of autoimmunity. The appearance of autoantibodies and clinical manifestations of autoimmune disease, including vitiligo, have been associated with statistically significant improvements in overall survival rates for patients with cutaneous melanoma.[55] The discovery of KIT and BRAF mutations and the development of novel immunotherapeutic agents that specifically target and inhibit these oncogenic pathways have provided new alternative treatments.[56] Small molecule targeted therapy (BRAF and MEK inhibitors) and immune checkpoint inhibitors (CTLA-4 and PD-1) have shown promising clinical outcomes. However, the adverse effects associated with BRAF and MEK inhibitors are extensive, ranging from inflammatory to malignant conditions. Similarly, immune checkpoint inhibitors may result in a number of adverse side effects including autoimmunity (e.g., bullous pemphigoid, lichen planus pemphigoid, dermatomyositis, etc.). Viral oncolytic therapies (using a modified herpes simplex virus-1) are now also available. Collectively, these novel therapeutic venues for the treatment of melanoma have improved overall survival.[57]

MULTIFOCAL/DIFFUSE PIGMENTATION

Physiologic Pigmentation

Physiologic pigmentation is the most common multifocal or diffuse oral mucosal pigmentation (Table 5-4). Dark-complexioned individuals, including black, Asian, and Latino people, frequently show patchy to generalized hyperpigmentation of the oral mucosal tissues. In many patients, the pigment is restricted to the gingiva; however, melanosis of other mucosal surfaces is not uncommon (Figure 5-14). The pigment is typically first observed during childhood and does not develop de novo in the adult. The sudden or gradual onset of diffuse mucosal pigmentation in adulthood, even in darker-skinned patients, should alert the clinician to contemplate a pathologic genesis. A wide differential diagnosis should be considered (i.e., drug-induced or smoking-induced melanosis, an endocrinopathy, or a syndromic condition). A thorough history and laboratory tests are necessary to obtain a precise diagnosis.

Microscopically, physiologic pigmentation is characterized by the presence of increased amounts of melanin within the basal cell layer. This pigmentation is considered a variation of normal. Nonetheless, the appearance of brown to black discoloration, even intraorally, can be esthetically displeasing to some patients. Thus, surgical intervention may be necessary. Gingivectomy, laser therapy, and cryosurgery can all effectively remove oral pigmentation.[58] However, with each of these modalities, there is a possibility that the pigmentation may eventually recur. The mechanism of such repigmentation remains unclear.

Table 5-4 Etiology of multifocal, diffuse, or generalized mucocutaneous melanosis.

Physiologic pigmentation
Laugier–Hunziker pigmentation
Postinflammatory hyperpigmentation
Drug-induced
Hormone-induced
Adrenal insufficiency
Cushing's syndrome/Cushing's disease
Hyperthyroidism
Primary biliary cirrhosis
Hemochromatosis (early stages)
Genetic disease
Vitamin B_{12} deficiency
HIV/AIDS (late stages)
Malignant melanoma

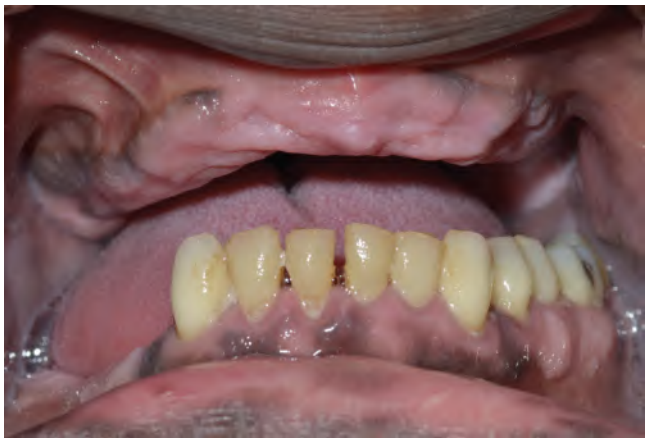

Figure 5-14 Physiologic pigmentation of the maxillary and mandibular gingiva. Note the patchy distribution of the pigment. *Source:* Courtesy of Dr. Christine Chu, private practice, New York, USA.

Drug-Induced Melanosis

Etiology and Pathogenesis

Medications may induce a variety of different forms of mucocutaneous pigmentation, including melanosis. Pigmentation that is caused by the soft tissue deposition of drug metabolites or complexes and pigment associated with deposition of lipofuscin or iron are discussed later in this chapter.

The chief drugs implicated in drug-induced melanosis are the antimalarials, including chloroquine, hydroxychloroquine, and quinacrine (Figure 5-15).[59] In the Western world, these medications are typically used for the treatment of autoimmune disease. Other common classes of medications that induce melanosis include the phenothiazines

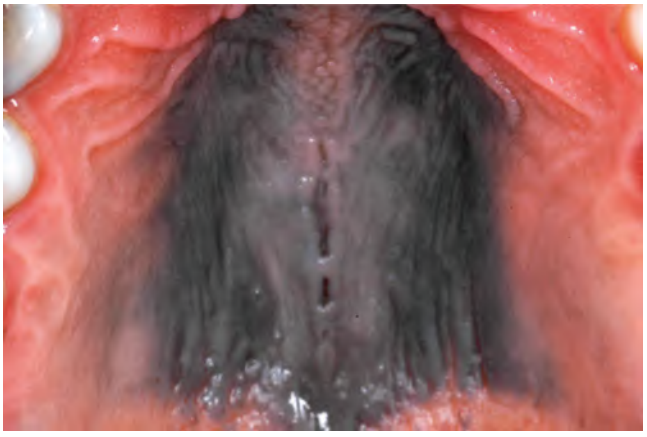

Figure 5-15 Drug-induced pigmentation of the palate in a patient who was taking quinacrine for the treatment of discoid lupus erythematosus. *Source:* Lerman MA, Karimbux N, Guze KA, Woo S-B. Pigmentation of the hard palate. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107(1):8–12. Reproduced with permission from Elsevier.

(e.g., chlorpromazine), oral contraceptives, cytotoxic medications such as cyclophosphamide and busulfan, as well as tyrosine kinase inhibitors used for the treatment of chronic myeloid leukemia and gastric intestinal stromal tumor (imatinib) (Figure 5-16).[60]

Table 5-5 lists selected known melanin-inducing medications.

Clinical Features

It has been estimated that 10–20% of all cases of acquired melanocytic pigmentation may be drug induced. Intraorally, the pigment can be diffuse yet localized to one mucosal surface, often the hard palate, or it can be multifocal and involve multiple surfaces. Some drugs may even be associated with a specific pattern of pigmentation. Much like other forms of diffuse pigmentation, the lesions are flat and without any evidence of nodularity or swelling. Sun exposure may exacerbate cutaneous drug-induced pigmentation.[59]

Pathology

Microscopically, there is evidence of basilar hyperpigmentation and melanin incontinence without a concomitant increase in the number of melanocytes. Although the mechanisms by which melanin synthesis is increased remain unknown, it is possible that the associated drugs or drug metabolites may stimulate melanogenesis. Alternatively, some drugs, including chloroquine and chlorpromazine, have been shown to physically bind melanin.[61] This complexation of melanin and drugs within melanocytes may contribute to the adverse mucocutaneous effects.

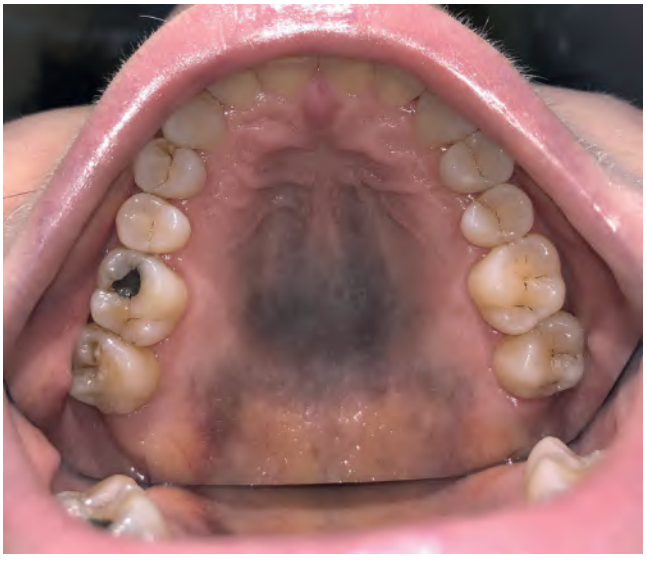

Figure 5-16 Imatinib-induced pigmentation of the palate. A 65-year-old white female treated with imatinib for gastrointestinal stromal tumor. Courtesy of Dr. Suman Sra, private practice, San Jose, CA, USA.

Table 5-5 Medications associated with mucocutaneous pigmentation.

Amiodarone
Amodiaquine
Azidothymidine
Bleomycin
Chloroquine
Chlorpromazine
Clofazamine
Gold
Hydroxychloroquine
Hydroxyurea
Imatinib
Imipramine
Ketoconazole
Mepacrine
Methacycline
Methyldopa
Minocycline
Premarin
Quinacrine
Quinidine

Differential Diagnosis

A differential diagnosis includes other causes of diffuse mucosal pigmentation. Laboratory tests may be necessary to rule out an underlying endocrinopathy.

Management

If the onset of the melanosis can be chronologically and accurately associated with the initial use of a specific medication (frequently within several weeks or months before development of the pigmentation), then no further intervention is warranted. In most cases, the discoloration tends to fade within a few months after the drug is discontinued.[59] However, pigmentation associated with hormone therapy may tend to persist for longer periods of time, despite discontinuation of the medications.

Smoker's Melanosis

Diffuse melanosis of the anterior vestibular maxillary and mandibular gingivae, buccal mucosa, lateral tongue, palate, and floor of the mouth is occasionally seen among cigarette smokers.[15] Most smokers (including heavy smokers) typically

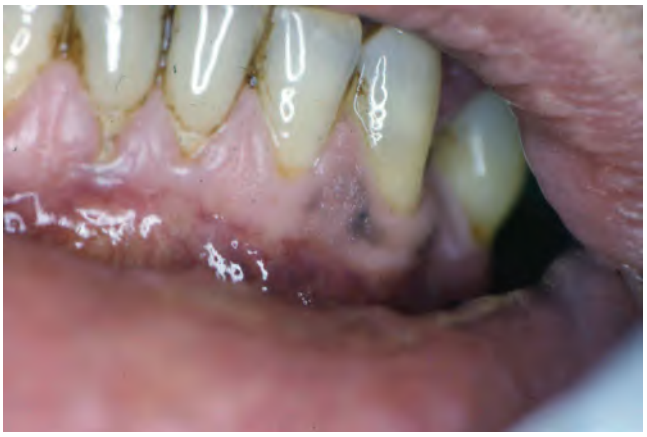

Figure 5-17 Smoker's melanosis. The attached mandibular left gingiva shows pigmented macules on the side where the patient places the cigarette to smoke.

fail to show such changes. However, in certain individuals, melanin synthesis may be stimulated by tobacco smoke products. Indeed, among dark-skinned individuals who normally exhibit physiologic pigmentation, smoking can stimulate a further increase in oral pigmentation.[62] These pigmented areas present as brown, flat, and irregular, with some even geographic or map-like in configuration (Figure 5-17).

The mechanism by which smoking induces pigmentation remains unknown. Smokeless tobacco (snuff) does not appear to be associated with an increase in oral melanosis.[63] Thus, it is possible that one or more of the chemical compounds incorporated within cigarettes, rather than the actual tobacco, may be causative. Another possibility is that the heat of the smoke may stimulate oral pigmentation. Interestingly, passive smoking in children may also result in increased gingival pigmentation.[64]

Epidemiologic studies suggest that the incidence of oral melanosis conspicuously increases during the first year of smoking.[63] A reduction in smoking may lead to fading of the pigmentation. Histologically, basilar melanosis and melanin incontinence are observed. Unlike other smoking-related oral conditions, smoker's melanosis is not a preneoplastic condition.[65]

Alcohol has also been associated with increased oral pigmentation of the posterior regions of the mouth, including the soft palate. It has been suggested that alcoholic melanosis may be associated with a higher risk of cancers of the upper aerodigestive tract.[66]

Diffuse or patchy melanotic pigmentation is also associated with oral submucous fibrosis. Unlike smoker's melanosis, oral submucous fibrosis is a preneoplastic condition caused by habitual chewing of the areca (betel) nut. This custom is common in some East Asian cultures. In cases of alcoholic melanosis, increased fibrosis of the oral soft tissues is characteristically present.

Postinflammatory (Inflammatory) Hyperpigmentation

Postinflammatory hyperpigmentation is a well-recognized phenomenon that tends to develop more commonly in dark-complexioned individuals. Most cases present as either focal or diffuse pigmentation in areas that were subjected to previous injury or inflammation.[67] The acne-prone face is a relatively common site for this phenomenon. Although unusual, postinflammatory pigmentation may also develop in the oral cavity.[68] In rare cases, the mucosa overlying a nonmelanocytic malignancy may become pigmented.[69]

Oral pigmentation has also been described in patients with lichen planus (lichen planus pigmentosus).[68] This phenomenon has been described in various races, including Caucasians (Figure 5-18). In addition to the typical microscopic features associated with lichen planus, there is also evidence of basilar hyperpigmentation and melanin incontinence. Upon resolution of the lichenoid lesion, in most cases the pigmentation eventually does subside. Although it may be mere semantics, it is unclear whether lichen planus–associated pigmentation should be appropriately characterized as postinflammatory or inflammatory pigmentation. In addition, spontaneous postsurgical healing pigmentation of palatal donor sites for free gingival grafts has been reported.[70]

Melasma (Chloasma)

Melasma is a relatively common, acquired symmetric melanosis that typically develops on sun-exposed areas of the skin and frequently on the face. More than 5 million people in the United States have this condition.[71] The forehead,

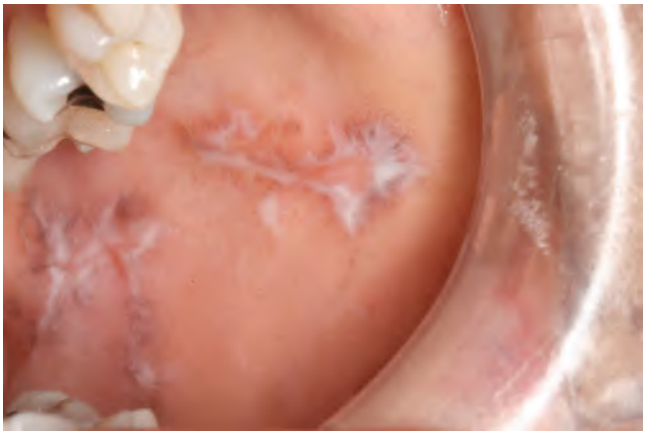

Figure 5-18 Lichen planus–associated pigment. Classic-appearing Wickham's striae and surrounding pigmentation are seen in this Caucasian patient with biopsy-proven lichen planus. *Source:* Courtesy of Dr. Carl Allen. The Ohio State University, Columbus, OH, USA.

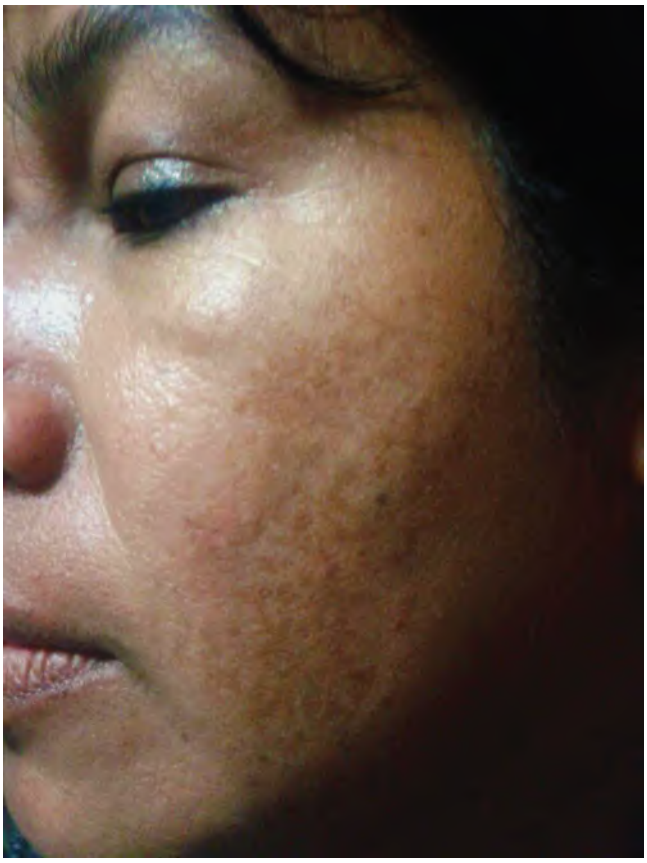

Figure 5-19 Melasma. A 48-year-old Hispanic female with patchy pigmentation on the left side of her face that developed during her first pregnancy 15 years earlier.

cheeks, upper lips, and chin are the most commonly affected areas (Figure 5-19). There is a distinct female predilection, and most cases arise in darker-skinned individuals. Unlike other forms of diffuse melanosis, melasma tends to evolve rather rapidly over a period of a few weeks.

The term *melasma* has been used to describe any form of generalized facial hyperpigmentation, including that related to postinflammatory changes and medication use. However, the term is most appropriately used to describe the pigmentary changes associated with sun exposure and hormonal factors, including pregnancy and contraceptive hormones.[71] Both pregnancy and use of oral contraceptives have also been associated with oral mucosal melanosis.[72] Rare cases of idiopathic melasma have also been described in females and, much less commonly, in males.[73,74] In most cases, it is the combination of estrogen and progesterone that induces the pigment. Estrogen replacement therapy alone, without progesterone, does not precipitate melasma. In idiopathic cases, significantly elevated levels of luteinizing hormone have been identified in both sexes, with associated decreases in serum estradiol (in women) and testosterone (in males). Despite the existence of evidence on the hormonal pathogenesis of melasma, the available data is conflicting, which is perhaps due to the varied genetic background of the populations studied. In light of the findings from some research studies, it appears that hormones may play a role in some patients' melasma; however, the association is weaker than previously believed.[71] Various thyroid abnormalities, including hypothyroidism, also may play a role in the pathogenesis of pregnancy- and non-pregnancy-associated melasma.[75]

A biopsy typically reveals basilar melanosis with no increase in the number of melanocytes. However, the melanocytes that are present may be larger than those in the adjacent normally pigmented areas.[76] Melasma may spontaneously resolve after parturition, cessation of the exogenous hormones, or regulation of endogenous sex-hormone levels. A successful therapeutic approach for the treatment of melasma consists of the topical administration of a triple-combination product (4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide) along with photoprotection (SPF 30 sunscreen).[77]

MELANOSIS ASSOCIATED WITH SYSTEMIC OR GENETIC DISEASE

Hypoadrenocorticism (Adrenal Insufficiency, Addison's Disease)

Etiology and Pathogenesis

Hypoadrenocorticism is a potentially life-threatening disease, as much for its systemic complications as its underdiagnosis. A variety of etiologies may precipitate adrenal insufficiency.[15] In adults, autoimmune disease represents one of the most common causes where the majority of patients show the presence of circulating autoantibodies to steroidogenic enzyme 21-hydroxylase. However, infectious agents, neoplasia, trauma, certain medications, and iatrogenic causes may also lead to adrenal destruction or an impairment of endogenous steroid production. In rare cases, adrenal insufficiency may also be a consequence of genetic disease.[78] Regardless of etiology, the end result is essentially the same: a decrease in endogenous corticosteroid levels.

As steroid levels decrease, there is a compensatory activation of ACTH secretion from the anterior pituitary gland. ACTH then acts on the adrenal cortex to stimulate steroid production and ACTH secretion stops. If low steroid levels persist, there will be a loss of feedback inhibition, resulting in persistent secretion of ACTH into the serum. Concurrently, the serum levels of α-melanocyte-stimulating hormone (α-MSH) will also increase. At the molecular level, this is explained by the fact that the precursor pro-opiomelanocortin gene contains the sequences of both the *ACTH* and *α-MSH* genes. During

processing of the progenitor hormone, the *ACTH* and *α-MSH* genes may be cleaved independently of one another, thus creating two distinct hormones. However, the *α-MSH* sequence is actually contained within a portion of the *ACTH* gene; in fact, the first 13 amino acids of the ACTH hormone are identical to α-MSH. Upon cellular processing of the ACTH messenger ribonucleic acid transcript, the sequence containing the α-MSH gene is cleaved and is further processed into its own secretable form. Apart from the wide array of tissues and organs that these hormones act upon, both α-MSH and ACTH are also thought to have stimulatory effects on melanocytes.[79] However, the exact mechanism by which melanin synthesis increases remains unclear.

Clinical Features

Weakness, poorly defined fatigue, and depression are some of the typical presenting signs of the illness. However, in some patients the first sign of disease may be mucocutaneous hyperpigmentation. Generalized bronzing of the skin and diffuse/patchy melanosis of the oral mucosa are hallmarks of hypoadrenocorticism. Any oral surface may be affected. In some patients, oral melanosis may be the first manifestation of adrenal disease (Figure 5-20).[15] Diffuse hyperpigmentation is more commonly associated with chronic rather than acute-onset disease.

Differential Diagnosis

The diagnosis of oral Addisonian pigmentation requires a clinicopathologic correlation. Endocrinopathic disease should be suspected whenever oral melanosis is accompanied by cutaneous bronzing. A biopsy of the area will typically reveal increased melanin in the basal cell layer with melanin incontinence. Therefore, the differential diagnosis will include other causes of diffuse pigmentation, including physiologic and drug-induced pigmentation. Laboratory tests, including the evaluation of serum cortisol and electrolyte levels, are necessary to make a diagnosis of Addisonian hyperpigmentation. Serum cortisol levels of less than 100 nmol/L at 9:00 a.m. are diagnostic of deficiency.[80] Hyponatremia and hyperkalemia are frequently associated with adrenal insufficiency.

Management

Treatment consists of exogenous steroid replacement therapy with glucocorticoids and mineralocorticoids. There is evidence supporting the use of adrenal androgens such as dehydroepiandrosterone (DHEA) to improve the quality of life of patients with Addison's disease.[80] With appropriate therapy, the pigmentation will eventually resolve.

Cushing's Syndrome/Cushing's Disease

Etiology and Pathogenesis

Cushing's syndrome develops as a consequence of prolonged exposure to relatively high concentrations of endogenous or exogenous corticosteroids. Most cases are iatrogenic in origin and associated with poorly controlled or unmonitored use of topical or systemic steroids. However, Cushing's syndrome may also arise as a result of various endogenous etiologies, such as an activating pituitary tumor (Cushing's disease) or a primary, activating, adrenal pathology (hyperadrenocorticism), as well as from the ectopic secretion of corticosteroids, ACTH, or corticotropin-releasing hormone

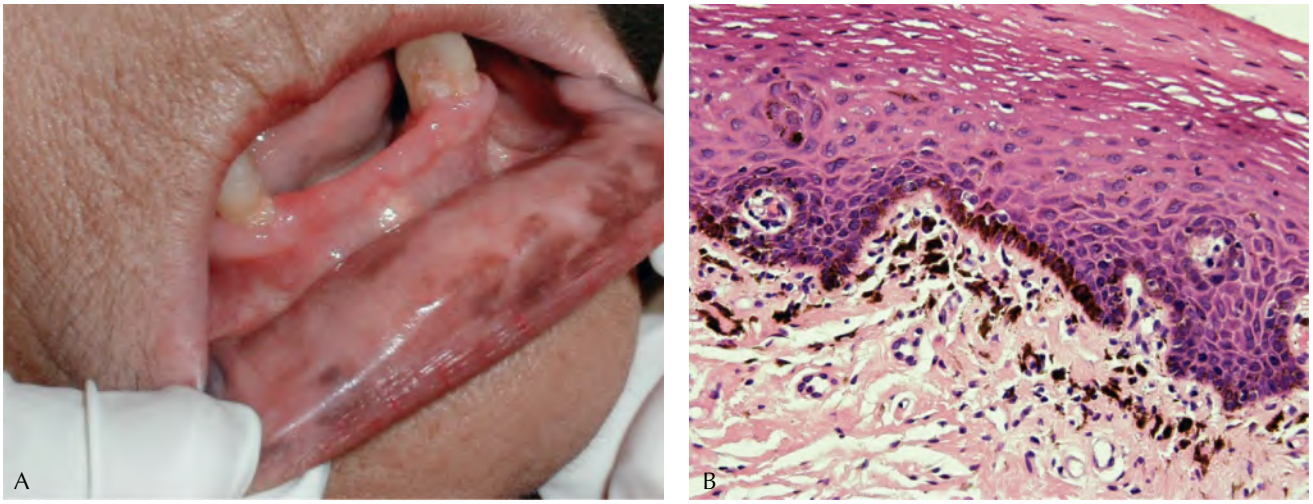

Figure 5-20 Addison's disease. (A) Patchy brown areas of pigmentations in the labial mucosa of an individual with Addison's disease. Courtesy of Dr. Jose Castillo, School of Dentistry, University Mayor, Santiago, Chile. (B) Prominent melanin pigmentation in the basal cell layer and melanin incontinentia in the papillary and reticular lamina propria (hematoxylin and eosin stain; ×400 original magnification). *Source:* Courtesy of Dr. Benjamin Martinez, School of Dentistry, University Mayor, Santiago, Chile.

by various neoplasms, including small cell carcinoma of the lung.[48] In addition, Cushing's syndrome has been described in patients with activating, germline mutations in the ACTH receptor.[81]

Clinical Features

Overall, Cushing's syndrome is more prevalent in female patients. However, prepubertal onset is more commonly seen in boys. Apart from the wide array of systemic complications, including weight gain and the characteristic "moon facies," diffuse mucocutaneous pigmentation may be seen in a subset of patients, specifically those whose pathology is associated with increased ACTH secretion. Thus, in most cases, the affected patients have a primary pituitary neoplasm.[48] Interestingly, the pattern of oral pigmentation is essentially identical to that seen in patients with adrenal insufficiency.

Diagnosis

Three main tests are used for the diagnosis of Cushing's syndrome: low-dose dexamethasone suppression, midnight plasma cortisol, and 24-hour urinary free cortisol.[48] The pigmentation often resolves following appropriate surgical, radiation, or drug therapy for the specific source of the endocrinopathy. Pasireotide (a somatostatin analogue) is US Food and Drug Administration (FDA) approved for the treatment of Cushing's syndrome.[82]

Hyperthyroidism (Graves' Disease)

Melanosis is a common consequence of hyperthyroidism (Graves' disease), particularly in dark-skinned individuals. Studies suggest that at least 40% of black patients with thyrotoxicosis may present with mucocutaneous hyperpigmentation.[83] In contrast, melanosis is very rarely observed in Caucasian patients with the disease. The pigmentation tends to resolve following treatment of the thyroid abnormality. The mechanism by which excessive thyroid activity stimulates melanin synthesis remains unclear.

Primary Biliary Cirrhosis

Diffuse mucocutaneous hyperpigmentation may be one of the earliest manifestations of primary biliary cirrhosis.[84] Up to 47% of patients with this condition develop diffuse melanosis. This uncommon disease is of unknown etiology, although it is thought to be autoimmune in nature, as evidenced by the presence of antimitochondrial antibodies. Primary biliary cirrhosis develops mainly in middle-aged women. The disease results from damage to small intrahepatic bile ducts. The mechanism by which the associated melanosis develops is unknown.

Primary biliary cirrhosis may also be a source of generalized nonmelanocytic mucocutaneous discoloration.[84,85] Jaundice is usually an end-stage complication of primary biliary cirrhosis.[85] However, jaundice may also be associated with a variety of other etiologies, including liver cirrhosis, hepatitis, neoplasia, gallstones, congenital disorders, and infection. Jaundice is caused by excessive levels of serum bilirubin (a breakdown product of hemoglobin). Hyperbilirubinemia often induces a yellowish discoloration of the skin, eyes, and mucous membranes. Treatment of the underlying disease will lead to resolution of jaundice. A differential diagnosis should include carotenemia (excessive β-carotene levels) and lycopenemia (excessive lycopene, a compound found within tomatoes and other fruits and vegetables).[86] However, the oral mucosal tissues are not affected in either of these latter conditions.

Vitamin B_{12} (Cobalamin) Deficiency

Vitamin B_{12} deficiency may be associated with a variety of systemic manifestations, including megaloblastic anemia, neurologic signs and symptoms, and various cutaneous and oral manifestations, which may include a generalized burning sensation, erythema, and atrophy of the mucosal tissue. Diffuse mucocutaneous hyperpigmentation is a rare, and poorly recognized, complication of vitamin B_{12} deficiency.[87] This hyperpigmentation is reminiscent of Addison's disease. The mechanisms by which this melanosis develops are unknown. However, the pigmentation resolves following restoration of vitamin B_{12} levels.[88]

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome is an autosomal dominant disease that is associated with mutations in the *STK11/LKB1* tumor suppressor gene. Clinical manifestations include intestinal polyposis, cancer susceptibility, and multiple, small, pigmented macules of the lips, perioral skin, hands, and feet (Figures 5-21 and 5-22). The macules may resemble ephelides, usually measuring <0.5 cm in diameter. However, the intensity of the macular pigment is not influenced by sun exposure. Although uncommon, similar-appearing lesions may also develop on the anterior tongue and buccal and labial mucosae. The lip and perioral pigmentation is highly distinctive, although not pathognomonic for this disease (see "Laugier–Hunziker Pigmentation").[15] Histologically, these lesions show increased basilar melanin without an increase in the number of melanocytes. The medical management for Peutz–Jeghers syndrome consists of surveillance and treatment of the hamartomatous polyps.[48]

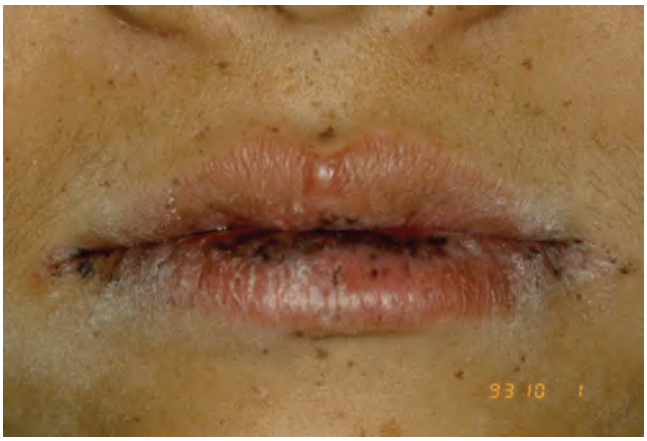

Figure 5-21 Multiple small macules and patches with a perioral distribution in an 11-year-old male with Peutz–Jeghers syndrome. *Source:* Courtesy of Dr. Mario E. Ramos, private practice, Midland Park, NJ, USA.

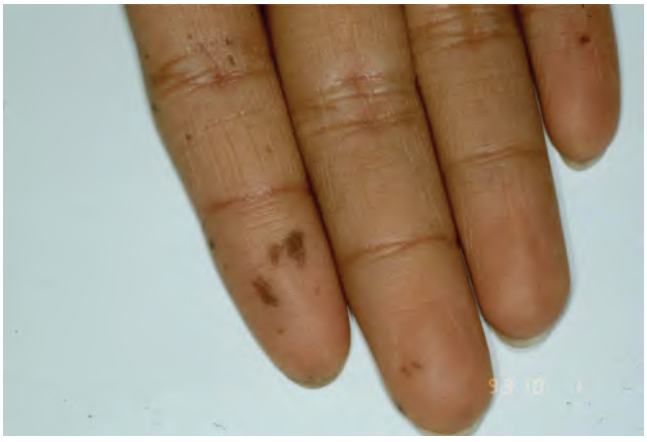

Figure 5-22 Multiple pigmented macules on the fingertips in in an 11-year-old male with Peutz–Jeghers syndrome. *Source:* Courtesy of Dr. Mario E. Ramos, private practice, Midland Park, NJ, USA.

Other genetic and acquired diseases associated with a triad of gastrointestinal disorder, cancer susceptibility, and mucocutaneous pigmented macules, among other findings, include Cowden syndrome (and the allelic Bannayan–Riley–Ruvalcaba as well as Lhermitte–Duclos syndromes) and Cronkhite–Canada syndrome.[89]

Café au Lait Pigmentation

Solitary, idiopathic café au lait ("coffee with milk") spots are occasionally observed in the general population, but multiple café au lait spots are often indicative of an underlying genetic disorder. Café au lait pigmentation may be identified in a number of different genetic diseases, including neurofibromatosis type I, McCune–Albright syndrome, and Noonan's syndrome (Table 5-6).[90] Café au lait spots typically present as tan- or brown-colored, irregularly shaped macules of variable size, which may occur anywhere on the skin. Although unusual, examples of similar-appearing oral macular pigmentation have been described in some patients.[91]

Table 5-6 Diseases commonly associated with café au lait pigmentation.

Ataxia-telangiectasia
Familial café au lait spots
Familial cavernous malformation
Fanconi's anemia
Hereditary nonpolyposis colorectal cancer
Idiopathic epilepsy
Johanson–Blizzard syndrome
McCune–Albright syndrome
Microcephalic osteodysplastic primordial dwarfism
Neurofibromatosis type 1
Neurofibromatosis type 1, Noonan's syndrome
Neurofibromatosis type 2
Nijmegen breakage syndrome
Noonan's syndrome
Ring chromosome 7 syndrome
Ring chromosome 11 syndrome
Ring chromosome 12 syndrome
Ring chromosome 15 syndrome
Ring chromosome 17 syndrome
Russell–Silver syndrome
Tuberous sclerosis
Turcot's syndrome

Source: Based on Shah KN. The diagnostic and clinical significance of cafe-au-lait macules. PediatrClin North Am. 2010(5);57:1131–53.

Neurofibromatosis type I is an autosomal dominant disease caused by a mutation or a deletion of the *NF1* gene localized in chromosome 17.[90] Neurofibromatosis type 1 is associated with the development of multiple neurofibromas of various histologic subtypes. In addition, the size, number, and age at onset of the cutaneous café au lait spots are of diagnostic importance for this disease. Axillary and/or inguinal freckling (Crowe's sign) and pigmented lesions of the iris (Lisch nodules) are also highly characteristic of neurofibromatosis type I.[92]

McCune–Albright syndrome and the genetically and phenotypically similar Mazabraud disease are sporadically occurring diseases that are characterized by polyostotic fibrous dysplasia, various endocrinopathies (McCune–Albright), and soft tissue myxomas (Mazabraud disease). In some patients, Addison's disease or Cushing's syndrome may be a potential consequence

of McCune–Albright syndrome. The appearance of the café au lait spots in McCune–Albright syndrome is distinct from those associated with neurofibromatosis. The borders of the pigmented macules are irregularly outlined, whereas in neurofibromatosis the borders are typically smooth.[90]

Noonan's syndrome and the allelic LEOPARD syndrome (multiple lentigines, electrocardiographic-conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness) are autosomal dominant disorders that, among other findings, are also associated with pigmented mucocutaneous macules and multiple melanocytic nevi.[93] The classic-appearing café au lait spots are more characteristically seen in patients with the Noonan's phenotype. The LEOPARD phenotype is typically associated with numerous, small, freckle-like macules, often involving the facial skin.

Microscopically, when compared with adjacent uninvolved skin, genetic café au lait spots exhibit basilar melanosis without an apparent concomitant increase in the number of melanocytes. The melanocytes show giant melanosomes (macromelanosomes) that may be visible under light microscopy. However, when compared with similar-appearing lesions in otherwise normal patients, genetic café au lait spots do exhibit increased numbers of melanocytes.[90]

The pathogenesis of genetic café au lait pigmentation remains elusive. However, it has been suggested that the colocalization of neurofibromin (the neurofibromatosis type 1 gene) and amyloid precursor protein in melanosomes may be important in the development of the pigmented lesions in neurofibromatosis patients.[94]

HIV/AIDS-Associated Melanosis

Diffuse or multifocal mucocutaneous pigmentation has been frequently described in HIV-seropositive patients.[95] The pigmentation may be related to intake of various medications, including antifungal and antiretroviral drugs,[96] or as a result of adrenocortical destruction by virulent infectious organisms. However, melanosis has also been identified in some patients, including those newly diagnosed, with no history of adrenocortical disease or medication intake. In these patients, the cause of the hyperpigmentation cannot be undetermined.

Several studies suggest that melanosis may be an actual, potentially late-stage, clinical manifestation of HIV/AIDS. Goldstein and colleagues demonstrated a significant correlation between mucocutaneous pigment and CD4 cell counts/μL of 200.[97] Studies have also shown that the immune dysregulation associated with HIV/AIDS leads to increased secretion of α-MSH from the anterior pituitary gland, which may also stimulate increased melanin synthesis.

HIV/AIDS patients may present with a history of progressive hyperpigmentation of the skin, nails, and mucous membranes. The pigmentation resembles most of the other forms of diffuse melanosis. The buccal mucosa is the most frequently affected site, followed by gingiva, palate, and tongue. Like all diffuse melanoses, HIV-associated pigmentation is characterized microscopically by basilar melanin pigmentation and incontinence.

IDIOPATHIC PIGMENTATION

Laugier–Hunziker Pigmentation

Etiology and Pathogenesis

Laugier–Hunziker pigmentation (also known as Laugier–Hunziker syndrome) was initially described as an acquired, idiopathic, macular hyperpigmentation of the oral mucosal tissues, specifically involving the lips and buccal mucosae. Subsequent reports detailed involvement of other oral mucosal surfaces, as well as pigmentation of the esophageal, genital, and conjunctival mucosae and the acral surfaces. Up to 60% of affected patients may also have nail involvement, usually in the form of longitudinal melanotic streaks and without any evidence of dystrophic change.[98] The fingernails are more commonly affected than the toenails.

A relatively limited number of cases have been reported in the literature. This suggests that either this form of pigmentation is exceedingly rare, or it is poorly recognized and thus underreported. Laugier–Hunziker pigmentation is typically identified in adult patients, with relatively equal sex predilection. It appears to develop more commonly in Caucasian or light-skinned individuals; however, it remains unclear whether this represents a distinct racial predilection or simply an example of clinician bias in the interpretation of the pigmentation.

No systemic abnormalities have been identified in any of the affected individuals. As a result, some investigators have suggested changing the name of this unusual condition to mucocutaneous lentiginosis of Laugier and Hunziker, idiopathic lenticular mucocutaneous pigmentation, or acquired dermal melanocytosis. Nevertheless, a recent report of Laugier–Hunziker pigmentation occurring in a mother and three of her adult children does suggest the possibility of a genetic predisposition.

Clinical and Microscopic Features

Patients typically present with multiple discrete, irregularly shaped brown or dark brown oral macules (Figure 5-23). Individual macules are usually no more than 5 mm in diameter.[99] In rare instances, the lesions may coalesce to produce a diffuse area of involvement. Recently, it was reported that

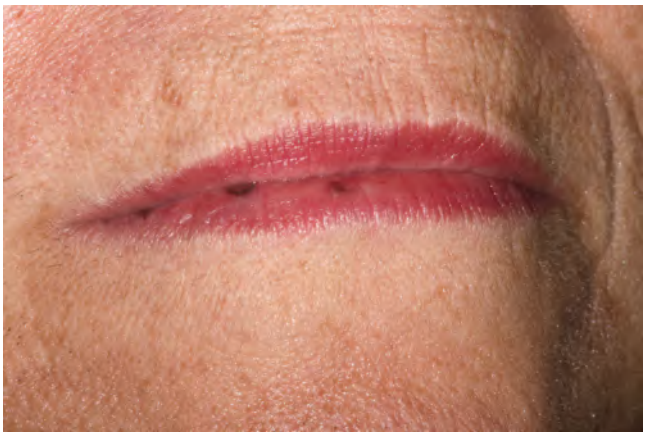

Figure 5-23 Laugier–Hunziker pigmentation. Multiple pigmented macules were observed in this healthy female who underwent colonoscopy and laboratory studies that ruled out Peutz–Jeghers syndrome and Addison's disease. This multifocal pattern of pigmentation is reminiscent of Peutz–Jeghers syndrome.

some of these pigmented macules may wax and wane. Increased melanin pigmentation in the basal cell layer without an increase in the number of melanocytes and melanin incontinentia in the superficial lamina propria are characteristic of this syndrome.[98]

Differential Diagnosis

A differential diagnosis may include physiologic, drug-induced pigmentation, endocrinopathic disease, and Peutz–Jeghers syndrome.[99] Thus, it is critical to confirm a lack of other systemic signs or symptoms associated with the pigmentation, including gastrointestinal bleeding. If all other potential sources for the pigmentation are ruled out, the clinician may consider the diagnosis of Laugier–Hunziker pigmentation. Hence, in most cases this is a diagnosis of exclusion. Despite the close resemblance of the labial pigmentation to that observed in Peutz–Jeghers syndrome, *STK11/LKB1* gene mutations have not been identified in patients with Laugier–Hunziker pigmentation.[98]

Management

The pigmentation may be esthetically unpleasing, but is otherwise innocuous. Although treatment is generally not indicated, laser and cryotherapy have been used with some success.[100]

TREATMENT OF MUCOCUTANEOUS MELANOSIS

In general, focally pigmented lesions warrant removal, for both diagnostic and therapeutic purposes. However, apart from those cases associated with neoplasia, surgical intervention is less of an option for the treatment of multifocal or diffuse pigmentation. Drug-induced melanosis and other examples of exogenously stimulated generalized pigmentation may spontaneously subside after withdrawal of the offending substance. In other cases, the discoloration may be persistent, if not permanent. This cosmetic disfigurement may result in significant social, psychologic, and emotional stress.

Different-thickness flap, gingivectomy, cryotherapy, electrosurgery, bur abrasion, and scraping with a scalpel have all been successfully used to treat gingival pigmentation. Laser therapy has also proven to be an effective modality for use in the treatment of bothersome oral pigmentation. However, the beneficial effects may only be temporary, with at least partial recurrence of pigmentation possible in upward of 20% of treated patients. Various types of lasers have been used, including superpulsed CO_2, Q-switched Nd-YAG, and Q-switched alexandrite lasers.[58]

Perioral and facial pigmentation are more challenging to treat, since skin type may dictate the occurrence of postoperative complications, such as postinflammatory hyperpigmentation. Although laser and cryotherapy have been used to successfully treat such cases, experimental forms of phototherapy have also been employed, including intense pulsed light and fractional photothermolysis. However, first-line therapy remains the application of topical medications, such as bleaching creams. Although single agents such as azelaic acid or hydroquinone have been used more commonly, dual- or triple-combination therapy is recommended. A combination of 4% hydroquinone–0.05% retinoic acid–0.01% fluocinolone acetonide has proven to be effective in greater than 90% of patients.[101] However, the majority of patients undergoing such therapy may experience immunologic sensitivity or other treatment-related adverse events, including the development of exogenous ochronosis.[77]

Exogenous ochronosis is a form of intense cutaneous hyperpigmentation with or without atrophic striae and coarsening of the skin or the formation of numerous coalesced, black papules. This phenomenon is more commonly observed in black individuals, usually female, who have undergone long-term bleaching therapy. The intense color changes develop in the areas where the cream was applied (frequently on the face) and are related to the accumulation of a yellow-brown pigmented substance (not melanin) in the dermis.[102] This pigmentation may be permanent. Q-switched Nd:YAG laser therapy appears to be effective in reducing the dyschromia associated with exogenous ochronosis.[103]

Finally, there are several substances, including novel tyrosinase inhibitors, that have demonstrable skin-lightening effects in animal models. However, these chemicals remain largely experimental and have not yet been proven to be effective in humans.

DEPIGMENTATION

Vitiligo

Etiology and Pathogenesis

Vitiligo is a relatively common, acquired, autoimmune disease that is associated with hypomelanosis. Vitiligo affects 0.5–2.0% of the world's population, with no sex or racial predilection. Although the precise etiology remains unknown, autoimmunity, cytotoxicity, genetics, and alterations from metabolic or oxidative stress have been implicated in this condition, where the end result is the destruction of melanocytes.[104]

The pathogenesis of vitiligo is multifactorial, with both genetic and environmental factors playing a role in the development of this disease. A study has identified a single-nucleotide polymorphism in a vitiligo-susceptibility gene that is also associated with susceptibility to other autoimmune diseases, including diabetes type 1, systemic lupus erythematosus, and rheumatoid arthritis. Additional putative vitiligo-susceptibility genes have been mapped to various other chromosomal regions.[105]

Clinical Features

The classification for vitiligo includes nonsegmental vitiligo, segmental vitiligo, and unclassified/undetermined vitiligo. Multiple achromic patches with a remitting–relapsing course are seen in nonsegmental vitiligo. Segmental vitiligo shows a characteristic dermatomeric distribution of the achromic patches with a rapid onset that is usually not progressive.[106]

The onset of vitiligo may occur at any age, but tends to develop more frequently during the second and third decades of life.[107] The depigmentation is more apparent in patients who have a darker skin tone, yet the disease actually occurs in all races. Vitiligo may also arise in patients undergoing immunotherapy for the treatment of malignant melanoma. Studies suggest that this phenomenon may be associated with a better prognosis for this group of patients.[55]

Vitiligo rarely affects the intraoral mucosal tissues. However, hypomelanosis of the inner and outer surfaces of the lips and perioral skin may be seen in up to 20% of patients (Figure 5-24).[108]

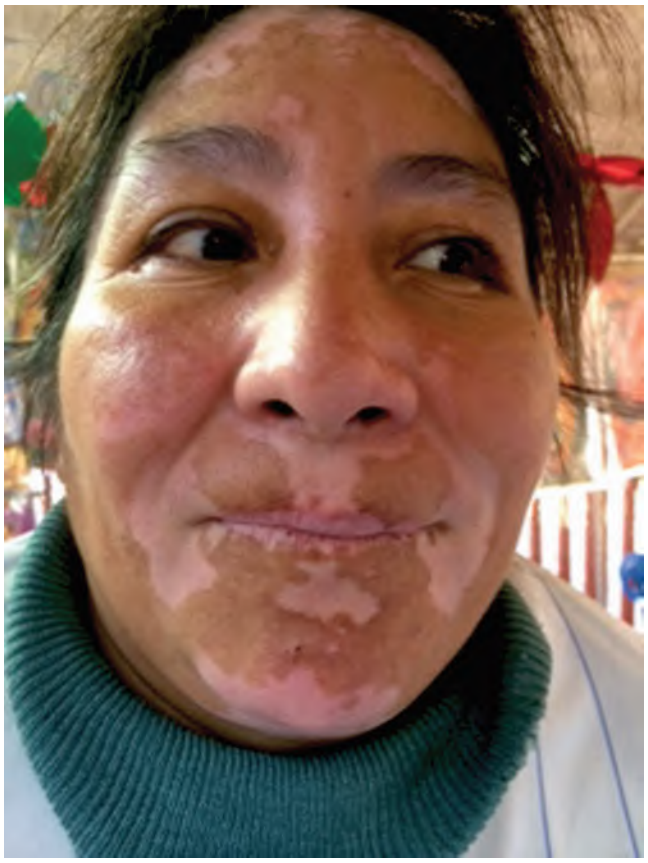

Figure 5-24 A 44-year-old Hispanic female presenting segmental vitiligo involving the forehead, face, and lips.

Pathology

Microscopically, there is a destruction of melanocytes by antigen-specific T cells and complete loss of melanin pigmentation in the basal cell layer.[104] The use of histochemical stains such as Fontana–Masson will confirm the absence of melanin.

Management

In most cases, the objective of therapeutic intervention is to stimulate repigmentation. Topical corticosteroids, topical calcineurin inhibitors, UVB narrow band (NB), and psoralen and ultraviolet A exposure (PUVA) have proven to be effective nonsurgical therapies.[106] In rare cases, small foci of normal pigmented skin may be contained within otherwise diffuse areas of hypomelanosis. Thus, to create a unified skin color, cutaneous bleaching may be considered.

Labial vitiligo is more resistant to treatment because of the lack of hair follicles at the affected site. Hair follicles typically have a reservoir of melanocytes that can be stimulated to produce pigment. Thus, surgical intervention may be the only option to achieve an esthetic result. Autologous epithelial grafts have also been reported to yield an acceptable cosmetic outcome. Split-thickness skin grafts have been reported as having the highest repigmentation success rate. Punch grafting and micropigmentation (whereby an exogenous brown pigment is injected into the lip, much like a tattoo) have also been used. In rare instances, surgical intervention may stimulate spontaneous repigmentation of vitiliginous lesions elsewhere on the body.[109,110]

HEMOGLOBIN AND IRON-ASSOCIATED PIGMENTATION

Ecchymosis

Traumatic ecchymosis is common on the lips and face, yet uncommon in the oral mucosa, except in cases related to blunt-force trauma or oral intubation. Immediately following the traumatic event, erythrocyte extravasation into the connective tissue will appear as a bright red macule or as a swelling if a hematoma has formed. The lesion will assume a brown discoloration within a few days, after the hemoglobin has degraded to hemosiderin. The differential diagnosis must include other focally pigmented lesions. If the patient recalls an episode of trauma, however, the lesion should be observed for two weeks, by which time it should have resolved.

When multiple brown macules or swellings are observed and ecchymosis is included in the differential diagnosis, a hemorrhagic diathesis or coagulation disorder should be considered.[111] Patients taking anticoagulants may present with oral ecchymosis, particularly on the buccal mucosa or tongue, either of which can be traumatized while chewing. Ecchymoses of the oral mucosa may also be encountered in patients with liver cirrhosis, leukemia, and additionally in patients with end-stage renal disease who are undergoing dialysis treatment. Laboratory tests, including bleeding time, prothrombin time, partial thromboplastin time, and international normalization ratio (INR), should be obtained in instances of spontaneous ecchymoses in order to explore defects in the coagulation pathways.

Purpura/Petechiae

Capillary hemorrhages will appear red initially and turn brown in a few days once the extravasated red cells have lysed and have been degraded to hemosiderin. The distinction between purpura and petechiae is essentially semantic and based solely on the size of the focal hemorrhages. Petechiae are typically characterized as being pinpoint or slightly larger than pinpoint, and purpura as multiple, small 2–4 mm collections of extravasated blood.[111] The same precipitating events can elicit either clinical presentation.

Oral purpura/petechiae may develop as a consequence of trauma, or viral or systemic disease (Table 5-7). Petechiae secondary to platelet deficiencies or aggregation disorders are usually not limited to the oral mucosa and may occur concurrently on the skin. Viral disease is more commonly associated with oral rather than cutaneous petechiae. In most cases, the petechiae are identified on the soft palate, although any mucosal site may be affected. When trauma is suspected, the patient should be instructed to cease whatever activity may be contributing to the presence of the lesions, which should then resolve within two weeks. Failure to do so should be viewed with caution as a hemorrhagic diathesis, a persistent infectious disease, or other systemic disease may be present and thus appropriate laboratory investigations must be undertaken.

Table 5-7 Causes of oral purpura/petechiae.

Amyloidosis
Aplastic anemia
Bulimia
Chronic renal failure
Fellatio
Forceful coughing
Hemophilia
Henoch–Schönlein purpura
HIV/AIDS
Infectious mononucleosis
Leukemia
Liver cirrhosis
Nonspecific trauma
Oral intubation
Oral submucous fibrosis
Overexertion
Papular–purpuric "gloves and socks" syndrome
Streptococcal infection
Systemic lupus erythematosus
Thrombocytopenia
Von Willebrand's disease

Hemochromatosis

Hemochromatosis is a chronic, progressive disease characterized by excessive iron deposition (usually in the form of hemosiderin) in the liver and other organs and tissues. Idiopathic, neonatal, blood transfusion, and heritable forms of this disease are recognized. Complications of hemochromatosis may include liver cirrhosis, diabetes, anemia, heart failure, hypertension, and bronzing of the skin. An increased incidence of cancer in patients with hemochromatosis has been reported.[112]

Cutaneous pigmentation is seen in over 90% of affected patients, regardless of the etiology of the disease.[113] The primary oral manifestation of hemochromatosis is a blue-gray to brown pigmentation, mainly affecting the palate and gingiva.[114]

Early in the course of disease, the pigmentation may be the result of basilar melanosis rather than an iron-associated pigment.[113] Iron deposition within the adrenal cortex may lead to hypoadrenocorticism and ACTH hypersecretion, with the associated Addisonian-type changes. In the later stages of hemochromatosis, the pigmentation is usually a result of hemosiderosis and melanosis.

A lower labial gland biopsy is a simple and effective method for the diagnosis of hemochromatosis.[115] Increased melanin pigment may be seen in the basal cell layer, whereas golden or brown-colored hemosiderin can be seen diffusely scattered throughout the submucosal and salivary gland tissues. A Prussian blue stain can confirm the presence of iron. Since hemochromatosis can cause a number of serious complications, medical referral is warranted.

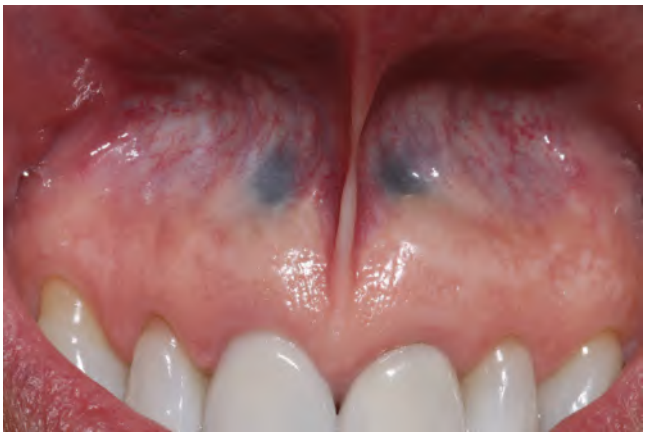

Figure 5-25 Amalgam tattoo of the maxillary alveolar mucosa. The pigment was associated with retrograde amalgam restorations.

EXOGENOUS PIGMENTATION

Amalgam Tattoos

Etiology and Pathogenesis

The most common pigmented lesion in the oral mucosa is the amalgam tattoo.[116] This is an iatrogenic condition resulting from the inadvertent deposition of amalgam restorative material into the submucosal tissue.

Clinical Features

Amalgam tattoos affect approximately 1–3% of the general population.[117] The lesions are typically small, asymptomatic, macular, and bluish gray or even black in appearance. They may be found on any mucosal surface. However, the gingiva, alveolar mucosa, buccal mucosa, and floor of the mouth represent the most common sites.[116] The lesions are typically discovered in the vicinity of teeth with large amalgam restorations or crowned teeth that probably once had amalgams, around the apical region of endodontically treated teeth with retrograde restorations or obturated with silver points, and in areas in and around healed extraction sites (Figure 5-25). Amalgam tattoo of the head and neck skin may occur in dentists and represents an occupational hazard resulting from failure to use facial protective barriers.

Pathology

Microscopically, amalgam tattoos show a fine brown granular stippling of collagen fibers, with a particular affinity for vessel walls and nerve fibers (Figure 5-26), with little or no inflammation. In some cases, large aggregates of black material may also be observed and this could result in a foreign body–type giant cell granulomatous inflammation. However, a mild to moderate lymphocytic inflammatory infiltrate is more commonly seen.[116]

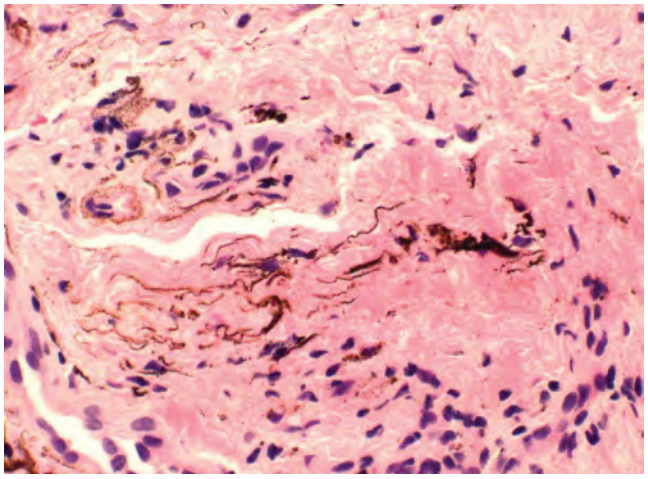

Figure 5-26 Amalgam tattoo. Spherules of restorative dental material (amalgam) are seen decorating collagen fibers. A characteristic perivascular distribution of the particles is observed (hematoxylin and eosin stain; ×400 original magnification).

Differential Diagnosis

A typical differential diagnosis includes melanotic macule, nevus, and melanoma.

Management

If large enough, amalgam particles can be identified on dental radiographs. In some patients, surgical removal may be warranted due to esthetic considerations. A two-stage surgical approach (subepithelial connective tissue graft followed by laser surgery) developed to eliminate amalgam tattoo has yielded excellent results.[118] However, since amalgam tattoos are innocuous, their removal is not always necessary, particularly when they can be documented radiographically. In the absence of radiographic evidence of amalgam, or in the event that the lesion appears suddenly or is not in proximity to a restored tooth, a biopsy is warranted.

Pigmentation associated with other dental restorative materials has also been described. Metal components from almost all forms of cast alloy material can be detected in adjacent tissues. Titanium has been associated with pigmentation of the skin, specifically in areas around orthopedic implants.[119] Thus, it is conceivable that dental implants may also be a potential source of exogenous oral pigmentation.

Graphite Tattoos

Graphite tattoos are an unusual source of focal exogenous pigmentation. They are most commonly seen on the palate and gingiva and represent traumatic implantation of graphite particles from a pencil (Figure 5-27). The lesions may be indistinguishable from amalgam tattoos, often presenting as a solitary gray or black macule. Since the traumatic event often occurs in childhood, many patients may not report a history of injury. Thus, a biopsy is often warranted. Microscopically, graphite particles resemble those of amalgam. When the graphite tattoo involves areas of cosmetic concern, removal of the lesion and a subsequent autogenous connective tissue graft provide a highly esthetic outcome.[120]

Ornamental Tattoos

Mucosal tattoos in the form of lettering or intricate artwork are becoming an increasingly common phenomenon (Figure 5-28). Amateur tattoo inks are permanent and consist of simple carbon particles originating from a variety of sources, including burnt wood, plastic, or paper, and from a variety of inks, such as India ink, pen ink, and plant-derived matter. Q-switched laser therapy has been used successfully to remove tattoos of the oral mucosa.[121]

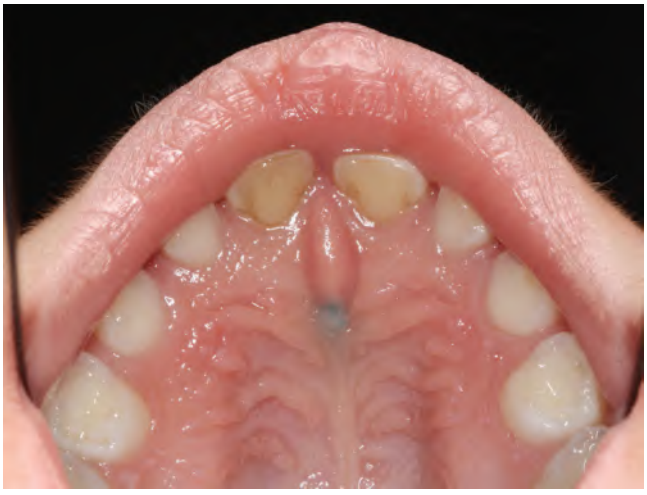

Figure 5-27 Graphite tattoo. A 4-year-old male with a round bluish macule on the hard palate, posterior to the incisive papilla. The child fell down with a pencil in his mouth and punctured his palate.

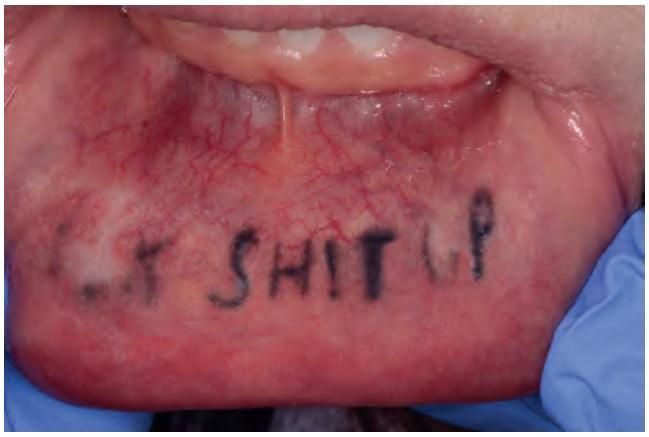

Figure 5-28 Intentional tattoo. Words written in the lower labial mucosa.

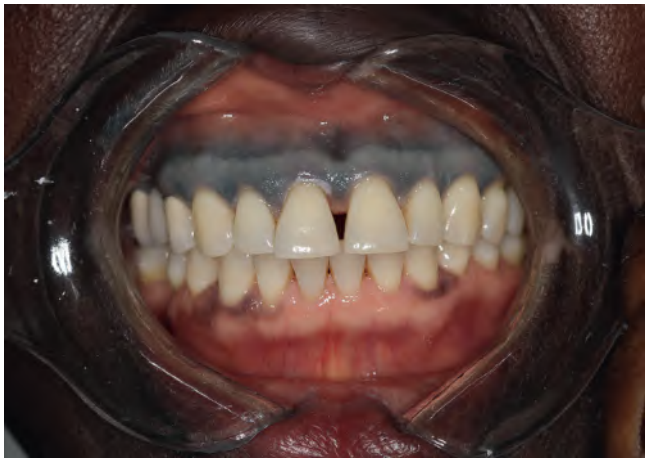

Figure 5-29 Ornamental tattoo. A 44-year-old Senegalese woman who performed her own gingival tattoo with eight needles bunched together, using the flame and soot from burning peanuts. *Source:* Courtesy of Dr. Darren Cox, University of the Pacific, San Francisco, CA, USA.

In certain tribal cultures, ornamental mucocutaneous tattooing is considered a rite of passage and esthetically pleasing. In these cases, the pigment is plant derived. Female members of certain tribes are more likely to exhibit this form of exogenous pigmentation, usually in an effort to make themselves more attractive or desirable (Figure 5-29).

An unusual South African female tribal custom includes brushing the teeth and gums with a chewed root of the tree *Euclea natalensis*, in the belief that it promotes oral health.[122] This plant root contains naphthoquinones and other organic substances that have putative antibacterial properties. Naphthoquinones are pigmented, and the mouths of root users are typically bright orange.[123] Unlike ornamental tattoos, this form of pigmentation is usually transient and reversible.

Medicinal Metal-Induced Pigmentation

Historically, a variety of metallic compounds have been used medicinally for the treatment of various systemic diseases. Fortunately, with the advent of methotrexate for the treatment of rheumatoid arthritis, gold therapy is less in demand.[124] Colloidal silver is another metal-based substance that has been historically touted for its beneficial health effects. Although its use in Western medicine has been significantly curtailed, it has become widely available among patients using complementary and alternative medicine therapies.[125] Gold and colloidal silver have both been associated with diffuse cutaneous pigmentation. Silver may cause a generalized blue-gray discoloration (argyria), whereas gold-induced pigment may appear blue-gray or purple (chrysiasis).[124,125] In both cases, the pigmentation may be persistent, if not permanent, even following discontinuation of the substance. Rare examples of diffuse oral argyria have been reported. Chrysiasis does not involve the oral mucosal tissues, since it is thought that exposure to ultraviolet light or other high-intensity light sources precipitates the pigmentation. However, oral lichenoid eruptions have been associated with systemic gold therapy.[60]

In contrast to the systemic therapies, metal salts remain a component of some topical medications and other substances that are used in clinical practice. Examples include silver nitrate and zinc oxide. Silver nitrate cautery has been used to treat recurrent aphthous stomatitis, and zinc oxide is a common component of sunblock creams. Both substances have been associated with focal mucocutaneous pigmentation. Zinc oxide–containing sunblock, which is used to treat severely chaffed lips, may result in the development of hyperpigmentation. Histologically, the findings are similar to an amalgam tattoo. However, scanning electron microscopy and radiographic microanalysis unveil the presence of zinc in elastic fibers.[126] Medicinal silver-associated pigment appears as brown or black particulate matter dispersed throughout the connective tissue. A clinicopathologic correlation is necessary since, clinically and microscopically, these forms of pigmentation may be difficult to differentiate from amalgam tattoos.

Generalized black pigmentation of the tongue has been attributed to the chewing of bismuth subsalicylate tablets, a commonly used antacid.[127] This phenomenon is unlike black hairy tongue, which is associated with elongation of the filiform papillae, hyperkeratosis, and superficial colonization of the tongue by bacteria. Black tongue induced by bismuth subsalicylate is caused by deposition of actual pigment (bismuth sulfide), without any other lingual changes. Discontinuation of the antacid and cleansing of the tongue are curative. It should be noted that typical black hairy tongue may also be attributed to the use of bismuth subsalicylate.

Heavy Metal Pigmentation

Diffuse oral pigmentation may be associated with ingestion of heavy metals. Nowadays, this phenomenon is rarely encountered. Yet, it remains an occupational and health hazard for some individuals who work in certain industrial plants and for those who live around these types of facilities. Other relatively common environmental sources include paints, old plumbing, and seafood.

Lead, mercury, bismuth, and arsenic have all been shown to be deposited in oral tissue if ingested in sufficient quantities or over an extended period of time.[72] These ingested metal salts tend to extravasate from vessels in areas of chronic inflammation. Thus, in the oral cavity, the pigmentation is usually found along the free marginal gingiva, where it often dramatically outlines the gingival cuff. This metallic line usually has a gray to black appearance. In some patients, the oral pigmentation may be the first sign of heavy metal toxicity. Additional systemic signs and symptoms of heavy metal poisoning may include behavioral changes, neurologic disorders, intestinal pain, and sialorrhea. Diffuse mucocutaneous melanosis may also be observed in some affected individuals.[128]

Drug-Induced Pigmentation

Minocycline (a tetracycline derivative frequently used in the treatment of acne) is a relatively common cause of drug-induced non-melanin-associated oral pigmentation. Like tetracycline, minocycline can cause pigmentation of developing teeth. However, most patients are prescribed minocycline in early adulthood. When taken chronically, minocycline metabolites may become incorporated into the normal bone. Therefore, whereas the teeth may be normal in appearance, the surrounding bone may appear green, blue, or even black. In addition, the roots show a green color, while developing roots tend to be black. As a result, the palatal and alveolar mucosae may appear similarly and diffusely discolored.[129]

Minocycline can also induce actual pigmentation of the oral soft tissues, as well as the skin and nails. Minocycline-induced soft tissue pigmentation may appear as gray, brown, or black. The pigmentation is either patchy or diffuse. Although a biopsy may reveal basilar melanosis, more commonly aggregates of fine brown or golden particles are identified within the lamina propria. The particles are often identified in the cytoplasm of macrophages. Superficially, the pigment in the lamina propria may

resemble melanin and will stain with a melanin-specific (Fontana–Masson) histochemical stain. However, an iron stain (Prussian blue) will also highlight many of the same particles.[129] Thus, it is likely that the particulate substance represents a precipitated drug metabolite rather than true melanin.

The mucosal discoloration produced by minocycline often subsides within months after discontinuation of the medication. Nowadays, acceptable esthetic outcomes are obtained even in severe cases of cutaneous pigmentation associated with minocycline intake when alexandrite 755 nm laser therapy is used.[130] However, the bone pigment may persist for longer periods of time, if not indefinitely.

Methacycline, another tetracycline derivative that is no longer widely used in clinical practice, can also produce a similar form of pigmentation.[131]

Hairy Tongue

Hairy tongue is a relatively common condition of unknown etiology.[132] The change in oral flora associated with chronic antibiotic therapy may be causative in some patients. The discoloration involves the dorsal tongue, particularly the middle and posterior one-third. Rarely are children affected. The filiform papillae are elongated, sometimes markedly, and have the appearance of fine hairs. The hyperplastic papillae then become pigmented by colonizing chromogenic bacteria, which can impart a variety of colors, including white, green, brown, or black (Figure 5-30). Various foods, drinks, and confectionery can contribute to the diffuse discoloration. The smoking of both tobacco and crack cocaine has been associated with black hairy tongue.[133] Rare examples of black hairy tongue have been linked to the use of psychotropic medications, tetracycline, linezolid, olanzapine, bismuth, and erlotinib.[134,135]

Black hairy tongue is so characteristic in its presentation that biopsy is not required, and a clinical diagnosis is usually appropriate. Microscopically, the filiform papillae can be seen as extremely elongated and hyperplastic with hyperkeratosis. Superficial microbial colonization of the papillae is a prominent feature. The treatment is mechanical and consists in using a tongue scraper, and limiting the ingestion of color-forming foods and drinks until the discoloration resolves. Since the cause is often unknown, the condition may recur.

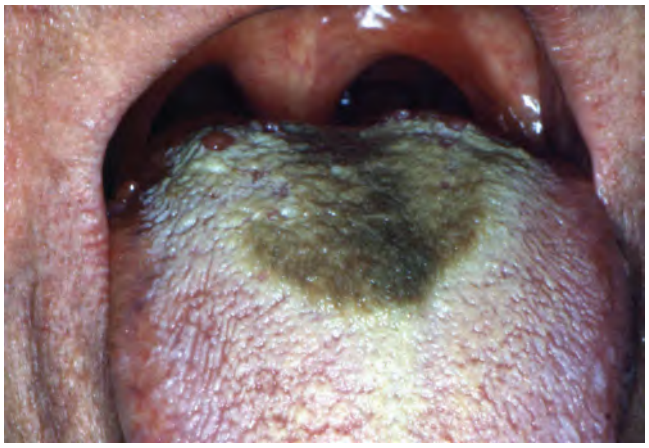

Figure 5-30 Hairy tongue. Elongated lingual filiform papillae displaying a gamut of colors ranging from white to brown and black discoloration of the dorsum of the tongue.

CONCLUSION

Oral pigmentation may be focal, multifocal, or diffuse. The lesions may be blue, red, purple, brown, gray, or black. They may be macular or tumefactive. Importantly, some are localized, harmless accumulations of melanin, hemosiderin, or exogenous metal, while others are harbingers of systemic or genetic disease and may be associated with life-threatening medical conditions that require immediate intervention. The differential diagnosis for any given pigmented lesion can be extensive and can include examples of endogenous and exogenous pigmentation. Although biopsy is a helpful and necessary aid in the diagnosis of focally pigmented lesions, the more diffuse lesions require a thorough history and laboratory studies in order to arrive at a definitive diagnosis.

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6

Benign Lesions of the Oral Cavity and the Jaws

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This chapter provides an overview of the etiology and pathogenesis, epidemiology, clinical and histopathologic manifestations, differential diagnosis, applicable laboratory findings, and management of nonmalignant growths and tumors of the oral cavity and the jaws. Prevalence data for these entities is variable and based on population screening studies[1,2,3] or large case series, and many of the entities described occur at a sufficiently low prevalence to be reported as rare. Most entities are not true neoplasms, and therefore a variety of miscellaneous etiologies are discussed. If left untreated, some of the entities considered in this chapter can lead to extensive tissue destruction and deformity, whereas others may have a lesser impact, albeit they negatively affect oral function. Regardless, one of the major clinical considerations in the management of these

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

growths and tumors is to identify their benign nature and to distinguish them from potentially life-threatening malignant neoplasms. Identification can only be established with certainty by microscopic examination of excised tissue; therefore, biopsy is often an essential step in their diagnosis and management.

VARIANTS OF NORMAL

Structural variations of the oral cavity and the jaws are sometimes mistakenly identified as pathologic, but they are usually easily recognized as being within the range of normal findings, and biopsy is rarely indicated. One cannot appreciate the abnormal before understanding the range of normal. Examples of such structural variants are tori, enlarged papillae associated with the opening of Stensen's duct, Fordyce spots, and sublingual varicosities in older individuals.

Tori/Exostoses

Etiology and Pathogenesis

Tori and exostoses are considered to be normal structural variants. Their etiology is multifactorial and poorly defined, although genetics is a dominant factor.[4] There is no strong evidence to either support or refute bruxism or other parafunctional habits as causes. The growth of tori and exostoses is highly variable and their negligible growth after an initial slow but steady period of development suggests that they are unlikely to be inflammatory hyperplasias or neoplasms.

Epidemiology

The prevalence of tori is highly variable, ranging from <5% to almost 30% in different studies and populations. Smaller studies using dental casts to determine the presence of any torus or exostosis demonstrate significantly higher prevalence, >50%. Their onset is at any age, but most commonly during the third decade, and with no consistent sex predilection.

Clinical and Histologic Manifestations

Exostoses manifest as localized nodular enlargements of the cortical bone of the midline of the palate (torus palatinus),[5] the lingual aspect of the mandible (torus mandibularis), and the buccal aspects of either jaws (Figure 6-1). Other than the torus palatinus, exostoses have a bilateral presentation. They are typically small, although rarely they may become sufficiently large to interfere with oral function. Histologically, tori consist of layers of dense cortical bone

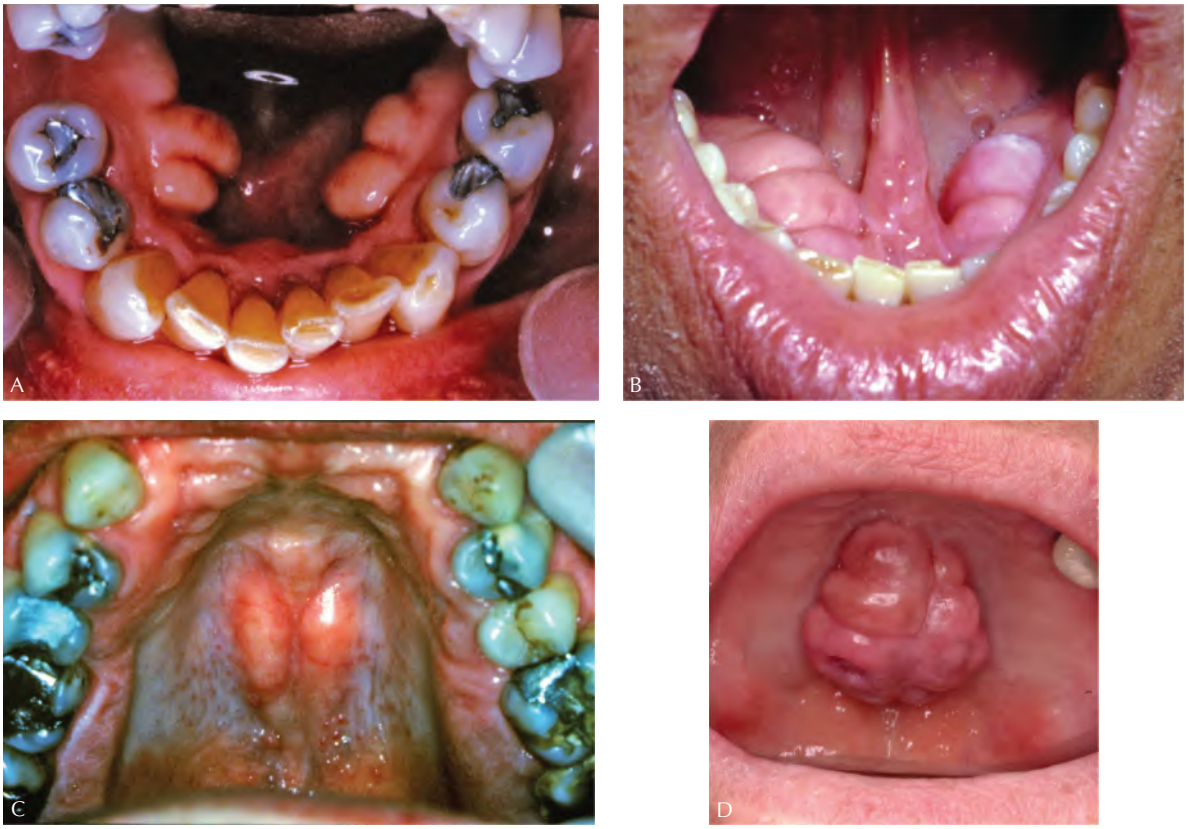

Figure 6-1 (A) Mandibular tori (tori mandibularis). (B) Mandibular tori. Note traumatic keratosis on the left side due to the large size of the tori. (C) Maxillary torus (torus palatinus). (D) Maxillary torus. Note the large size with a "pedunculated base."

covered by periosteum and a thin overlying layer of epithelium with minimal rete peg development.

Differential Diagnosis

Similar nodular growths or exostoses arising on the buccal aspect of the maxillary and mandibular alveolae must be differentiated from bony enlargement secondary to bone diseases such as fibrous dysplasia or Paget's disease.

Management

No management is required unless tori pose a functional problem such as a mechanical problem in the construction of dentures, or if they become frequently traumatized as a result of their prominent position and the resulting traumatic ulcers are slow to heal. In such cases, surgical removal is indicated.

Unencapsulated Lymphoid Aggregates

Etiology and Pathogenesis

These are normal structures, distinct from the palatine and lingual tonsils, and comprise part of Waldeyer's ring, They may increase in size as a result of benign (reactive) processes [6] or due to lymphoid neoplasms (i.e., lymphomas).

Clinical Manifestations

They may be located on the posterolateral aspects of the tongue (Figure 6-2), anterior tonsillar pillar, posterior pharyngeal wall, soft palate, and dorsal tongue. Histologic criteria based on architectural, cytologic, and immunologic features of the lymphoid aggregate have been described.

Differential Diagnosis

These may masquerade clinically as a malignancy.

Management

No management is required unless these aggregates demonstrate unilateral and progressive enlargement, in which case a biopsy is indicated to rule out malignancy.

Fordyce Spots

Etiology and Pathogenesis

These are ectopic sebaceous glands and it is unclear why some individuals develop them. The link between hyperlipidemia and Fordyce spots has not been substantiated.

Epidemiology

Fordyce spots are common and have been reported to occur in up to 80% of patients.[7]

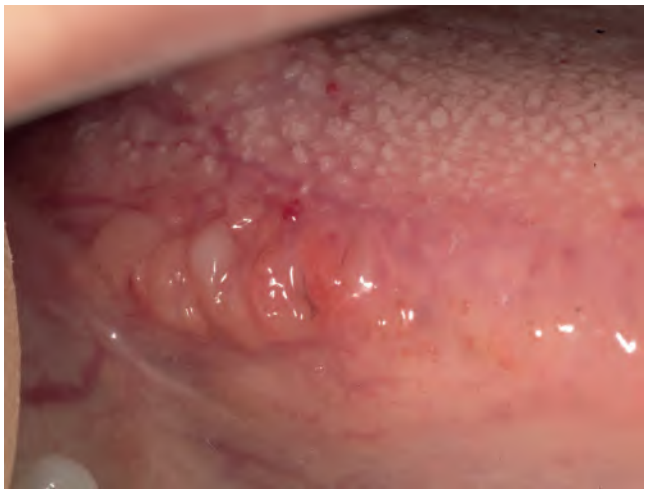

Figure 6-2 Right posterolateral tongue revealing a prominent foliate papilla region containing unencapsulated lymphoid aggregates. A similar presentation was seen on the left side.

Clinical Manifestations

The most common locations for Fordyce spots are the buccal mucosae and lip vermillion.

Management

Typically no treatment is required. There are surgical options for patients with a high concentration of labial Fordyce spots deemed esthetically obtrusive.

BENIGN SOFT TISSUE LESIONS

INFLAMMATORY/REACTIVE EXOPHYTIC SOFT TISSUE LESIONS

The term *inflammatory/reactive soft tissue tumors* is used to describe a large range of commonly occurring exophytic lesions of the oral mucosa that histologically represent inflamed fibrous and granulation tissue. The majority of these occur peripherally on the oral mucosal surfaces that may be subject to masticatory trauma (i.e., as the result of chronic trauma from ill-fitting dentures, biting, or contact with fractured teeth), related to the chronic inflammatory stimuli (i.e., overhanging restorations, calculus), or in some lesions the levels of circulating hormones or medications play a role. The number and size of these reactive hyperplastic lesions vary depending on the degree to which one or more of the components of the inflammatory reaction and healing response are exaggerated. Some are predominantly epithelial overgrowths with only scanty connective tissue stroma; others are fibromatous, with a thin epithelial covering, and may exhibit either angiomatous, desmoplastic (collagenous), or fibroblastic features. In many lesions, examples of each of these histologic patterns is revealed. Like scar tissue, some

inflammatory hyperplasias appear to mature and become less vascular (paler and less friable) and more collagenous (firmer and smaller) with time. Others appear to have a high proliferative ability for exophytic growth until they are excised. This variability of histologic appearance is reflected in the wide range of clinical characteristics exhibited by inflammatory hyperplasias.[8] If the chronic irritant is eliminated when the lesion is excised, the majority of inflammatory hyperplasias will not recur, thus confirming the benign nature of these lesions.

Irritation Fibroma

Etiology and Pathogenesis

Irritation fibromas develop following trauma, such as a cheek or lip bite.

Epidemiology

They are the most common exophytic soft tissue lesion, with a prevalence of approximately 1%, and they comprise 10–15% of exophytic soft tissue lesions submitted for histopathologic examination.

Clinical Manifestations

Irritation fibromas are usually asymptomatic and may occur as either pedunculated or sessile (broad-based) pink nodules on any surface of the oral mucosa, but most commonly involving the buccal or labial mucosae (Figure 6-3). The majority are rarely >1 cm in diameter.

Differential Diagnosis

These include giant cell fibroma, neurofibroma, schwannoma, granular cell tumor, leiomyoma, rhabdomyoma, mucocele, or malignant minor salivary gland neoplasms.

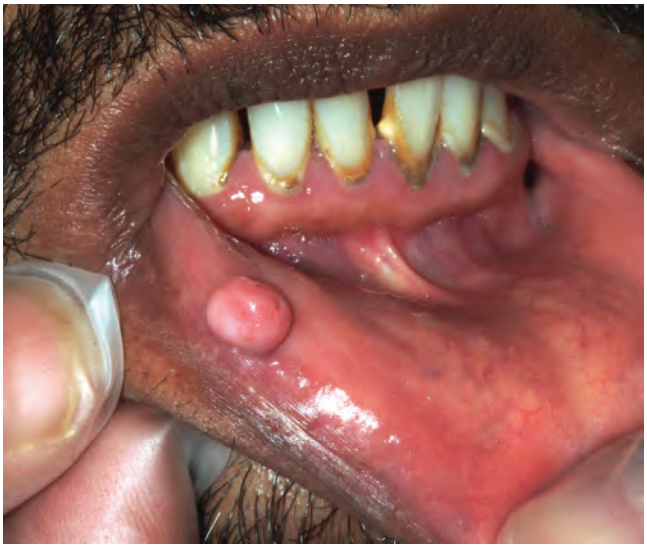

Figure 6-3 Irritation fibroma (traumatic fibroma). Patient reported a daily habit of biting this lesion for several months.

Management

An excisional biopsy is indicated except when the procedure would produce marked deformity; in such a case, incisional biopsy to establish the diagnosis is mandatory. The irritant, if present, should also be eliminated when the lesion is excised to reduce the risk for recurrence.

Other Solitary Fibrous Lesions

Pulp polyps (aka chronic hyperplastic pulpitis) are analogous to a fibroma. They occur when the pulpal connective tissue proliferates through a large carious pulpal exposure and fills the cavity in the tooth with a mushroom-shaped polyp that is connected by a stalk to the pulp chamber (Figure 6-4). Masticatory pressure may lead to keratinization of the epithelium covering these lesions. Pulp polyps contain few sensory nerve fibers and are remarkably insensitive. The crowns of teeth affected by pulp polyps are usually so badly destroyed by caries that endodontic treatment is not feasible.

Giant cell fibromas comprise a small subset (<5%) of solitary fibrous lesions. Their etiology is unknown, and these exophytic lesions are typically smaller than the irritation fibroma.[9] They most often involve the gingivae, exhibit a nodular surface, and are histologically distinguished from other fibromas by the presence of stellate-shaped and multinucleated cells in the connective tissue.

Although they are nonreactive, it is worth mentioning that fibromas are part of the manifestations in two rare syndromes: Cowden syndrome and tuberous sclerosis complex. Cowden syndrome (multiple hamartoma and neoplasia syndrome) is an autosomal dominant disorder affecting multiple organ systems[10] and caused by mutations in the phosphatase and tensin homolog gene (PTEN). Oral and perioral findings include multiple papules on the lips and gingivae, papillomatosis (benign fibromatosis) of the buccal, palatal, faucial, and oropharyngeal mucosae often producing a "cobblestone" effect, and the tongue may also present as pebbly or fissured. Multiple papillomatous nodules (histologically inverted follicular keratoses or trichilemmomas) are often present on the perioral, periorbital, and perinasal skin, the pinnae of the ears, and the neck. These nodules are often accompanied by lipomas, hemangiomas, neuromas, vitiligo, café au lait spots, and acromelanosis elsewhere on the skin. A variety of neoplastic changes occur in the organs exhibiting hamartomatous lesions, with an increased rate of breast and thyroid carcinoma and gastrointestinal malignancy. Squamous cell carcinoma of the tongue and basal cell tumors of the perioral skin have also been reported.

Tuberous sclerosis complex is an inherited disorder[11] caused by mutations in the tuberous sclerosis complex (*TSC1* or *TSC2*) genes that is characterized by seizures and intellectual disability, associated with hamartomatous glial proliferations and neuronal deformity in the central nervous system. Fine wart-like lesions (adenoma sebaceum) occur in a butterfly distribution over the cheeks and forehead (Figure 6-5A),

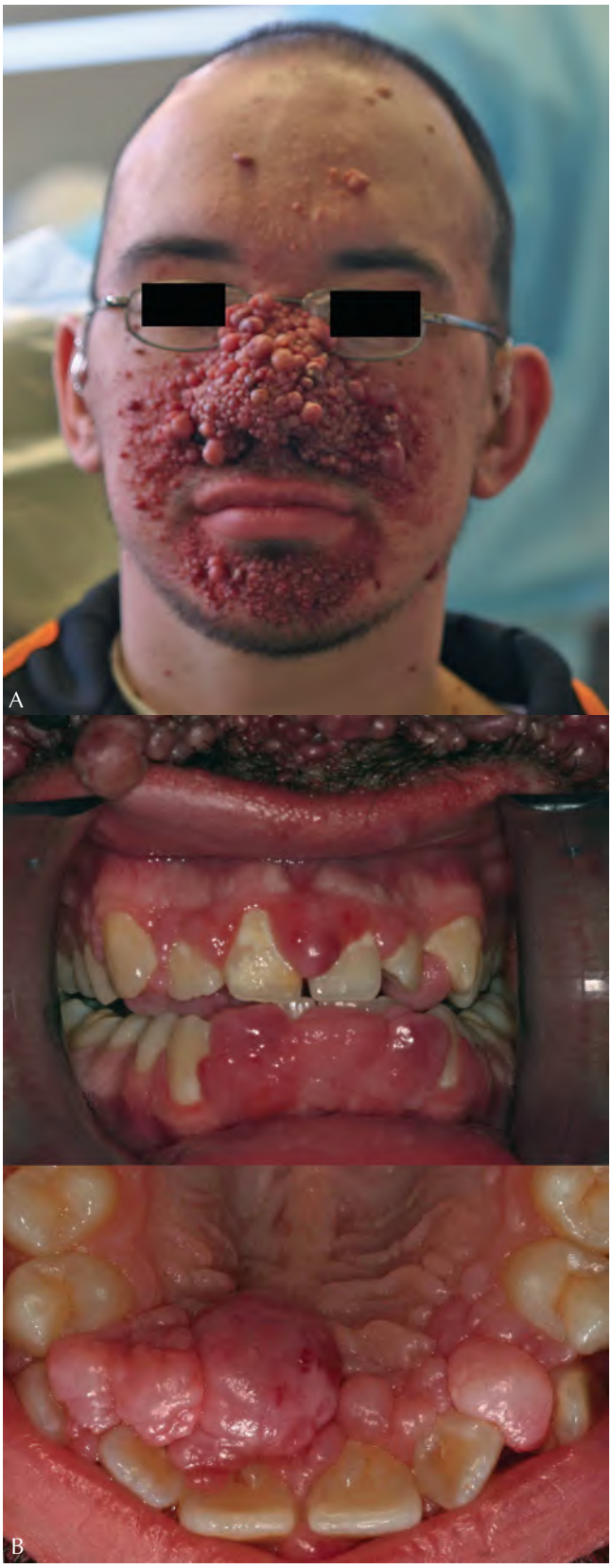

Figure 6-4 (A) Young male with tuberous sclerosis. There are extensive wart-like lesions (adenoma sebaceum) in a butterfly distribution over the face. (B) Same patient as in (A) showing intraoral fibromas. Generalized hypoplastic pitted enamel changes are absent.

and histologically similar lesions (vascular fibromas) have been described intraorally (Figure 6-5B). Characteristic hypoplastic enamel defects (pitted enamel hypoplasia) occur in 40–100% of those affected. Rhabdomyoma of the heart and other hamartomas of the kidney, liver, adrenal glands, pancreas, and jaw have been described.

Fibrous Inflammatory Hyperplasias/Epulis Fissuratum

Etiology and Pathogenesis

These are reactive inflammatory lesions associated with the periphery of ill-fitting dentures.[12] They have no malignant potential.

Epidemiology

The prevalence is <0.5% in the general population and comprises <2% of exophytic soft tissue lesions submitted for histopathologic examination.

Clinical and Histologic Manifestations

The growth is often split by the edge of the denture, resulting in a fissure, one part of the lesion lying under the denture and the other part lying between the lip or cheek and the outer denture surface (Figure 5-6). Histologically they resemble the irritation fibroma.

Differential Diagnosis

The rolled border, albeit nonindurated, can resemble some squamous cell carcinomas.

Management

Many such hyperplastic growths will become less edematous and inflamed following the removal of the associated chronic irritant, but they rarely resolve entirely. In the preparation of the mouth to receive dentures, these lesions are excised (i.e., by conventional scalpel or laser excision) to prevent further irritation and to ensure a soft tissue seal for the denture periphery. Recurrence following excision is almost always a result of a failure to eliminate the source of irritation. The occasional report of squamous cell carcinoma arising in an area of chronic denture irritation, however, underlines the importance of microscopic examination of the excised tissue.

Inflammatory Papillary Hyperplasia

Etiology and Pathogenesis

The exact pathogenesis is unclear, but this condition is usually associated with chronic denture irritation and denture stomatitis due to chronic candidal infection.[12]

Epidemiology

Inflammatory papillary hyperplasia is a common lesion in approximately 3–4% of denture wearers. Old and ill-fitting

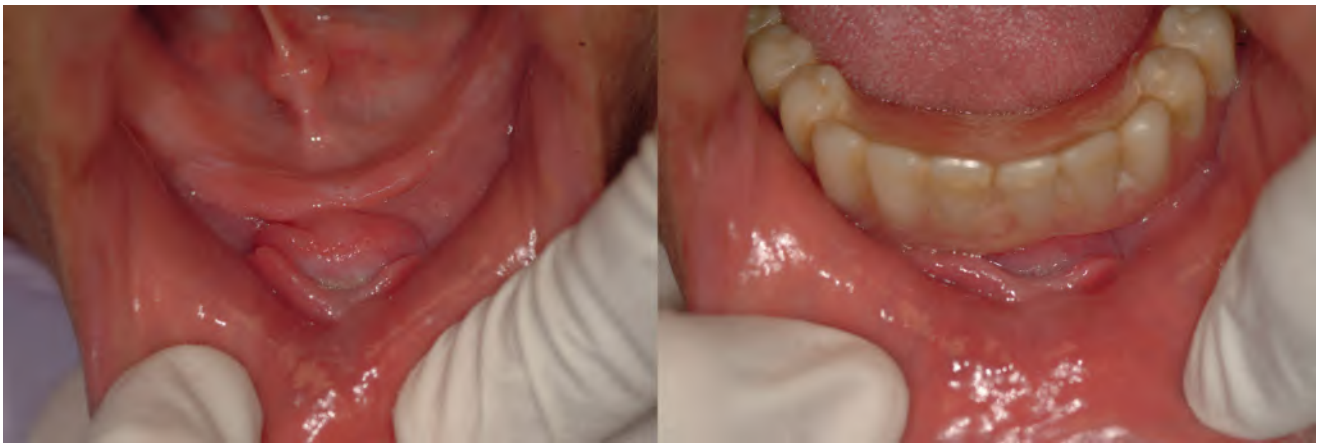

Figure 6-5 Fibrous hyperplasia (epulis fissuratum) secondary to a poorly fitting mandibular complete denture.

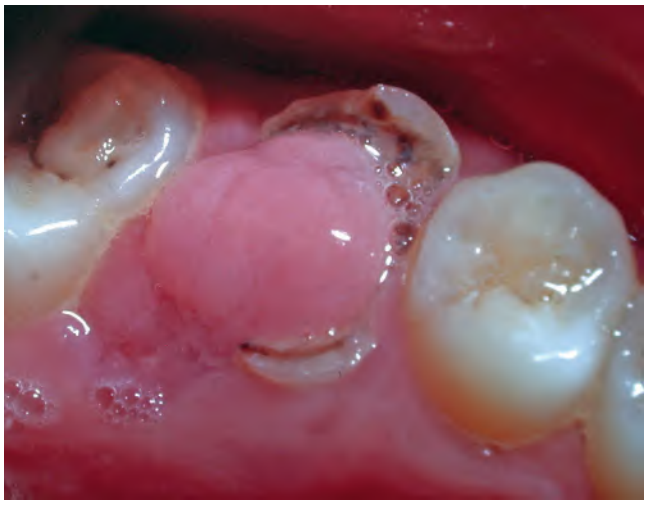

Figure 6-6 Pulp polyp (hyperplastic pulpitis) within a carious maxillary premolar.

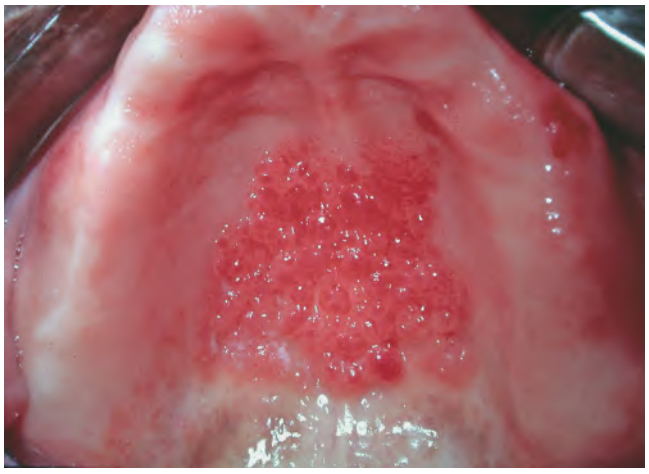

Figure 6-7 Papillary hyperplasia under a poorly fitting maxillary complete denture.

complete maxillary dentures appear to be the strongest stimuli, but the lesion may also be seen under partial maxillary dentures.

Clinical Manifestations

This condition develops on the central hard palate, with a characteristic red to scarlet lesion demonstrating swollen and tightly packed projections resembling the surface of an overripe berry (Figure 6-7). Such lesions are friable, and often bleed with minimal trauma.

Differential Diagnosis

Squamous cell carcinoma.

Management

Mild cases may be treated successfully by topical or systemic antifungals alone;[6] otherwise, papillary hyperplasia may be surgically excised or removed by electrocautery, cryosurgery, or laser surgery. The old denture or a palatal splint can be used as a postoperative surgical dressing, followed by fabrication of a new denture.

Pyogenic Granuloma and Pregnancy Tumor

Etiology and Pathogenesis

The etiology of pyogenic granulomas is thought to be in response to chronic irritation.[13] Their propensity for involving the gingival margin supports this etiology and suggests that calculus, food materials, and overhanging dental restoration margins are important irritants that should be eliminated when the lesion is excised. Hormones play a role in the etiology of the lesion in the setting of pregnancy (where the lesion is named a pregnancy tumor), although local irritation is also an important etiologic factor.

Epidemiology

Fewer than 5% of exophytic soft tissue lesions submitted for histopathologic examinations are pyogenic granulomas.

They have a female predilection (>2:1 ratio). Pregnancy tumors occur toward the end of pregnancy (when levels of circulating estrogens are highest), and they tend to shrink after delivery (when there is a precipitous drop in circulating estrogens).

Clinical and Histologic Manifestations

Pyogenic granulomas typically present as solitary hemorrhagic, often pedunculated, nodules of variable size that occur most frequently on the gingiva (Figure 6-8), although they may occur on any mucosal surface. Their friable, hemorrhagic, and frequently ulcerated appearance correlates with their histologic structure, demonstrating proliferating endothelial tissue, much of which is canalized into a rich vascular network with minimal collagenous support. Neutrophils, as well as chronic inflammatory cells, are consistently present throughout the edematous stroma, and form into microabscesses. These histologic features resemble hemangiomas. Despite the common name for the lesion, a frank discharge of pus is not present, and when such a discharge does occur it is likely a sinus tract emanating from an underlying periodontal or periapical abscess, the opening of which is often marked by a nodule of granulation tissue (parulis).

Differential Diagnosis

When involving the gingiva, the differential includes other reactive gingival lesions, including peripheral ossifying fibroma and peripheral giant cell granuloma. Hemangiomas may appear similar clinically. Malignant neoplasms may also be included in the differential (e.g., squamous cell carcinoma, or other rarer entities).

Management

Surgical excision and successful removal of the associated irritant are associated with a low rate of recurrence. Scrupulous oral hygiene can prevent pregnancy tumors.

Peripheral Ossifying or Cementifying Fibroma

Etiology and Pathogenesis

This is a reactive lesion of unclear etiology, most likely related to local trauma/irritation.

Epidemiology

These lesions occur in teenagers and young adults and are more common in women.

Clinical/Histologic Manifestations

They occur exclusively on the gingiva, typically located in the interdental papilla region (Figure 6-9), and vary in presentation from pale pink to cherry red. This reactive proliferation is named because of the histologic evidence of calcifications that are seen in the context of a hypercellular fibroblastic stroma.

Differential Diagnosis

The differential includes other reactive gingival lesions, including pyogenic granuloma and peripheral giant cell granuloma. Malignant neoplasms may also be included in the differential (e.g., squamous cell carcinoma, or other rarer entities).

Management

Treatment should include the elimination of subgingival irritants and periodontal pockets, as well as excision of the gingival growth.

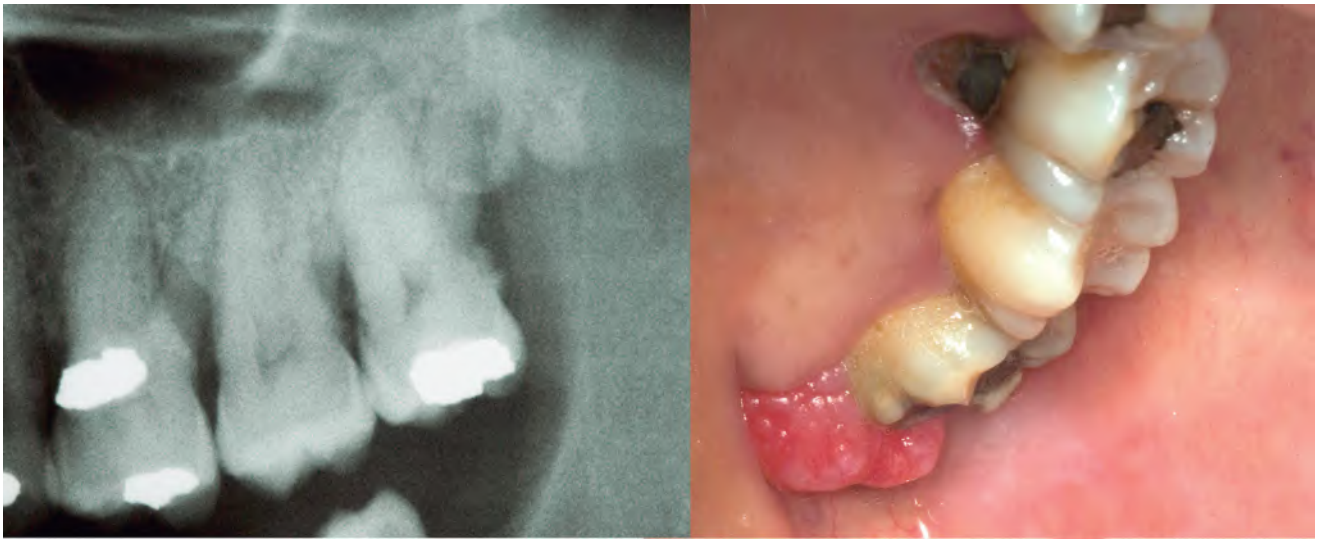

Figure 6-8 Pyogenic granuloma associated with a periodontal defect on the distal aspect of the maxillary left third molar. There is radiographic evidence of subgingival calculus, a likely etiologic factor.

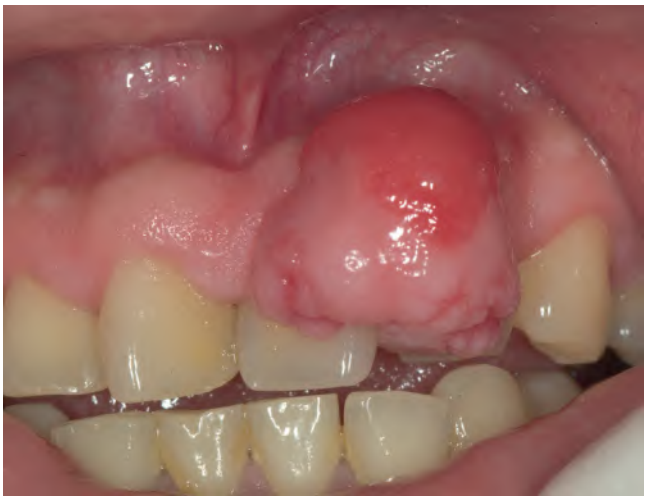

Figure 6-9 Peripheral ossifying fibroma in a teenage male associated with the maxillary buccal gingiva. The lesion was pedunculated.

Peripheral Giant Cell Granuloma

Etiology and Pathogenesis

This is a reactive lesion of unclear etiology, most likely related to local trauma/irritation. It is the soft tissue counterpart to the central giant cell granuloma.

Epidemiology

Peripheral giant cell granulomas are five times as common as the central lesions.

Clinical and Histologic Manifestations

Giant cell granulomas are solitary and occur either as a peripheral exophytic lesion found exclusively on the gingiva or as a centrally located lesion within the jaw, skull, or other facial bones (described in the section that includes bone lesions).

Differential Diagnosis

The differential includes other reactive gingival lesions, including pyogenic granuloma and peripheral ossifying or cementifying fibroma. Malignant neoplasms may also be included in the differential (e.g., squamous cell carcinoma, or other rarer entities).

Management

Peripheral giant cell granuloma is treated identically to the other reactive gingival lesions, by surgical excision and the elimination of local factors contributing to gingival/periodontal disease.

Nodular Fasciitis

Etiology and Pathogenesis

This is a reactive proliferation of myofibroblasts and although the etiology is unknown, trauma is a likely factor. Growth rates are variable but can be rapid.

Epidemiology

Oral nodular fasciitis is rare and occurs at all ages, with the majority during the fourth and fifth decades, with no sex predilection.

Clinical and Histopathologic Manifestations

The most common oral site is the buccal mucosa and most have an exophytic presentation. Nodular fasciitis has distinctive microscopic features revealing the myofibroblast as the predominant cell type. The microscopic features can resemble a sarcoma, and may present a diagnostic challenge for the pathologist.

Differential Diagnosis

Benign or malignant soft tissue growths.

Management

Conservative surgical excision and submission for histology.

Proliferative Myositis and Focal Myositis

Etiology and Pathogenesis

These entities are reactive fibroblastic lesions that infiltrate around individual muscle fibers.

Epidemiology

They are exceedingly rare.

Clinical Manifestations

Lesions most frequently involve the tongue and other neck and jaw muscles. Despite the nomenclature, these lesions do not show histologic signs of inflammation.

Differential Diagnosis

Lesions of skeletal muscle that have similar clinical features and are differentiated by histopathologic findings.

Management

Conservative surgical excision and submission for histopathology.

Reactive Gingival Enlargement

Gingival enlargement or overgrowth is usually caused by local inflammatory conditions such as poor oral hygiene, food impaction, or mouth breathing.[14] Systemic conditions such as hormonal changes or drug therapy may also cause or contribute to the severity of gingival enlargement. Histologically, there are a number of explanations for gingival enlargement: hypertrophy (an increase in cell size), hyperplasia (an actual increase in cell number), edema, vascular engorgement, the presence of an inflammatory cell infiltrate, or an increase in dense fibrous connective tissue. One or more of these explanations may predominate depending on the underlying cause.

Inflammatory Gingival Enlargement

Etiology and Pathogenesis

Inflammatory gingival enlargement occurs in sites where there has been chronic suboptimal oral hygiene with heavy biofilm accumulation, supragingival calculus formation, impaction of food, or the presence of aggravating factors such as orthodontic appliances, mouth breathing, hormonal changes, or other systemic diseases. Gingival enlargement primarily affecting the maxillary anterior region may be observed in mouth breathers, and hormonal changes (such as during pregnancy or puberty) may exaggerate the local immune response to local factors and contribute to gingival enlargement.

Epidemiology

Gingivitis is highly prevalent (>90%), particularly in a pediatric and adolescent population, but conservative estimates of severe gingivitis associated with gingival enlargement are <5%.

Clinical and Histologic Manifestations

The clinical diagnosis of inflammatory gingival enlargement is straightforward, with tissues exhibiting a glossy edematous bright red or purplish color, pitting edema, and a tendency to hemorrhage on slight provocation (Figure 6-10). A malodor may result from the decomposition of food debris and accumulation of bacteria. Pseudopockets formed by gingival enlargement make the maintenance of good oral hygiene difficult, perpetuating a cycle of inflammation. Longstanding inflammatory gingival enlargement may demonstrate relatively firm, resilient, and pink gingivae that do not bleed readily. This is due to a greater fibrous component with an abundance of fibroblasts and collagen fibers. Chronic inflammatory gingival enlargement is a risk factor for periodontal disease. Histologically, the exudative and proliferative features of chronic inflammation are seen: a preponderance of inflammatory cells, vascular engorgement, new capillary formation, and associated degenerative changes.

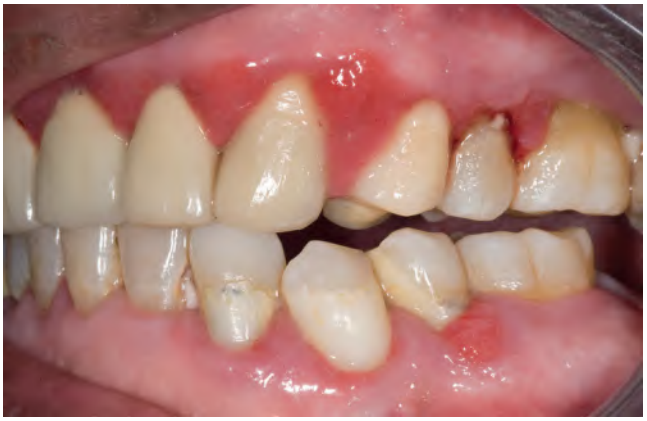

Figure 6-10 Inflammatory gingival enlargement secondary to local factors.

Differential Diagnosis

Drug-induced gingival enlargement, other systemic diseases (including acute myelogenous leukemia, von Recklinghausen's neurofibromatosis [neurofibromatosis 1], Wegener's granulomatosis, sarcoidosis, Crohn's disease, primary amyloidosis, Kaposi's sarcoma, acromegaly, and lymphoma), and hereditary gingivofibromatosis.

Management

Treatment of inflammatory gingival enlargement begins with the establishment of excellent oral hygiene, together with the elimination of all local and/or systemic predisposing factors if possible. This includes a professional debridement (supragingival scaling or subgingival root planing) and prophylaxis, and correction of faulty restorations, carious lesions, or food impaction sites. Close follow-up after initial therapy is required to assess improvements in home care and tissue response that will dictate subsequent treatment options.

For refractory cases, adjunctive topical or systemic antimicrobials or surgical options may be indicated. The successful treatment of gingival enlargement in mouth breathers depends primarily on the elimination of the habit. Patients should be referred to an otolaryngologist to determine if there is any obstruction of the upper air passages and/or to an orthodontist to assess the potential for treatment to permit the normal closure of the lips during sleep. A tissue biopsy should be considered whenever the cause is unclear, when there is a poor response to local therapy, or to rule out rare systemic diseases that may present with gingival enlargement (e.g., acute myelogenous leukemia).

Drug-Induced Gingival Enlargement

Etiology and Pathogenesis

Drug-induced gingival enlargement is most commonly associated with the administration of anticonvulsants (principally phenytoin), cyclosporine, and calcium channel blocking agents (principally nifedipine).[15] Contributing local factors aside, the extent of inflammation and fibrosis is largely influenced by the drug type, dosing, and duration. Phenytoin-induced gingival enlargement exhibits the most fibrosis, and in contrast cyclosporine induces the least fibrosis, but in both the gingivae are enlarged and highly inflamed. The blend of fibrosis versus inflammation falls between these two extremes for calcium channel blocker–induced enlargement. These drugs likely exert their influence by the dysregulation of cytokines and growth factors, and also differentially affect the response of innate and adaptive immune systems.

Epidemiology

Phenytoin-induced gingival enlargement (Figure 6-11) is the most prevalent, affecting approximately 50% of patients who use the drug for longer than three months. Although rare, gingival enlargement has also been reported in patients taking

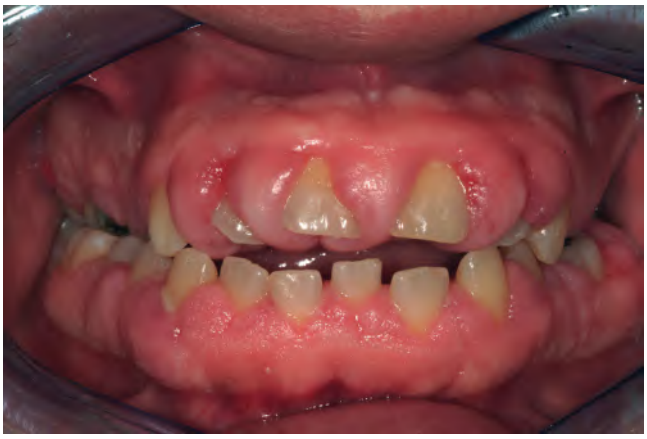

Figure 6-11 Gingival enlargement secondary to longstanding phenytoin use.

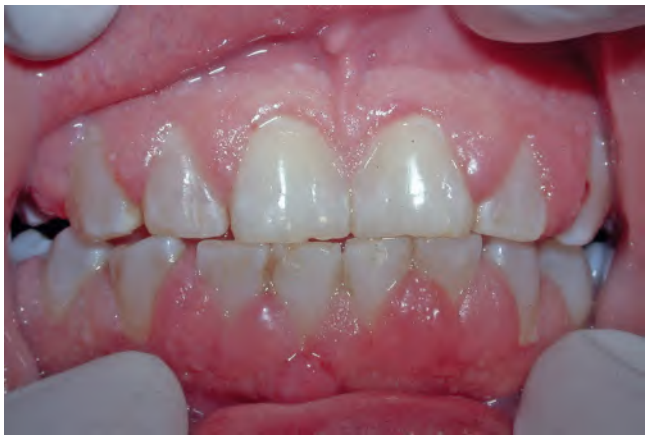

Figure 6-12 Gingival enlargement secondary to longstanding cyclosporine use.

other anticonvulsants, namely valproic acid, phenobarbital, and vigabatrin. The immunosuppressant agent cyclosporine causes gingival enlargement in 25–30% of adults and, notably, in more than 70% of children (Figure 6-12). Nifedipine and dilitiazem are responsible for most cases of calcium channel blocker–induced gingival enlargement, with a prevalence of 5–20%. There are also reports of gingival enlargement following use of verapamil, felodipine, and amlodipine.

Clinical Manifestations

There is a characteristic clinical appearance of drug-induced gingival enlargement. After approximately one month of use of the drug, interdental papillae enlargement begins, usually in the anterior regions, and enlargement may become more extensive, leading to gingival disfigurement and associated esthetic and functional complications.

Differential Diagnosis

Inflammatory gingival enlargement, other systemic diseases (including acute myelogenous leukemia, von Recklinghausen's neurofibromatosis [neurofibromatosis 1], Wegener's granulomatosis, sarcoidosis, Crohn's disease, primary amyloidosis, Kaposi's sarcoma, acromegaly, and lymphoma), and hereditary gingivofibromatosis.

Management

Prevention through optimal oral hygiene is essential to minimize the severity of enlargement. For patients treated for epilepsy, medications must be reviewed before orthodontic treatment begins. There are several treatment options for drug-induced gingival enlargement. The most predictable treatment is either the withdrawal or change of medication and there are a variety of new-generation anticonvulsants, immunosuppressants, and antihypertensives available. Tacrolimus has been shown to be an effective replacement for cyclosporine and does not seem to cause gingival enlargement.

Nonsurgical treatments such as professional gingival debridement and topical or systemic antimicrobials may ameliorate gingival enlargement. Surgical management is reserved for severe cases, although recurrence is common. Conventional gingivectomy is commonly performed, although periodontal flap surgery may be indicated if there are mucogingival considerations, or in pediatric patients in whom tooth eruption might be affected. Laser ablation gingivectomy may offer an advantage over conventional surgery since procedures are faster and there is improved hemostasis and more rapid healing.

Other Causes of Gingival Enlargement

Although not strictly reactive, gingival enlargement may rarely be the result of genetic predisposition. Hereditary gingivofibromatosis (Figure 6-13), is linked to both autosomal dominant and recessive patterns of inheritance, and genetic heterogeneity and variable expressivity contribute to the difficulty encountered in assigning this diagnosis to a specific syndrome.[16] Putative inherited mutations are in the *SOS1 or CAMK4* genes. In contrast, there are a number of syndromes in which gingival enlargement is one of the manifestations. Enlargement may be present at birth or may become apparent only with the eruption of the deciduous or permanent dentitions. Tooth migration, prolonged retention of the primary dentition, and diastemata are common, and enlargement may completely cover the crowns of the teeth, resulting in compromised oral function.

Patients with acute myelogenous leukemia (principally acute monocytic [M4] or acute myelomonocytic [M5] leukemia) may present with gingival leukemic infiltrates (Figure 6-14). Others include von Recklinghausen's neurofibromatosis (neurofibromatosis 1), Wegener's granulomatosis, sarcoidosis, Crohn's disease, primary amyloidosis, Kaposi's sarcoma, acromegaly, and lymphoma.

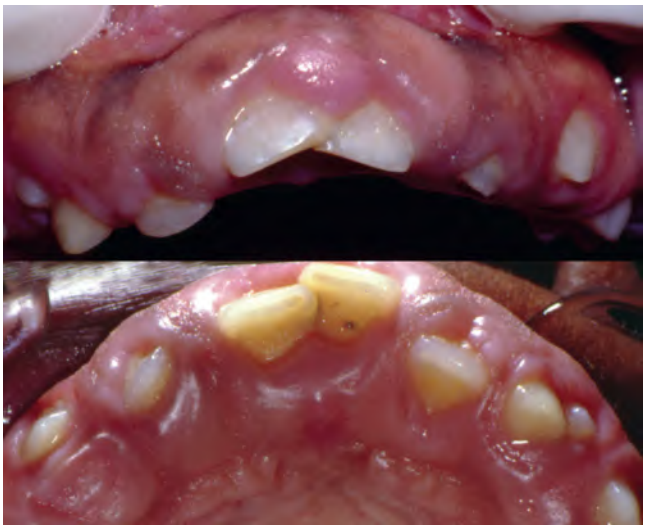

Figure 6-13 Hereditary gingival fibromatosis. Note the severity, with almost complete coverage of teeth in some locations.

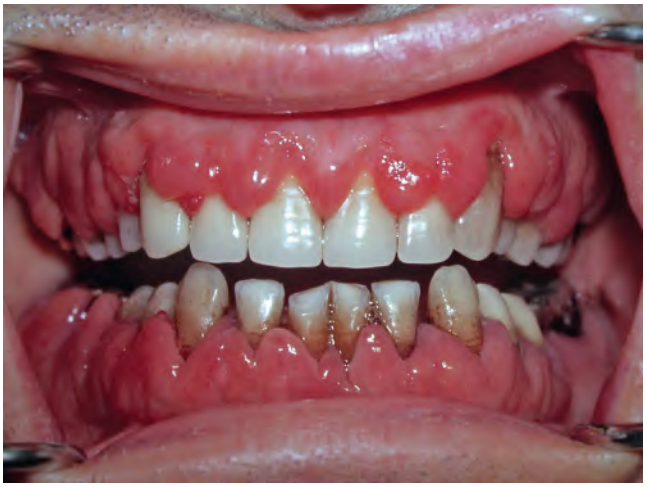

Figure 6-14 Gingival enlargement associated with acute myelogenous leukemia.

BENIGN SOFT TISSUE TUMORS

Oral mucosal benign tumors comprise lesions that are formed from epithelium, fibrous connective tissue, adipose tissue, nerve, and muscle. Benign proliferations of blood vessels and lymphatic vessels resemble neoplasms, but do not have unlimited growth potential and therefore are more appropriately considered hamartomatous proliferations.

Epithelial Tumors

Human Papillomavirus-Induced Growths

Etiology and Pathogenesis

These growths are not true neoplasms, but rather virally induced tissue proliferations.[17] There are almost 200 human papillomavirus (HPV) genotypes, of which at least 30 have been detected in oral lesions. Much attention has been focused on the relationship between oncogenic genotypes (predominantly HPV 16) and oropharyngeal carcinogenesis (see Chapter 7, "Head and Neck Cancer"). Benign HPV-induced lesions are not routinely genotyped, and in case series where such lesions were genotyped, HPV positivity was variable (ranging from 13 to 100%), suggesting methodologic inconsistencies. In those lesions that are HPV positive, nononcogenic genotypes predominate. The virus infects the basal cell layer of the epithelium following mucosal trauma, there is integration of the viral genome, and proliferation of the epithelium leading to the development of a clinically visible lesion or lesions. The virus is most often transmitted by direct contact with another infected person, although such a history may not be evident, suggesting transmission by autoinoculation or casual contact. Lesions associated with sexual contact (referred to as condyloma acuminatum) or vertical transmission are also covered in Chapter 21, "Infectious Diseases."

Epidemiology

HPV-induced growths are estimated to have a prevalence of <0.4% and comprise <5% of all oral biopsy specimens submitted for histology. Current effective vaccines for HPV may be expected to result in a decrease in prevalence of HPV-induced lesions. Patients living with HIV infection are at higher risk for developing HPV-induced growths than immunocompetent patients. Viral papillomas (also called squamous papilloma), largely associated with HPV 6 and 11, are the most commonly appearing of the HPV-induced growths (Figure 6-15) and they usually occur in the third to fifth decades. Verruca vulgaris is predominantly cutaneous (associated with HPV 2 and 57), and condyloma accuminatum, similar to genital warts, is associated with HPV 6 and 11. Heck's disease is endemic in some Eskimo and Native American communities and associated with HPV 13 and 32.

Clinical and Histologic Manifestations

Viral papillomas most commonly present as an isolated small growth (<1 cm diameter) on the palate, ranging in color from white to pink, their surface is papillary/verrucous, and they are pedunculated more often than sessile. Condyloma accuminata are typically larger in size than viral papillomas, are often flat-topped, and may present as a single main growth associated with smaller satellite lesions. The common wart, verruca vulgaris, is generally found on the skin (sometimes in association with similar skin lesions, often on the fingers). When involving the oral cavity, these warts are similar in appearance to viral papillomas and they tend to involve the lips, gingivae, and hard palate.

Focal epithelial hyperplasia (Heck's disease) is characterized by numerous soft, well-circumscribed, comparatively flat, and sessile papules distributed throughout the oral

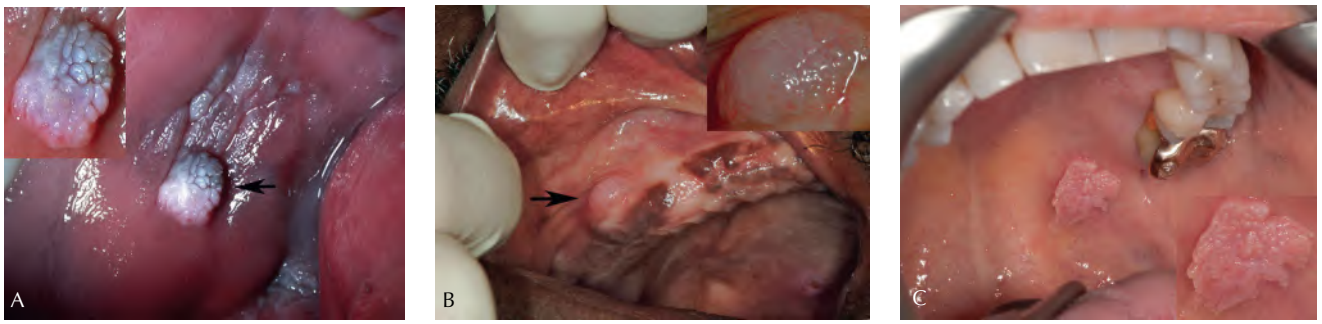

Figure 6-15 (A) Viral papilloma involving the right buccal mucosa. Note the papillary and highly keratinized surface, presumably related to the location (see inset). (B) Viral papilloma with a pebbled surface (inset) involving the right maxillary alveolar ridge. (C) Viral papilloma with a papillary surface (inset) involving the soft palate.

mucosa. Histologically, FEH is characterized by non-dyskeratotic nodular acanthosis, which forms the basis of the papules, and a subepithelial lymphocytic infiltration. Intraoral papillomatosis, often florid, has been found in a small subset of HIV-infected patients (Figure 6-16), particularly since the advent of active antiretroviral therapy, and may be associated with numerous HPV genotypes. Florid papillomatosis may also occur in patients with conditions such as ichthyosis hystrix (a congenitally acquired deforming skin papillomatosis) and Down syndrome.

Differential Diagnosis

Verruciform xanthoma, giant cell fibroma, or a verrucous leukoplakia or papillary squamous cell carcinoma can mimic solitary benign HPV-induced growths. White sponge nevus, or proliferative verrucous leukoplakia, may mimic florid benign HPV-induced growths.

Management

Oral viral papillomas and warts are clinically similar, and local excision is desirable. Care should be exercised when removing HPV-induced oral growths with electrocautery or laser, as there exists the possibility of aerosolizing viral particles. Due to the widespread manifestations, florid disease is challenging to manage surgically, and there is no current evidence-based medical management.

Keratoacanthoma

Etiology and Pathogenesis

The rapid growth of a keratoacanthoma may be quite frightening, to the point where it is often mistakenly diagnosed as squamous or basal cell carcinoma.

Epidemiology

They are exceedingly rare.

Clinical and Histologic Manifestations

The usual location is on the upper lip, where they are dome-like, sharply demarcated, appear fixed to the surrounding tissue, and are usually capped by thick keratin.[18] The proliferating epithelium consists of masses of well-differentiated squamous cells that often produce keratin pearls, yet show little cellular atypia.

Differential Diagnosis

Squamous cell or basal cell carcinoma.

Management

Occasionally, the lesion matures, exfoliates, and heals spontaneously. In most cases, however, treatment of this lesion is conservative excision, although some believe that it is not clearly separable from squamous cell carcinoma and advocate wide excision to prevent recurrence.

Other Benign Epithelial Growths

Molluscum contagiosum is a dermatologic infection caused by a poxvirus that is acquired by direct skin contact. Both intraoral and labial lesions of molluscum contagiosum occur, predominantly in HIV-infected patients, and these are characterized by clusters of tiny firm papules. Histologically, these papules are composed of clumps of proliferating epithelial cells with prominent eosinophilic molluscum inclusion bodies that are commonly associated with poxvirus infections.

Vascular Anomalies

These entities have been classified using standardized terminology developed by the International Society for the Study of Vascular Anomalies and may be subdivided into vascular tumors and vascular malformations.[19]

Hemangiomas

Etiology and Pathogenesis

Hemangiomas of the head and neck are vascular tumors and true endothelial cell neoplasms. They appear a few weeks after birth and grow rapidly, and in most cases undergo involution over time, with residual telangiectatic, fatty, or scar tissue apparent in approximately 50% of patients.

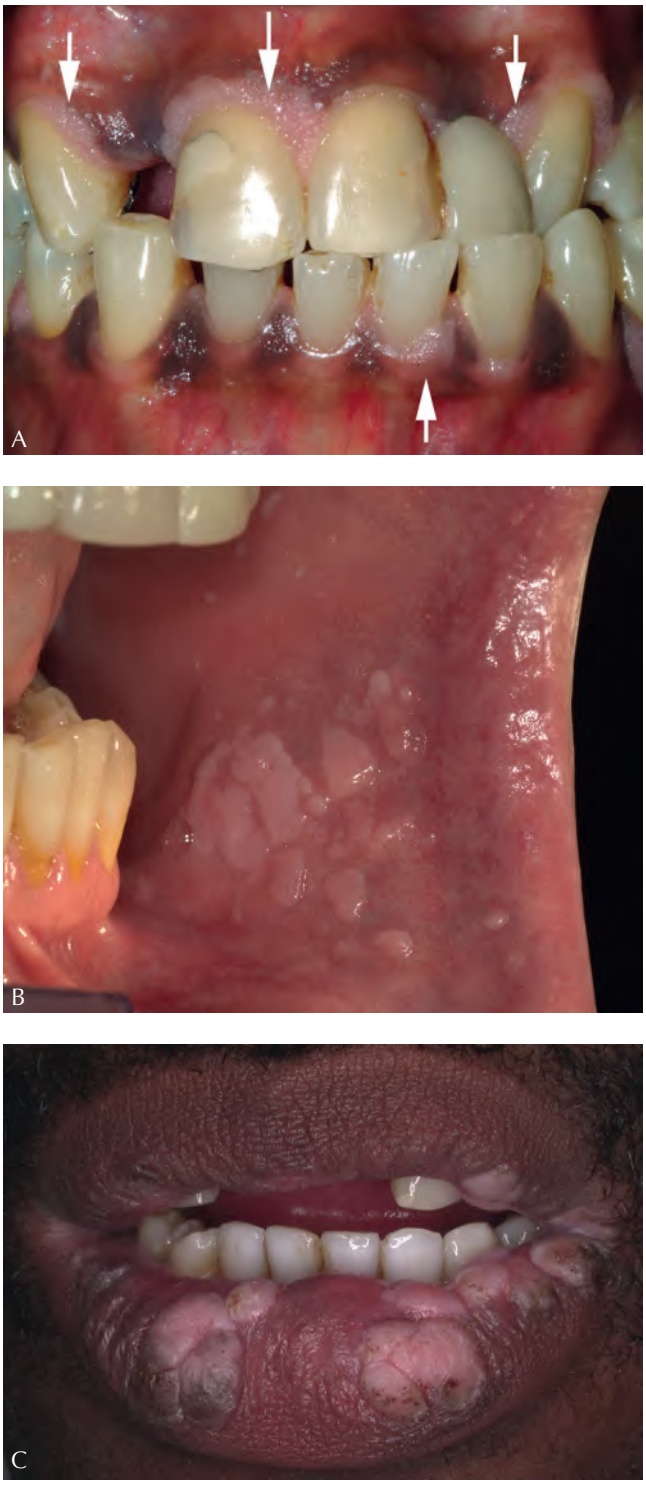

Figure 6-16 (A) HIV-associated florid papillomatosis involving free marginal gingivae. (B) HIV-associated florid papillomatosis involving buccal mucosa. Note coalescing papules, which are flat. (C) HIV-associated florid papillomatosis involving the lips.

Epidemiology

Hemangiomas are present in approximately 4–5% of infants. The majority (approximately 70%) involve the head and neck.

Clinical and Histologic Manifestations

They have been described in almost all head and neck locations in a variety of presentations: superficial and deep, small and large, most commonly as solitary lesions but also as multiple lesions. Small lesions may be clinically and histologically indistinguishable from pyogenic granulomas and superficial venous varicosities.

Differential Diagnosis

Oral hemangiomas may be similar in appearance to vascular malformations, or pyogenic granulomas.

Management

Given the propensity for involution, surgery should only be considered for those that do not involute, are esthetically obtrusive, or bleed easily.

Capillary, Venous, and Arterial/Arteriovenous Vascular Malformations

Etiology and Pathogenesis

These malformations are classified depending on the vessel type involved or flow types: arterial and arteriovenous (high flow), capillary (Figure 6-17), or venous (low flow). They are structural aberrations in components of the vascular apparatus and may be clinically apparent at birth, grow slowly proportional to the growth of the child (characterized by hypertrophy), and never involute. Centrally located malformations must be distinguished from the many osteolytic tumors and cyst-like lesions that affect the jaws (see later). Arterial and arteriovenous malformations may first develop following hormonal changes (such as puberty), infections,

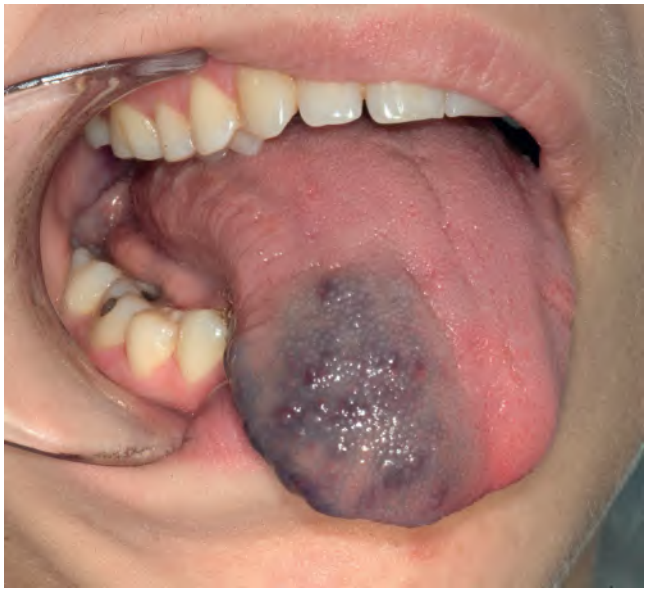

Figure 6-17 Vascular malformation involving the tongue, which developed two months before in a 25-year-old female.

or trauma. Venous malformations can sometimes appear first in early adulthood.

Epidemiology

It is challenging to estimate the prevalence of vascular malformations because of the older classification systems for vascular anomalies implemented in large screening studies. However, the prevalence of oral vascular malformations is approximately 0.2–0.5%.

Clinical Manifestations

Arterial or arteriovenous malformations may be firm, pulsatile, and warm. Venous malformations are soft and easily compressible. Diascopy is the technique of applying pressure to a suspected vascular lesion to visualize the evacuation of coloration (Figure 6-18) and may facilitate the differentiation of a small vascular lesion from ot her nonblanchable red or pigmented lesions.

Differential Diagnosis

The diagnosis of malignant neoplasms must always be entertained if lesions demonstrate progressive enlargement.

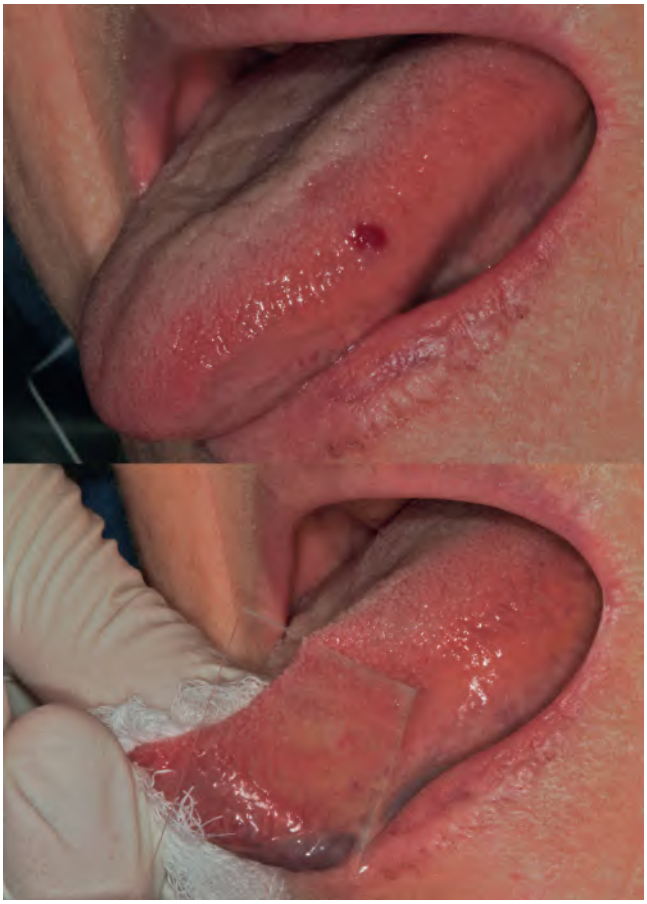

Figure 6-18 Diascopy of a small capillary malformation on the lateral border of the tongue. Note blanching of the lesion.

Management

Care should be taken in performing biopsies or excising all vascular lesions, as they have a tendency for uncontrolled hemorrhage and the extent of the lesion is unknown, since only a small portion may be evident in the mouth. Therefore, identification of the precise anatomic location and depth of tissue extent is warranted before treatment, particularly for the high-flow lesions. A number of imaging modalities may be indicated, including ultrasound, contrast-enhanced magnetic resonance imaging or computed tomography (CT), and dynamic MR angiography. Treatment modalities (alone or in combination) for peripheral vascular malformations depend on the type of malformation and include sirolimus, sclerotherapy, embolization, or surgical excision/resection using electrocoagulation.

Other Angiomatous Syndromes

A number of syndromes are associated with vascular malformations, including Osler–Weber–Rendu syndrome (hereditary hemorrhagic telangiectasia; Figure 6-19), blue rubber bleb nevus syndrome, Bannayan–Zonana syndrome, Sturge–Weber syndrome (Figure 6-20),[20] Klippel–Trénaunay syndrome, Servelle–Martorell syndrome, von Hippel–Lindau syndrome, and Maffucci syndrome.

Lymphatic Malformations

Etiology and Pathogenesis

Macrocystic, microcystic, or mixed cystic lymphatic malformations may be localized or regional, and they are characterized by an abnormal proliferation of lymphatic vessels. The most common extraoral and intraoral sites are the neck (predominantly in the posterior triangle) and tongue, respectively. The vast majority (80–90%) of lymphangiomas arise

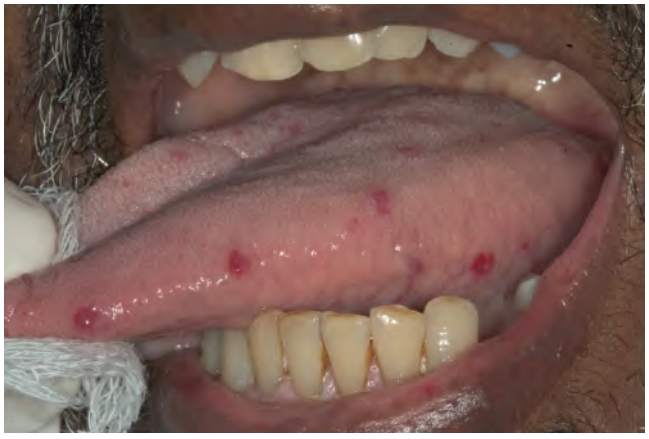

Figure 6-19 Osler–Wendu–Rendu syndrome (hereditary hemorrhagic telangiectasia). Note discrete multiple red papules associated with dilated vessels. Patient has similar papules distributed on his labial mucosae and finger tips.

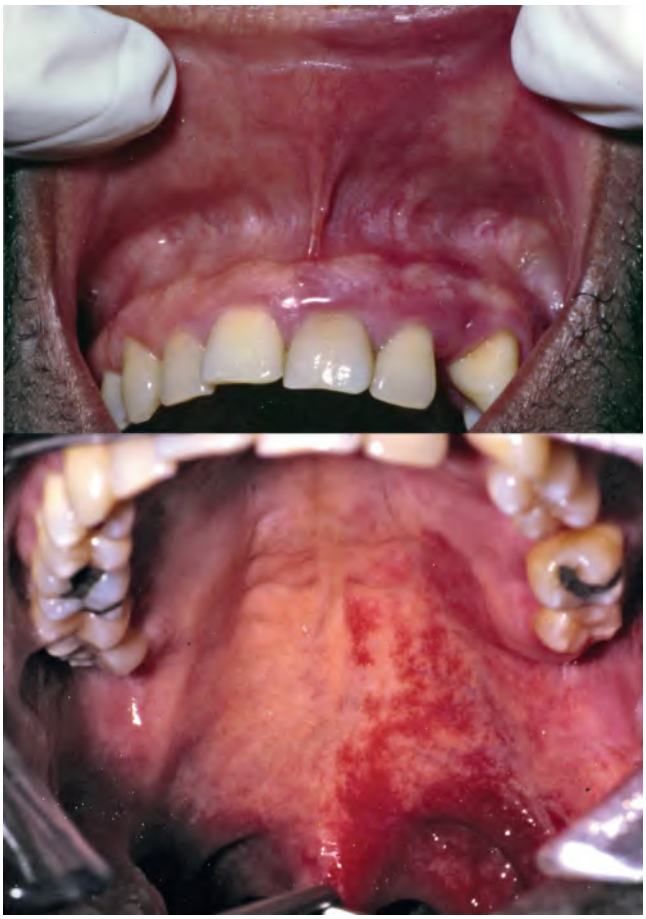

Figure 6-20 Sturge–Weber syndrome. Hypervascular changes are unilateral, which is consistent with a trigeminal nerve distribution, in this case following the second (maxillary) branch of the left trigeminal nerve.

within the first two years of life and are an important cause of congenital macroglossia.

Epidemiology

Lymphatic malformations are rare.

Clinical and Histologic Manifestations

Clinically, lymphangiomas are a slow-growing and painless soft tissue mass. Frequently they are without a clear anatomic outline, dissecting tissue planes, and can be more extensive than anticipated. Intraosseous lymphangiomas have been reported. Occasionally, they may undergo a rapid increase in size secondary to inflammation from an infection or hemorrhage from trauma. Large lymphangiomas may become life-threatening if they compromise the airway or vital blood vessels, and those spreading into and distending the neck are macrocystic and are referred to as cystic hygromas. Abnormalities of the tongue mucosa overlying a lymphatic malformation may give the appearance of a localized glossitis and may draw attention to the presence of a lesion buried deep in the tongue. The typical oral lymphatic malformation has a racemose or pebbly surface.

Differential Diagnosis

Includes other vascular malformations, amyloidosis, neurofibromatosis, and other causes of macroglossia.

Management

The treatment of lymphatic malformations is dictated by their type, anatomic site, and extent of infiltration into surrounding structures. Sclerotherapy (with chemotherapeutic agents such as picabinil [OK-432], bleomycin, or doxycycline) is advocated over surgical excision in most cases. Recurrence of oral lymphangiomas has been reported, presumably because the lesion is interwoven between muscle fibers, preventing complete removal.

Other Vascular Growths

An unusual abnormality, glomus tumor (glomangioma), develops as a small, painful, unencapsulated nodule. It represents a proliferation of the modified smooth muscle pericytic cells found in the characteristic type of peripheral arteriovenous anastomosis known as the glomus. In addition to having a distinctive histology, these lesions also may secrete various catecholamines. The glomus tumor is rare in the mouth and occurs more often around the carotid body, in the jugulotympanic region, and in the vagus nerve. Glomus tumors arising in the carotid bodies may produce neck masses and are referred to as chemodectomas or paragangliomas.

Neurogenic Tumors[21]

Traumatic Neuroma

Etiology and Pathogenesis

A traumatic neuroma is a reactive lesion caused by injury to a peripheral nerve. When a nerve and its sheath are damaged, the proximal end of the damaged nerve proliferates into a mass of nerve and Schwann cells mixed with dense fibrous scar tissue.[22] In the oral cavity, injury to a nerve may occur from injection of local anesthesia, surgery, or other sources of trauma.

Epidemiology

Traumatic neuromas are rare and tend to occur in adults.

Clinical Manifestations

Traumatic neuromas in the oral cavity may occur in any location where a nerve is damaged, and the mental foramen area, tongue, and lower lip are the most common sites. Traumatic neuromas may lead to either reduced sensation or, in approximately 20% of cases, elicit discomfort.[22] The discomfort may

range from pain on palpation or pressure from an overlying denture (in the case of a neuroma involving the mental foramen area) to severe and constant pain.

Differential Diagnosis

Any smooth-surfaced submucosal exophytic lesion may be included in a differential diagnosis, including the palisaded encapsulated neuroma, neurofibroma, schwannoma, irritation fibroma, tumors of muscles, and minor salivary gland neoplasms.

Management

Traumatic neuromas are treated by surgical excision and recurrence is rare.

Palisaded Encapsulated Neuroma

Etiology and Pathogenesis

This is considered a reactive neoplasm, likely in response to trauma.

Epidemiology

This lesion is rare and most often occurs in older adults.

Clinical and Histologic Manifestations

The lesions are solitary, a feature that distinguishes them from the neuromas in MEN syndrome (see later). They are typically painless and the most common location is the hard palate.[23] Histologically, there is a well-circumscribed, partially encapsulated nodule composed of spindle-shaped cells exhibiting areas of nuclear palisading, often admixed with axons. They contain Schwann cells, perineural cells, and axons, and can be distinguished from neurofibromas and schwannomas both by their light microscopic appearance and by immunohistochemical stain that is positive for EMA and S-100.

Differential Diagnosis

Any smooth-surfaced submucosal exophytic lesion may be included in a differential diagnosis, including the palisaded encapsulated neuroma, neurofibroma, neurilemmoma, irritation fibroma, tumors of muscle tissue, and minor salivary gland neoplasms.

Management

Palisaded encapsulated neuromas are treated by surgical excision and recurrence is rare.

Oral Mucosal Neuromas and Multiple Endocrine Neoplasia Syndrome 2B (MEN 2B)

MEN 2B is caused by inherited mutations in the Met918Thr *RET* gene and characterized by tumors or hyperplasias of neuroendocrine tissues.[24] Patients with MEN 2B present with a characteristic phenotype that includes medullary thyroid carcinoma, pheochromocytoma, prominent corneal nerve fibers, a "Marfanoid" body habitus, enlarged lips, and neuromas on the eyelids and oral mucosal tissues. Identification of mucosal neuromas may precede other components of the syndrome. Management includes prophylactic total thyroidectomy, ideally before the age of 1 year.

Neurofibroma and Schwannoma (aka Neurilemmoma)

Etiology and Pathogenesis

These are benign tumors derived from the tissue that envelops nerves and includes Schwann cells and fibroblasts.[25] Although distinct tumors microscopically, they are quite similar in their clinical presentation and behavior.

Epidemiology

These benign tumors are rare and may occur at any age, without any sex predilection.

Clinical and Histologic Manifestations

They are typically asymptomatic and the tongue is the most common intraoral location (Figure 6-21). Microscopic examination of a neurofibroma reveals a fairly well-delineated but diffuse proliferation of spindle-shaped Schwann cells. A schwannoma is encapsulated and exhibits varying amounts of two different microscopic patterns. One pattern consists of cells in a palisaded arrangement around eosinophilic areas, and the other consists of less cellular spindle-shaped cells in a loose myxoid-appearing stroma. Differences in immunohistochemical staining have been demonstrated and may be helpful in establishing the definitive diagnosis.

Differential Diagnosis

Any smooth-surfaced submucosal exophytic lesion may be included in a differential diagnosis, including the palisaded encapsulated neuroma, irritation fibroma, tumors of muscle tissue, and minor salivary gland neoplasms.

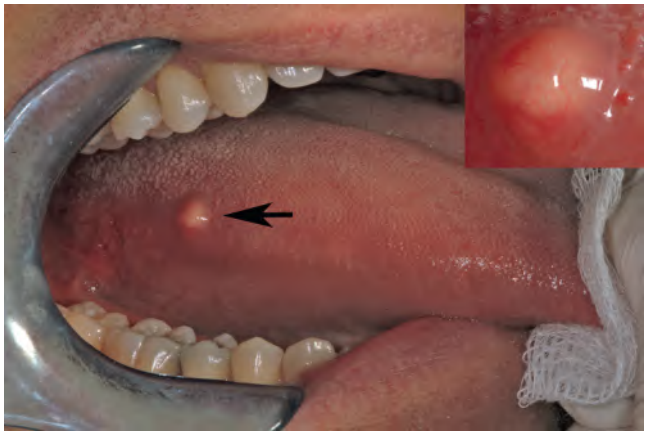

Figure 6-21 Neurogenic tumor involving the right lateral tongue.

Management

The treatment for a neurofibroma or schwannoma is surgical excision. They generally do not recur.

Multiple neurofibromas occur in a genetically inherited disorder known as neurofibromatosis 1 (NF1) or von Recklinghausen's disease. This disease is transmitted as an autosomal dominant trait, and a germline mutation in the *NF1* gene has been identified. Oral neurofibromas are a common feature of the disease. The presence of numerous neurofibromas or a plexiform-type neurofibroma is pathognomonic of NF1. Patients with NF1 are at increased risk of the development of a number of malignant tumors, especially malignant peripheral nerve sheath tumor, leukemia, and rhabdomyosarcoma.

Granular Cell Tumor

Etiology and Pathogenesis

The pathogenesis of this tumor has not been established, but most evidence suggests that it is reactive and arises from Schwann cells or their primitive mesenchymal precursors.

Epidemiology

These are rare, and the majority of cases occur in adults, with a female predilection.

Clinical and Histologic Manifestations

The granular cell tumor most often occurs on the dorsal tongue (Figure 6-22A), followed by the buccal and labial mucosae. Other intraoral sites include the palate (Figure 6-22B), gingiva, and floor of the mouth. The tumor appears as a painless, often yellowish, nonulcerated nodule. The granular cell tumor is a benign tumor composed of large oval-shaped cells with a granular cytoplasm.[26] The granular cells are found in the connective tissue and the overlying surface epithelium exhibits pseudoepitheliomatous hyperplasia. Immunocytochemical staining reveals reactivity to S-100 protein, vimentin, CD-68, calretinin, NKI/C3, Inhibin-α, p75, and PGP9.5.

Differential Diagnosis

Any smooth-surfaced submucosal exophytic lesion may be included in a differential diagnosis, including the palisaded encapsulated neuroma, neurofibroma, schwannoma, irritation fibroma, verruciform xanthoma, tumors of muscle tissue, and minor salivary gland neoplasms.

Management

This tumor is treated by conservative surgical excision and does not recur.

The congenital epulis of the newborn is a very rare benign neoplasm composed of cells that closely resemble those seen in the granular cell tumor that occurs in adults. It is present at birth and usually presents as a smooth-surfaced, sessile, or pedunculated mass on the anterior maxillary alveolar ridge. It almost always occurs in girls. The ultrastructural and immunohistochemical features are distinct from the granular cell tumor, confirming that this lesion is a separate entity. The congenital epulis is treated by surgical excision and does not recur, and occasionally it will regress without treatment.

Melanotic Neuroectodermal Tumor of Infancy

Etiology and Pathogenesis

Melanotic neuroectodermal tumor of infancy is a benign neoplasm originating from neural crest cells that almost always occurs during the first year of life.

Epidemiology

This entity is exceedingly rare.

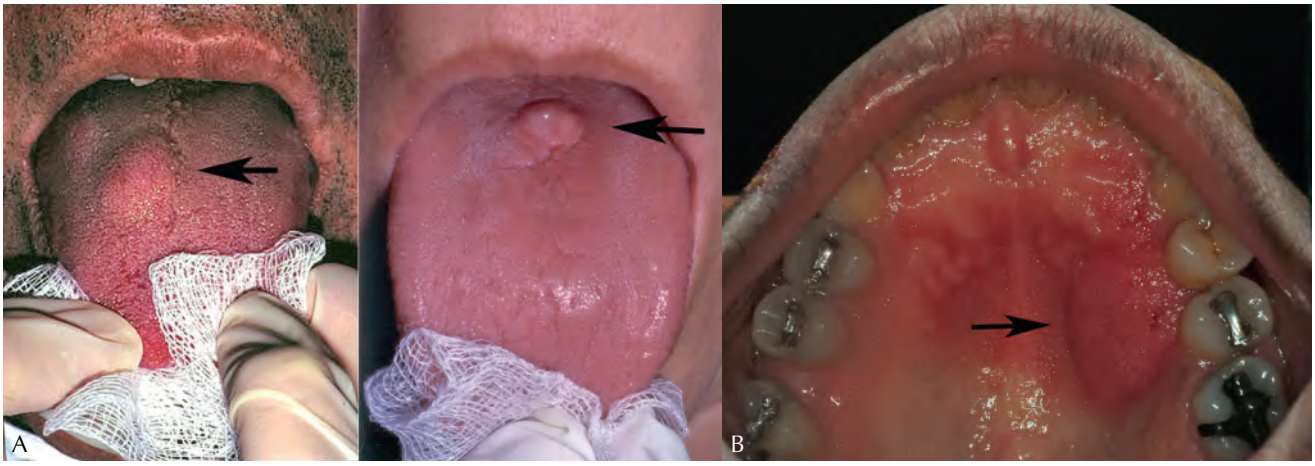

Figure 6-22 (A) Granular cell tumors of the tongue, the most common site for this benign lesion. (B) Granular cell tumor involving the palate, an unusual site.

Clinical and Histologic Manifestations

The tumor most commonly occurs in the maxilla, followed by the skull, mandible, and brain. The tumor presents as a rapidly enlarging mass that destroys bone and may exhibit blue-black pigmentation. Histologically, the tumor is composed of collections of cells that resemble melanocytes, admixed with smaller round cells and variable amounts of melanin.

Differential Diagnosis

Given the rapid growth, malignant neoplasms must be considered, including sarcomas, and lymphomas.

Laboratory Findings

High levels of urinary vanillylmandelic acid are often found in patients with this tumor.

Management

Conservative surgical removal is usually adequate, but this tumor has a high recurrence rate and malignant transformation has been reported rarely.

Lipoma

Etiology and Pathogenesis

The lipoma is a benign mesenchymal tumor of mature adipocytes.

Epidemiology

Lipomas involving the oral cavity are rare (<3% of all lipomas). They occur in individuals over 40 years of age, and without any sex predilection.

Clinical and Histologic Manifestations

The majority of oral lipomas are found on the buccal mucosa and tongue. When occurring in the superficial soft tissue, the lipoma appears as a yellow/orange mass with a thin epithelial surface, demonstrating a delicate pattern of blood vessels (Figure 6-23). There are several microscopic variants of the lipoma. The classic description is of a well-delineated tumor composed of lobules of mature fat cells that are uniform in size and shape.[27] The most common variants are fibrolipomas (i.e., those with a significant fibrous connective tissue component), followed by spindle cell lipomas (i.e., those with an admixture of uniform spindle cells), rarely sialolipomas, angiolipomas, myxoid lipomas, and an intramuscular lipoma.

Differential Diagnosis

The yellow/orange color is pathognomic. Other yellowish entities include abscess, sialolith, lymphoepithelial cyst, or granular cell tumor.

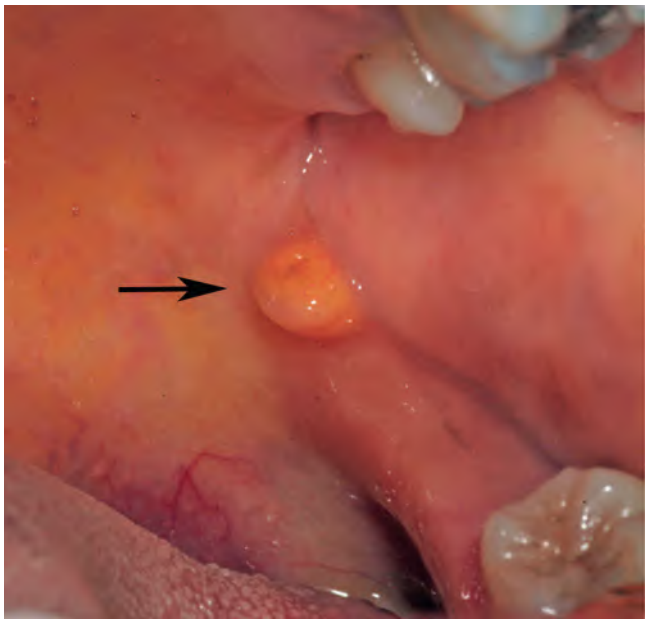

Figure 6-23 Lipoma involving the buccal mucosa. Note the yellow color.

Management

The lipoma is treated by conservative surgical excision and generally does not recur. Intramuscular lipomas have a somewhat higher recurrence rate because they are more difficult to remove completely.

Tumors of Muscle

Etiology and Pathogenesis

These are benign neoplasms of striated (rhabdomyoma) and smooth (leiomyoma) muscle.

Epidemiology

Tumors of muscle are exceedingly rare in the oral cavity.

Clinical Manifestations

Oral rhabdomyomas have been reported to occur almost exclusively on the tongue. The vascular leiomyoma (angioleiomyoma) is the least rare of the leiomyoma variants and solitary lesions have been reported to involve multiple oral sites.[28]

Differential Diagnosis

Any smooth-surfaced submucosal exophytic lesion may be included in a differential diagnosis, including the palisaded encapsulated neuroma, neurofibroma, schwannoma, irritation fibroma, granular cell tumor, and minor salivary gland neoplasms.

Management

Treatment is local surgical excision, and recurrence is rare.

BENIGN HARD TISSUE LESIONS

BENIGN FIBRO-OSSEOUS LESIONS

The term "benign fibro-osseous lesion" (BFOL) is a generic histologic designation for a diverse group of bone lesions that are named for the similarity of their histopathologic morphology (see classification in Box 6-1). They are composed of cellular fibrous connective tissue admixed with either osteoid matrix, woven new bone and bone trabeculae, or rounded small to large calcified masses that have traditionally been described as cementoid material. BFOLs of the jaws include fibrous dysplasia, ossifying fibroma, and the cemento-osseous dysplasias. Since the histopathology is so similar in these lesions, imaging with radiographic correlation is critical for the diagnosis.

Fibrous Dysplasia

Fibrous dysplasia is a condition that is characterized by the replacement of normal bone with fibro-osseous tissue. The well-vascularized and cellular fibrous tissue contains trabeculae or spherules (small spheres) of poorly calcified nonlamellar bone that are formed by osseous metaplasia.

Etiology and Pathogenesis

The pathogenesis is related to *GNAS* (guanine nucleotide binding protein, alpha stimulating) gene mutation. The most widely accepted theory is that fibrous dysplasia results from an abnormality in the development of bone-forming mesenchyme.

Epidemiology

Fibrous dysplasia presents in childhood, typically with a slowly progressive enlargement of bone that generally slows or ceases with puberty.

Box 6-1 Benign Fibro-osseous Lesions

Fibrous Dysplasia

- Monostotic
- Polyostotic

Ossifying Fibroma
  Juvenile (active or aggressive)

Cemento-osseous Dysplasia

- Periapical
- Focal
- Florid

Clinical and Histologic Manifestations

Radiographically, fibrous dysplasia classically presents with a "ground glass" appearance and may have varying degrees of radiopacity and lucency depending on the amount of calcified material present. The abnormal bone merges with the adjacent normal bone, which leads to a lack of circumscription or delineation of these lesions. Plain film imaging and CT are useful in the diagnosis of fibrous dysplasia.

Biopsy of involved bone reveals a tissue that is often described clinically as "gritty" or "sandy." Several forms of fibrous dysplasia have been described. The monostotic form, characterized by the involvement of a single bone, is the most common form. Polyostotic forms are characterized by the involvement of more than one bone and include different types: (1) craniofacial fibrous dysplasia, in which the maxilla and adjacent bones are involved; (2) Jaffe's type (or Jaffe–Lichtenstein type), in which there is multiple bone involvement along with an irregular macular melanin pigmentation of the skin (café au lait spots); and (3) rare cases in children (McCune–Albright syndrome or Albright syndrome), in which there is severe, progressive bone involvement with café au lait skin pigmentation and endocrine abnormalities such as precocious puberty.

Laboratory Findings

An elevation in serum alkaline phosphatase may be seen in patients with extensive polyostotic disease.

Management

In most cases, once diagnosis has been confirmed, management with close monitoring or with superficial recontouring of the lesion is sufficient. Curettage is sometimes used for large radiolucent lesions. Radiotherapy is contraindicated in the treatment of fibrous dysplasia. Early treatment using radiotherapy may have played a role in the rare cases of malignant transformation to fibrosarcoma or osteogenic sarcoma. Attempts at treating advanced cases of the polyostotic form with calcitonin have not been successful, but more recently use of bisphosphonates has had some use in limiting bone loss.

The *clinical problems* associated with fibrous dysplasia of bone are related to the site and extent of involvement. In the long bones, deformity and fractures are common complications that often lead to the initial diagnosis. In the jaws and other parts of the craniofacial skeleton, involvement of adjacent structures such as the cranial sinuses, cranial nerves, and ocular contents can lead to serious complications in addition to cosmetic and functional problems. Intracranial lesions arising from the cranial bones may produce seizures and electroencephalographic changes. Extension into and occlusion of the maxillary and ethmoid

sinuses and mastoid air spaces are common. Proptosis, diplopia, and interference with jaw function also often prompt surgical intervention.

Systematic review of craniofacial fibro-osseous disease demonstrates an increased risk of developing a malignant transformation in patients with fibrous dysplasia. The most common malignant transformation is to osteogenic sarcoma and the average time from initial diagnosis of BFOL to malignancy was 18.2 years; therefore, long-term follow-up is indicated.

Ossifying Fibroma

Etiology and Pathogenesis

Ossifying fibroma is a slow-growing, well-circumscribed, benign tumor of bone that probably arises from cells of the periodontal ligament.

Epidemiology

This benign tumor occurs in the mandible more frequently than the maxilla. It is usually diagnosed in the third to fourth decades of age, but has a broad age range and a female predilection.

Clinical, Radiographic, and Histologic Manifestations

Radiographically, the tumor has a well-circumscribed margin (Figure 6-24). The cementifying fibroma has been reclassified under the category of ossifying fibroma.[29] The ossifying fibroma is a benign fibro-osseous lesion that is histologically composed of cellular fibrous connective tissue containing varying amounts of osteoid, rounded cementoid calcifications and irregularly shaped bone trabeculae.

Differential Diagnosis

The clinical/radiographic differential diagnosis includes enostosis, osteoblastoma/osteoid osteoma, complex odontoma, and perhaps dense bone island/idiopathic osteosclerosis, depending on the size and radiographic appearance.

Management

Treatment involves conservative surgical excision of the tumor.

Juvenile Ossifying Fibroma

Juvenile ossifying fibroma is a controversial lesion that is separated from ossifying fibroma based on the patient's age (most are children and young adults), location of lesion, and clinical behavior. This tumor exhibits more aggressive behavior and a greater propensity for recurrence than ossifying fibroma.

Cemento-Osseous Dysplasias

Etiology and Pathogenesis

The etiology and pathogenesis of these conditions are unknown. The lesions begin as radiolucencies that become more radiopaque with time; large calcified masses become a characteristic histologic feature.[30] Three forms of this dysplastic process involving bone of the jaws are described: periapical cemento-osseous dysplasia, focal cemento-osseous dysplasia, and florid cemento-osseous dysplasia.

Epidemiology

Periapical cemento-osseous dysplasia and florid osseous dysplasia are most commonly reported in black women over the age of 40 years. Focal cemento-osseous dysplasia is also reported to occur frequently in middle-aged white women.

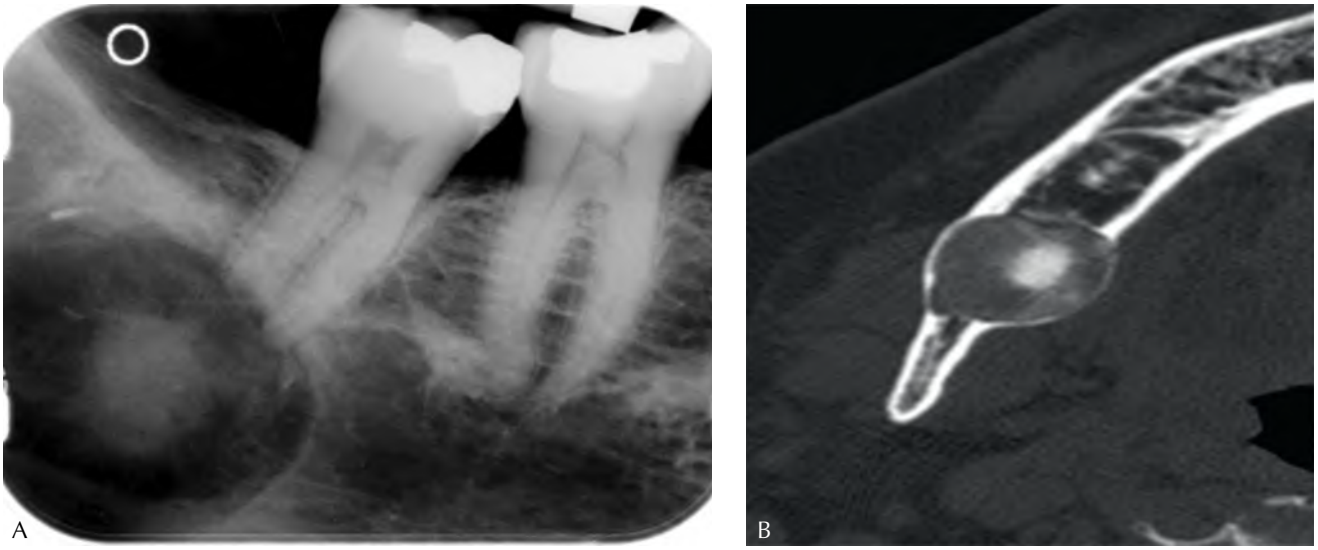

Figure 6-24 Ossifying fibroma in a 64-year-old female. (A) Periapical and (B) cropped axial CT bone window images show a well-circumscribed, mixed radiolucent-radiopaque entity of the posterior right mandible. The entity has concentric expansion and remodeled the overlying buccal and lingual cortices.

Clinical and Histopathologic Manifestations

Periapical and florid types are generally most appropriately diagnosed on the basis of the clinical and radiographic features. The focal type requires a biopsy to establish a definitive diagnosis. Periapical cemento-osseous dysplasia, previously called cementoma, is a lesion that occurs at the apical aspect of vital mandibular anterior teeth. The condition is asymptomatic and does not require treatment.

Focal cemento-osseous dysplasia differs from the periapical form since it occurs at the apical aspect of posterior teeth. Florid cemento-osseous dysplasia presents as an exuberant form of cemento-osseous dysplasia, involving more than one and often multiple quadrants of the maxilla and mandible. Cystic changes similar to simple bone cysts may be seen in association with florid cemento-osseous dysplasia (Figure 6-25A). The calcified masses of the dysplastic bone do not resorb with the alveolar process in edentulous patients (Figure 6-25B). In patients with tissue-borne removable dentures, secondary infection may occur from mucosal perforation and subsequent communication between the dysplastic bone and oral cavity. Additionally, the affected bone becomes sclerotic with little vasculature, complicating the healing process.

Differential Diagnosis

The differential diagnosis of periapical cento-osseous dysplasia when the lesion is radiolucent includes dental pulp–related periapical inflammatory disease, and establishment of tooth vitality is critically important. Florid cemento-osseous dysplasia may resemble Paget's disease; however, florid cemento-osseous dysplasia is limited to the gnathic bones. The differential for focal cemento-osseous dysplasia could include numerous lesions, depending on whether it is radiolucent or demonstrates opacity.

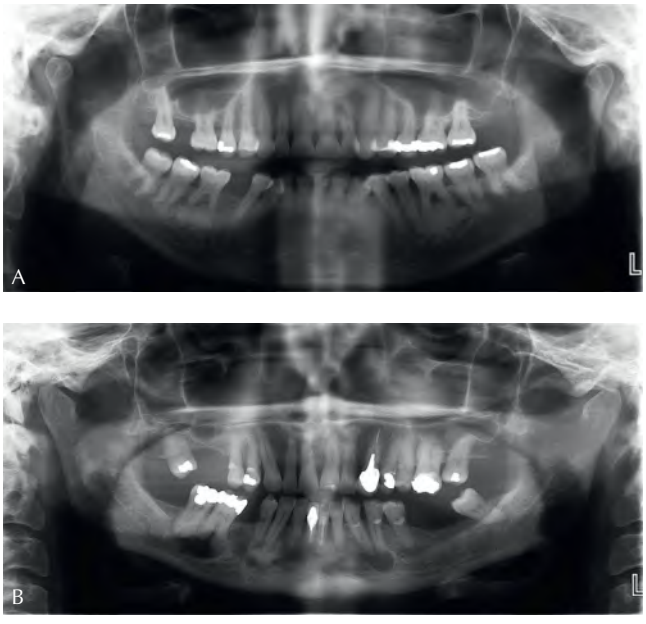

Figure 6-25 Florid cemento-osseous dysplasia (A) without and (B) with simple bone cyst association.

Management

Surgery (e.g., extractions, placement of implants) should be avoided due to potential poor healing and the increased risk of osteomyelitis associated with the affected bone, especially once the bone is sclerotic. Asymptomatic patients should be counseled and followed regularly for prophylactic dental care. This will help to eliminate odontogenic or periodontal disease and any associated surgical intervention.

LANGERHANS CELL HISTIOCYTOSIS (HISTIOCYTOSIS X)

Etiology and Pathogenesis

Langerhans cell histiocytosis, formerly called histiocytosis X, comprises a group of conditions that are characterized histologically by a monoclonal proliferation of large mononuclear cells accompanied by a prominent eosinophilic infiltrate.[31] The mononuclear cells have been identified as Langerhans cells (the most peripheral cell of the immune system) by their immunologic staining characteristics and the presence of a cytoplasmic inclusion called the Birbeck granule. Historically, the clinical spectrum of Langerhans cell histiocytosis includes (1) single or multiple bone lesions with no visceral involvement (eosinophilic granuloma); (2) a chronic disseminated form that includes the classic Hand–Schüller–Christian triad of skull lesions, exophthalmos, and diabetes insipidus; and (3) an acute disseminated form (Letterer–Siwe disease) that affects multiple organs and has a poor prognosis. Langerhans cell histiocytosis is currently classified by the clinical extent and severity of disease at diagnosis (Table 6-1).[31] Studies have shown that 40–60% of lesions have a *BRAF* mutation. This finding has lent support to the theory that this should be considered a neoplastic condition rather than one of reactive etiology as previously accepted.

Epidemiology

Each of the forms of Langerhans cell histiocytosis tends to affect patients at different ages, with the eosinophilic granuloma affecting older children and young adults, the chronic disseminated form affecting young children, and the acute disseminated form affecting infants and children under the age of 2 years.

Clinical, Radiographic, and Histologic Manifestations

Single or multiple eosinophilic granulomas with no systemic or visceral involvement are the most common presentation. Both the maxilla and the mandible may be affected in Langerhans cell histiocytosis, both with and without systemic involvement. Early lesions present radiographically as well-defined, noncorticated radiolucencies. With time, the

Table 6-1 Current clinical classification of langerhans cell histiocytosis.

Single organ system disease
Unifocal
Multifocal
Multiorgan system disease
No organ dysfunction
Organ dysfunction
• Low-risk, excellent prognosis organs: skin, bone, lymph node, pituitary
• High-risk, poor prognosis organs: lung, liver, spleen, hematopoietic

lesions enlarge and coalesce with one another, resulting in more bone destruction (Figure 6-26). Involvement of the alveolar process may mimic periodontal disease, but Langerhans cell histiocytosis starts at the mid-root level. The gingival soft tissues may also be involved, and this may resemble periapical or periodontal inflammatory disease.

Differential Diagnosis

This includes disorders causing alveolar bone loss in children. Aggressive periodontitis, Papillon–Lefèvre syndrome, cyclic neutropenia/agranulocytosis, and Burkitt's lymphoma could all be considered in the differential diagnosis. Each of these, as well as Langerhan's histiocytosis, can cause a significant destruction of bone around the teeth, leading to a radiographic appearance of "teeth floating in air."

Management

The treatment varies, based on the clinical presentation of the disease. Solitary eosinophilic granuloma may be treated by surgical curettage. Low-dose radiation therapy has been used successfully for lesions that are multiple, less accessible, or persistent. The older the patient with Langerhans cell histiocytosis and the less visceral involvement, the better the prognosis. Langerhans cell histiocytosis is a life-threatening disease in infants and very young children.

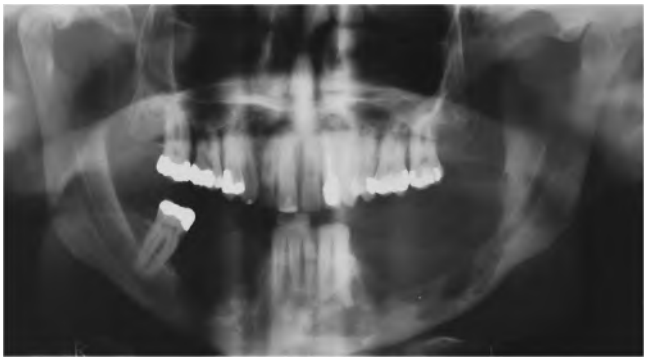

Figure 6-26 Langerhans cell histiocytosis. Multiple, well-defined, noncorticated radiolucencies have coalesced to give the appearance of diffuse mandibular bone destruction.

GIANT CELL LESIONS OF BONE

Giant cell lesions include the peripheral giant cell granuloma (see "Benign Soft Tissue Tumors") and the central giant cell granuloma, aneurysmal bone cyst, and cherubism (discussed here). These conditions are all non-neoplastic lesions that are characterized by a similar histologic appearance. Common to all of them is the presence of numerous multinucleated giant cells in a background of mesenchymal cells that contain round to ovoid nuclei. Extravasated red blood cells and hemosiderin deposits are commonly found in these lesions, as are reactive bone trabeculae. The aneurysmal bone cyst contains varying-sized blood-filled spaces, frequently admixed with trabeculae of bone. The bone lesions of cherubism are similar to those of the central giant cell granuloma.

Central Giant Cell Granuloma (Central Giant Cell Lesion)

Etiology and Pathogenesis

As already noted, the majority of these lesions are thought to be non-neoplastic.

Epidemiology

Central giant cell granuloma occurs more frequently in the mandible than the maxilla, generally anterior to the first molar, and often crossing the midline. Most central giant cell granulomas are diagnosed before age 30 years.

Clinical, Radiographic, and Histologic Manifestations

The radiographic features vary from small, well-circumscribed radiolucencies mimicking periapical inflammatory disease to large, destructive, multilocular radiolucencies (Figure 6-27). The lesions have been reported to perforate the corticle plate and extend into the soft tissue adjacent to the bone. Complaint of pain is an inconsistent feature of these lesions.

Laboratory Findings

The diagnosis of a central giant cell granuloma requires an evaluation for hyperparathyroidism (see also Chapter 22, "Disorders of the Endocrine System and of Metabolism"). Serum calcium, phosphorus, and alkaline phosphatase levels should be obtained prior to surgical removal of a giant cell granuloma, and if abnormal, parathyroid hormone (PTH) levels should be assessed. Lesions radiographically and histologically identical to the giant cell granuloma occur in primary and secondary hyperparathyroidism, and treatment of the lesion in these cases involves treatment of the hyperparathyroidism rather than treatment of the giant cell granuloma. Primary hyperparathyroidism is a result of uncontrolled PTH due to a parathyroid gland abnormality. Secondary hyperparathyroidism develops, usually in patients

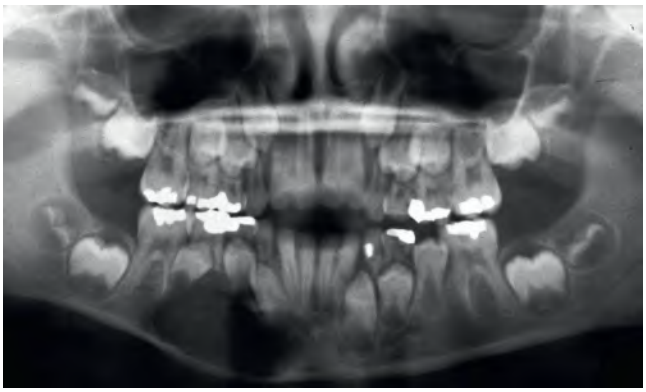

Figure 6-27 Giant cell granuloma. A panoramic radiograph of a giant cell granuloma in a child with a mixed dentition.

with chronic renal disease, due to an increase in PTH production in response to chronic low levels of serum calcium.

Differential Diagnosis

The radiographic differential is rather extensive considering this can appear as a small unilocular radiolucency or a larger multiloculated lesion. For the multilocular lesions ameloblastoma, odontogenic keratocyst, odontogenic myxoma, and central hemangioma are all considerations depending on the presentation.

Management

Treatment usually involves conservative curettage. Other treatment modalities include systemic calcitonin, intralesional injections of corticosteroids, and use of RANKL inhibitors like denosumab. Recurrence rates ranging from 11 to 49% have been reported.

Aneurysmal Bone Cyst

Etiology and Pathogenesis

The term *aneurysmal bone cyst* is a misnomer, since this lesion is not a true cyst and exhibits no epithelial lining. It does contain varying-sized blood-filled spaces. While most lesions are generally believed to be reactive, primary aneurysmal bone cysts have been found to result from oncogenic activation of the *USP6* gene on chromosome 17p13.[32]

Epidemiology

The lesion occurs less frequently in the jaws than in the long bones, but when in the jaws it usually involves the mandible rather than the maxilla. Tissue histologically consistent with aneurysmal bone cyst can be seen in association with other bone diseases, such as fibrous dysplasia. Consequently, aneurysmal bone cysts have been categorized as either primary, for those occurring alone, or secondary, for those occurring in association with another bone disease. Both sexes are equally affected and 80% of aneurysmal bone cysts occur in patients younger than 30 years.

Clinical, Radiographic, and Histologic Manifestations

The clinical signs and symptoms are nonspecific. Pain has been reported (although not consistently) and enlargement of the involved bone is common. The radiographic appearance varies from unilocular to multilocular (Figure 6-28).

Management

Treatment depends on the size of the lesions and includes curettage, enucleation, and resection. Recurrence is attributed to incomplete removal.

Cherubism

Etiology and Pathogenesis

Cherubism is inherited as an autosomal dominant trait, with a penetrance of nearly 100% in males and 50–75% in females. Genetic overexpression of *SH3BP2* on chromosome 4p16 for the 3BP2 protein is the accepted cause of the disease.[33] Other patterns of inheritance and the occurrence of cherubism in association with other syndromes have been described.

Epidemiology

Cherubism is a rare disease that usually presents in early childhood.

Clinical, Radiographic, and Histologic Manifestations

Cherubism is characterized by bilateral painless swellings (mandible and maxilla) that cause fullness of the cheeks;

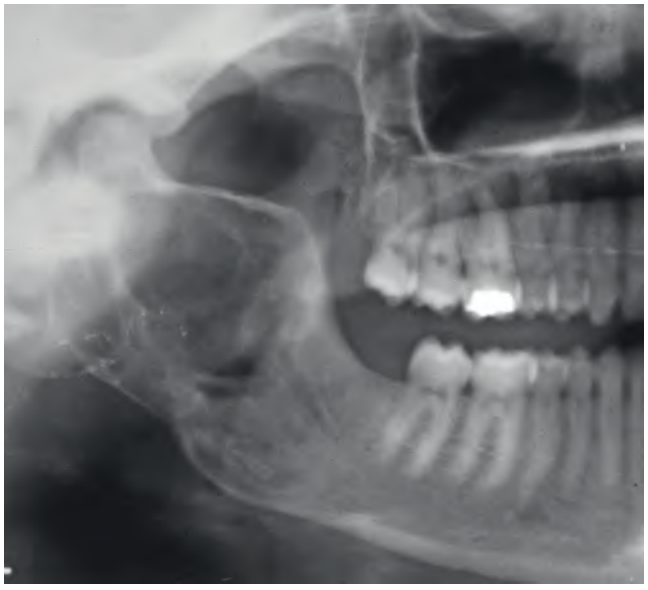

Figure 6-28 Aneurysmal bone cyst. An aneurysmal bone cyst presenting as a multilocular radiolucency in the angle of the mandible of a 31-year-old woman.

firm, protuberant, intraoral, alveolar masses; and missing or displaced teeth.[33] Submandibular lymphadenopathy is an early and constant feature that tends to subside after the age of 5 years and usually has regressed by the age of 12 years. Maxillary involvement can often produce a slightly upward turning of the child's eyes, revealing an abnormal amount of sclera beneath them. It was the upward "looking toward heaven" cast of the eyes combined with the characteristic facial chubbiness of these children that prompted the term *cherubism*. The clinical appearance may vary from barely discernible posterior swellings of a single jaw to significant deformation from anterior and posterior expansion of both jaws, with concomitant difficulties in mastication, speech, swallowing, and respiration.

Disease activity declines with advancing age. Radiographically, the lesions are multiple well-defined multilocular radiolucencies in the mandible and maxilla. They are irregular in size and usually cause marked destruction of the alveolar bone. Numerous displaced and unerupted teeth appear to be floating in radiolucent spaces. Histologically, the lesions of cherubism resemble the central giant cell granuloma, but may exhibit eosinophilic deposits surrounding blood vessels throughout the lesion.

Laboratory Findings

Serum calcium and phosphorus are within normal limits, but serum alkaline phosphatase may be elevated.

Differential Diagnosis

When considering multiquadrant, multilocular radiolucencies in children, Gorlin syndrome (nevoid basal carcinoma syndrome) and Noonan syndrome should be in the differential.

Management

A variety of treatments have been recommended: no active treatment and regular follow-up, extraction of teeth in the involved areas, surgical contouring of expanded lesions, or complete curettage. Long-term longitudinal investigations have reported that the childhood lesions become partially or completely resolved in the adult.

PAGET'S DISEASE OF BONE (OSTEITIS DEFORMANS)

Etiology and Pathogenesis

The etiology of Paget's disease is not well understood. The possibility of an infective viral etiology is suggested by the ultrastructural demonstration of intranuclear inclusions in the abnormal osteoclasts, both in Paget's disease and in the cells of Paget's disease–associated osteosarcoma. Also of note is a significant decrease in the number of new cases in areas of previous high prevalence over the past two decades. However, a viral etiology remains controversial. In recent years, genetic mutations affecting osteoclastogenesis, such as inactivation of *TNFRSF11B* for osteoprotegerin and mutation of *SQSTM1* for the NFKappaB signaling pathway, have been found in some cases of Paget's disease of bone.

It has been reported that close to 30% of patients with Paget's disease have a first-degree relative who has also been affected. This supports the case that both genetic and environmental factors may be playing a role in the disease. About 40% of familial cases have been found to have a mutation of the *SQSTM1* gene.

Epidemiology

Paget's disease of bone affects about 3% of the population over 45 years of age and is rare in patients younger than 40 years. It has a predilection for those of Anglo-Saxon ancestry. Paget's disease is exceeded only by osteoporosis in numbers of patients affected by a metabolic bone disease. Malignant transformation to osteosarcoma and giant cell tumor occurs in less than 1% of patients.

Clinical, Radiographic, and Histologic Manifestations

Paget's disease of bone is a chronic disease of the adult skeleton characterized by focal areas of excessive bone resorption followed by bone formation. Histologically, the involved bone demonstrates prominent reversal lines that result from the resorption and deposition of bone. There is also replacement of the normal bone marrow by vascular fibrous connective tissue. Although some patients with Paget's disease have no symptoms, many experience considerable pain and deformity. The narrowing of skull foramina can cause ill-defined neuralgic pains, severe headache, dizziness, and deafness. The bony lesions of Paget's disease produce characteristic deformities of the skull, jaw, back, pelvis, and legs that are readily recognized both clinically and radiographically. Enlargement of the affected bone is common. Irregular overgrowth of the maxilla may lead to the facial appearance described as "leontiasis ossea," and edentulous patients may complain that their dentures no longer fit. Radiographically, there are patchy radiolucent and radiopaque changes that have been described as a "cotton wool" appearance. Other radiographic findings of the jaw bones include loss of the lamina dura, root resorption, and hypercementosis. CT and Tc 99m diphosphonate bone scanning are used to define the extent of bone involvement.

Laboratory Findings

Urinary levels of calcium and hydroxyproline (a measure of collagen metabolism) and serum alkaline phosphatase levels

(a measure of osteoblastic activity) are useful for diagnosing Paget's disease and for monitoring bone resorption and deposition during treatment.

Management

Craniofacial disorders, associated medical problems (e.g., cardiac failure, hypercalcemia), and the incidence of malignant transformation have encouraged the use of a variety of new treatments.[34] These agents include antibiotics (i.e., intravenous mithramycin, an effective inhibitor of osteoclastic activity), hormones of human and animal origin (high-dose glucocorticoids and porcine, salmon, and human calcitonin administered subcutaneously or by nasal spray or suppository), salts such as the diphosphonate etidronate (which effectively reduces bone resorption), and cytotoxic agents such as plicamycin and dactinomycin.

In addition to cosmetic issues, dental concerns include poor healing of dental extraction sites and excessive postsurgical bleeding from the highly vascular bone that is characteristic of this disease. Bone that exhibits unusually rapid change or enlargement suggests the possibility of malignant transformation. In view of the rarity of a giant cell tumor in the jaws except as a complication of Paget's disease, the finding of this lesion in a patient who is older than 40 years of age should raise the possibility of previously undiagnosed Paget's disease.

CYSTS OF THE JAWS AND ADJACENT SOFT TISSUES

Cysts are defined as fluid-filled epithelium-lined pathologic cavities. Odontogenic cysts are those derived from tooth-forming tissues and/or associated with teeth. Odontogenic and nonodontogenic cysts occur in the oral soft tissues and in both maxilla and mandible. The cysts included here are those that are most common in the jaws and adjacent soft tissues.[35,36]

Odontogenic Cysts

Radicular Cyst (Periapical Cyst)

Etiology and Pathogenesis

A radicular cyst is a true cyst that occurs in association with the root of a nonvital tooth. It is the most commonly occurring cyst in the oral region. An inflammatory response occurs in the periapical tissue, resulting in resorption of bone and formation of granulation tissue that is infiltrated by acute and chronic inflammatory cells. The epithelial lining for the radicular cyst is thought to develop as a result of proliferation of the rests of Malassez entrapped in the inflamed granulation tissue. Histologically, the radicular cyst appears as a squamous epithelium-lined cyst lumen surrounded by inflamed fibrous connective tissue.

Epidemiology

The majority of radicular cysts are seen in adults and the anterior maxilla is the most common location for these cysts.

Clinical and Radiographic Manifestations

Most radicular cysts are asymptomatic and discovered on radiographic examination. Symptoms tend to present when the cyst becomes acutely inflamed. On imaging, they appear as well-circumscribed radiolucencies at the apex or lateral to a tooth root (Figure 6-29). These cysts respond in a negative way to electric and thermal pulp testing.

Differential Diagnosis

Any well-circumscribed unilocular radiolucency adjacent to the root of a tooth could be in the differential. Periapical cemento-osseous dysplasia, periapical granuloma, and periapical scar are included, as is lateral periodontal cyst for the lateral radicular cyst. However, more aggressive lesions such as odontogenic keratocyst, ameloblastoma, and even lymphoma may initially present as a small unilocular radiolucency, therefore submission of removed tissue for microscopic examination is essential.

Management

The radicular cyst is treated by endodontic therapy, apicoectomy, or extraction and curettage of the periapical tissues. A residual cyst forms when the tooth is removed and all or part of a radicular cyst is left behind. Radiographically, the residual cyst appears as a well-circumscribed radiolucency

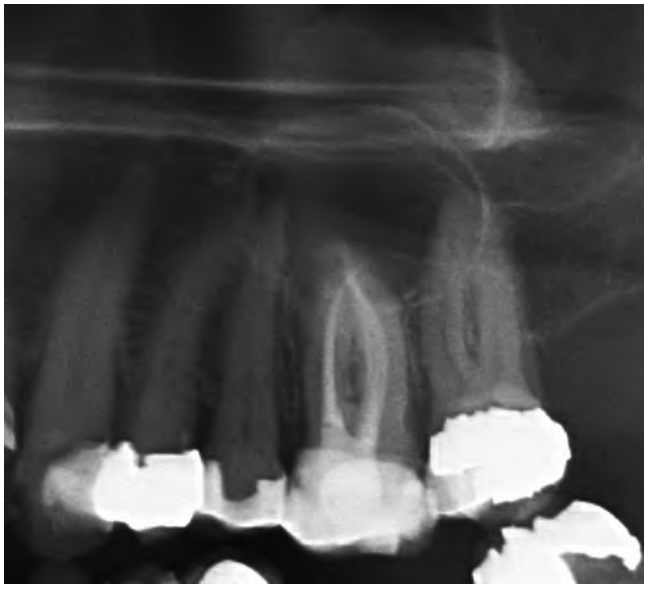

Figure 6-29 Radicular (periapical) cyst.

located at the site of a previously extracted tooth. Either biopsy or excision of the lesion with histologic examination of the tissue is necessary for diagnosis and the treatment is based on the diagnosis. The treatment of a residual cyst involves conservative surgical excision. The cyst does not recur, since the tooth associated with the pathogenesis of the cyst has been removed.

Dentigerous Cyst (Follicular Cyst)

Etiology and Pathogenesis

The dentigerous cyst arises from the epithelium of the dental follicle and remains attached to the neck of the tooth, enclosing the crown within the cyst.

Epidemiology

Some unerupted teeth (e.g., third molars and canines) appear to be more susceptible than others to the development of such cysts. Neoplastic changes such as plexiform ameloblastoma and carcinoma have been reported to occur within segments of the wall of dentigerous cysts. This potential for neoplastic change, infiltration beyond the cyst wall, and the occasional finding of other odontogenic tumors in association with a dentigerous cyst fully justify the need for histopathologic examination of all material derived from jaw cysts.

Clinical and Radiographic Manifestations

A dentigerous or follicular cyst is diagnosed on the basis of its very specific location. The dentigerous cyst forms around the crown of an unerupted or impacted tooth, which may be part of the regular dentition or a supernumerary tooth. Dentigerous cysts have the potential for attaining a large size and also tend to resorb the roots of adjacent teeth. Histologically, the epithelial lining varies from cuboidal to squamous and from very thin to hyperplastic.

Differential Diagnosis

Ameloblastoma, odontogenic keratocyst, and hyperplastic dental follicles should all be considered in the differential. Early calcifying lesions, such as calcifying odontogenic cyst, could also be considered.

Management

Enucleation of the cyst with extraction of the tooth is the most common treatment, with low risk of recurrence. If the cyst is associated with a tooth being considered for eruption, such as with an impacted canine, partial removal of the cyst wall may be indicated along with opening to the oral cavity and potential bracketing of the tooth for orthodontic movement. Larger dentigerous cysts may be decompressed prior to enucleation.

The eruption cyst is the soft tissue analogue of the dentigerous cyst; it presents clinically as a bluish gray swelling of the mucosa over an erupting tooth, most commonly first permanent molars and maxillary incisors. These are also referred to as eruption hematomas. If any treatment is needed, excision of a wedge of the mucosa to expose the tooth crown is usually adequate.

Odontogenic Keratocyst (Keratocystic Odontogenic Tumor)

Etiology and Pathogenesis

In 2005, the World Health Organization (WHO) classified the odontogenic keratocyst as the keratocystic odontogenic tumor. *This decision was then reconsidered by the WHO and reversed in 2016, returning the classification to odontogenic keratocyst (OKC).* Reasons to consider this lesion as a cystic neoplasm include its aggressive clinical course, its tendency for recurrence, its association with certain genetic abnormalities, and its occurrence in the nevoid basal cell carcinoma (Gorlin–Goltz) syndrome.[37]

Epidemiology

The posterior mandible is the most common site of occurrence. However, the odontogenic keratocyst may occur in any location in the maxilla or mandible.

Clinical, Radiographic, and Histologic Manifestations

Radiographically, the OKC may present as a small, asymptomatic, unilocular radiolucency (Figure 6-30A). However, larger, multilocular radiolucencies are common presentations of this cystic neoplasm (Figure 6-30B). The lesions tend to grow along the medullary space of the jaw bone prior to causing expansion of the cortical plate. The odontogenic keratocyst is characterized by its unique histologic appearance. The lumen is lined by epithelium that is generally 8–10 cell layers thick and surfaced by parakeratin. The interface between the epithelium and connective tissue is devoid of rete ridges and the basal cell layer is palisaded and prominent. The parakeratin forms a wavy, corrugated surface.[37] Budding of the cyst lining into the connective tissue is also described as a feature of this cystic neoplasm.

Differential Diagnosis

Early lesion may be unilocular and depending on location a number of lesions would be considered in the differential. Multilocular radiolucencies are typically in the differential with OKC, therefore ameloblastoma, central giant cell granuloma, odontogenic myxoma, and calcifying epithelial odontogenic tumor (early lesions prior to calcifications becoming apparent on imaging) would be included, among others.

Management

Complete removal of the OKC is necessary to prevent recurrence and may be difficult due to the thin, fragile nature of the cyst wall. Treatment ranges from decompression and enucleation to peripheral ostectomy, and chemical cauterization to resection.

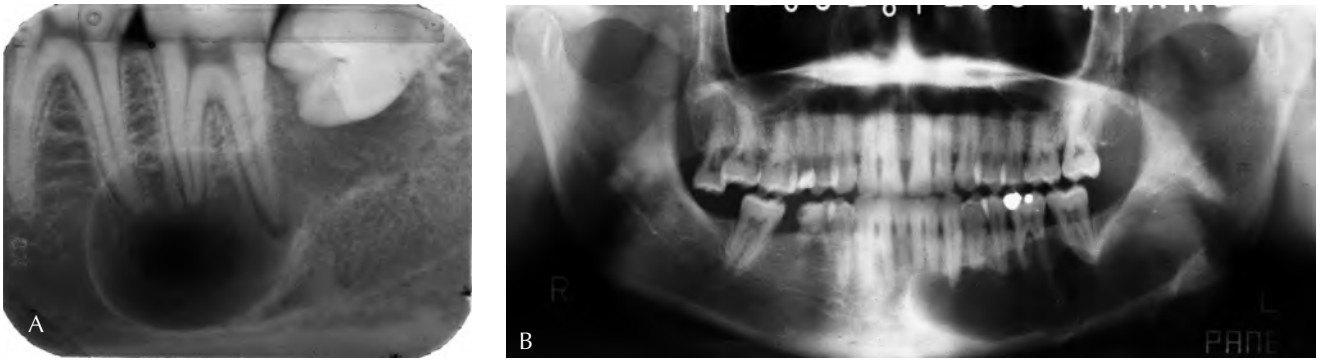

Figure 6-30 Keratocystic odontogenic tumor. (A) A keratocystic odontogenic tumor presenting as a well-circumscribed radiolucency mimicking a periapical inflammatory lesion. (B) A keratocystic odontogenic tumor presenting as a large radiolucency in the mandible.

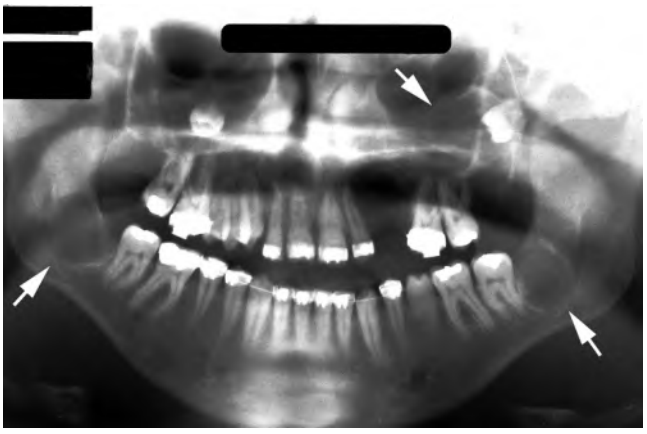

Figure 6-31 Keratocystic odontogenic tumor in nevoid basal cell carcinoma syndrome. The multiple radiolucencies seen in this patient with the syndrome ere histologically shown to be keratocystic odontogenic tumors.

The OKC can occur as an isolated cyst or as a component of the nevoid basal cell carcinoma syndrome (Figure 6-31). This syndrome is inherited as an autosomal dominant trait that exhibits high penetrance and variable expressivity. Mutation of the *PTCH1* gene on chromosome 9q22.3-31 has been shown to be the cause of the syndrome. In addition to keratocystic odontogenic tumors (usually multiple), components of the syndrome include (among many others) basal cell carcinomas developing at an early age in non-sun-exposed skin, mild hypertelorism, enlarged calvarium, calcification of the falx cerebri, and rib abnormalities. Pitting of the soles and palms (local areas of undermaturation of the epithelial basal cells) is an additional finding in about half of individuals affected by the syndrome. Despite the syndrome's name, multiple basal cell carcinomas occur in only 50% of cases. Appropriate treatment for OKC is simple curettage or marsupialization of the cysts.

Lateral Periodontal Cyst (Botryoid Odontogenic Cyst)

Although the lateral periodontal cyst has a distinct and characteristic histologic appearance, the cyst is named for its location.

Etiology and Pathogenesis

These developmental cysts are believed to be derived from remnants of the dental lamina.

Epidemiology

These cysts are most commonly found in adults.

Clinical, Radiographic, and Histologic Manifestations

Lateral periodontal cysts most often present as an asymptomatic unilocular (rarely multilocular) radiolucency, lateral to the root of a vital tooth (Figure 6-32). They are located in the mandibular premolar/canine/lateral incisor area 75% of the time.[38] Divergence of the affected roots is not uncommon. Histologically, the lateral periodontal cyst exhibits a very thin lining of stratified squamous epithelium with focal epithelial thickenings.

Differential Diagnosis

Any unilocular radiolucency in a position lateral to the tooth root would be considered in the differential. This would include lateral radicular cysts, early adenomatoid odontogenic tumors, as well as small ameloblastomas and odontogenic keratocysts.

Management

These cysts are treated by conservative surgical excision. A few cases of recurrence of lateral periodontal cysts have been reported.

The gingival cyst is the soft tissue analogue of the lateral periodontal cyst. The botryoid odontogenic cyst is a variant of the lateral periodontal cyst and clinically may appear multilocular.

Calcifying Odontogenic Cyst (Gorlin Cyst)

Etiology and Pathogenesis

The etiology of the cystic and solid variants of this lesion have been debated for some time. It is now generally considered that the solid variant is a benign tumor (the WHO classifies this as a dentinogenic ghost cell tumor) and the more common variant is a cystic lesion, and both are thought to arise from the dental lamina.[39] These lesions can be seen in

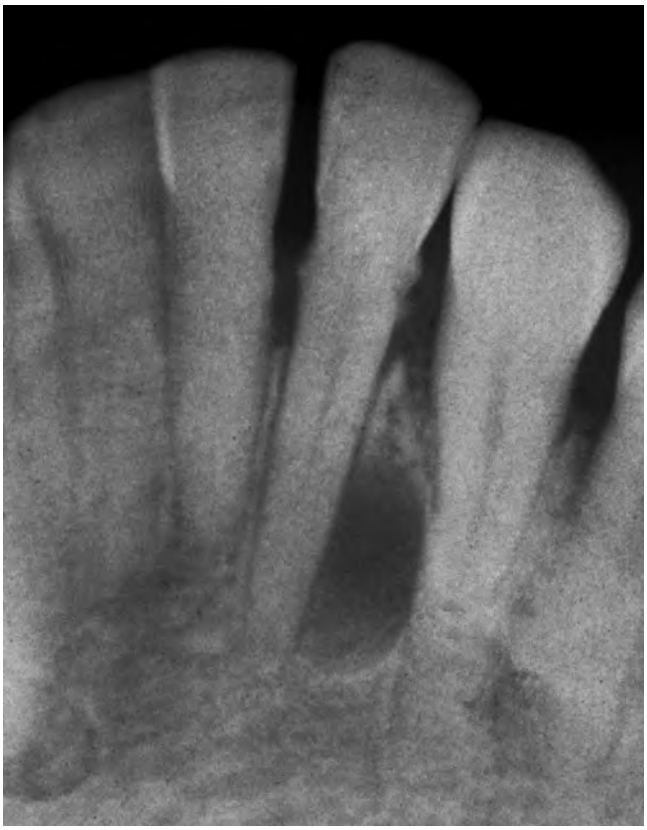

Figure 6-32 A lateral periodontal cyst presenting as a well-circumscribed radiolucency between the roots of a mandibular lateral and cuspid.

association with odontomas (~20% of reported cases) and other odontogenic tumors.

Epidemiology

A rare lesion making up less than 1% of odontogenic cysts. It is seen over a large age range, but most are seen in the second to fourth decades of life. Calcifying odontogenic cysts have about equal prevalence in the maxilla and mandible and approximately two-thirds are seen in the canine/incisor area.

Clinical, Radiographic, and Histologic Manifestations

It is usually a well-defined lesion that can present either as a unilocular or a multilocular radiolucency.[39] Calcifications are seen radiographically as radiopaque areas within a radiolucent lesion. Odontomas have been seen in association with calcifying odontogenic cysts. The calcifying odontogenic cyst is usually a nonaggressive cystic lesion lined by odontogenic epithelium that resembles that of the ameloblastoma, but with characteristic ghost cell keratinization. A solid, noncystic variant histologically resembling the calcifying odontogenic cyst has been described.

Differential Diagnosis

Early lesions with no calcifications would be in the differential with other well-circumscribed unilocular radiolucencies such as dentigerous cyst, early odontogenic keratocyst, and ameloblastoma. Once calcifications appear on imaging, the differential changes and would include adenomatoid odontogenic tumor and calcifying epithelial odontogenic tumor.

Management

The calcifying odontogenic cyst is generally treated by surgical enucleation and usually does not recur. The solid variant has been reported to exhibit more aggressive behavior and a higher recurrence rate and therefore needs more aggressive surgical management, such as peripheral ostectomy or resection.

Glandular Odontogenic Cyst (Sialo-odontogenic Cyst)

Etiology and Pathogenesis

Since 1987, the glandular odontogenic cyst has been recognized as a distinct developmental cyst of the jaws, bearing a histologic resemblance to the botryoid odontogenic cyst and mucoepidermoid carcinoma.[40]

Epidemiology

Clinically, the glandular odontogenic cyst commonly affects middle-aged adults, with no sex predilection. The anterior mandible is a frequent site of occurrence.

Clinical, Radiographic, and Histologic Manifestations

Patients may be asymptomatic or have a painless jaw swelling at presentation. Radiographically, the glandular odontogenic cyst can manifest as a well-defined unilocular or multilocular radiolucency. Histologically, key diagnostic features of the cyst lining include eosinophilic cuboidal (hobnail) cells, clear cells, intraepithelial microcysts, and epithelial spheres.

Differential Diagnosis

Well-circumscribed unilocular radiolucencies would be in the differential with lesions like radicular cyst, but larger lesions may appear multilocular and be in the differential with ameloblastoma, odontogenic keratocyst, and central giant cell granuloma.

Management

The glandular odontogenic cyst is locally aggressive and tends to recur after surgery.

Buccal Bifurcation Cyst

The buccal bifurcation cyst is exceedingly rare and recognized as an inflammatory odontogenic cyst of the pediatric population. Clinically, the cyst typically manifests as a swelling buccal to the furcation of the mandibular first or second molar. The cyst may also present bilaterally. The affected tooth is vital, but may have a deep periodontal pocket. Radiographically, the buccal bifurcation cyst appears as a well-defined unilocular radiolucency centered on the furcation of the mandibular molar (Figure 6-33A). An occlusal radiographic projection will show the cyst tipping the roots of the affected molar lingually

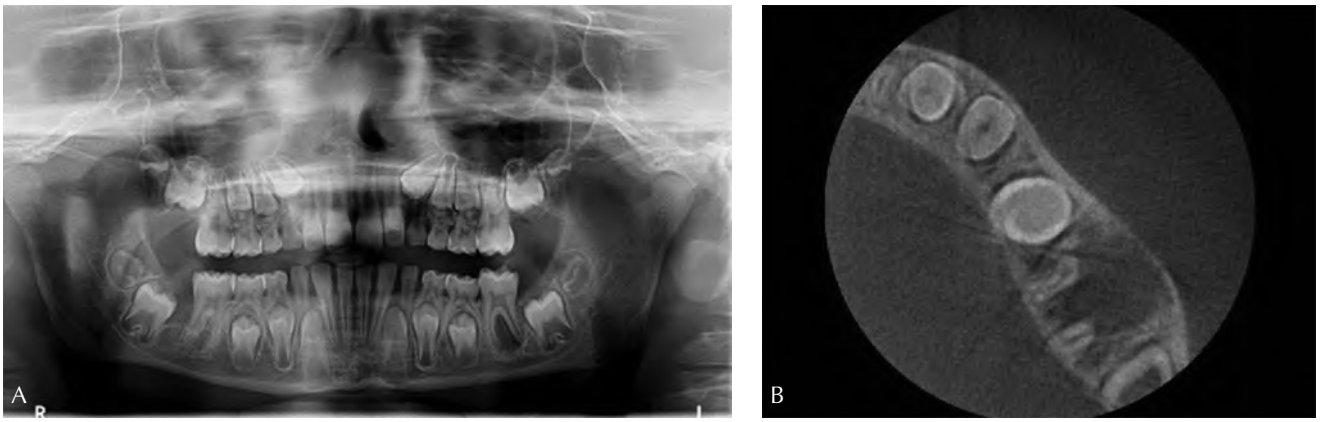

Figure 6-33 Buccal bifurcation cyst. (A) Panoramic and (B) axial cone beam computed tomographic images of a buccal bifurcation cyst associated with the mandibular left first molar. The cyst has tipped the molar roots to the lingual mandibular cortex.

(Figure 6-33B). Histologic features of the buccal bifurcation cyst consist of a nonspecific, inflamed cyst lining. The buccal bifurcation cyst should not recur after curettage.

Nonodontogenic Cysts

Nasopalatine Canal (Duct) Cyst

Etiology and Pathogenesis

The nasopalatine canal (duct) cyst is a developmental cyst derived from remnants of epithelium-lined vestigial oronasal duct tissue.

Epidemiology

The nasopalatine canal cyst is the most common nonodontogenic cyst of the oral cavity and has a mean age of diagnosis in the fifth decade.[41]

Clinical, Radiographic, and Histologic Manifestations

Lesions are often asymptomatic and found on routine imaging, but larger lesions can lead to expansion of the bone and/or soft tissue in the palate. The cyst is located within the nasopalatine canal and presents as a unilocular radiolucency between the roots of vital maxillary central incisors (Figure 6-34).[41] The cyst lining varies from squamous to respiratory (pseudostratified ciliated columnar in about one-third of cases) epithelium. Blood vessels and nerve tissue, contents of the nasopalatine canal, are frequently seen in the connective tissue wall of the cyst.

Differential Diagnosis

The clinical evaluation involves differentiating this cyst from a normal nasopalatine foramen and a radicular cyst. The cyst of the incisive papilla is the soft tissue analogue of the nasopalatine canal cyst.

Management

The cyst is treated by conservative excision and does not recur if completely removed.

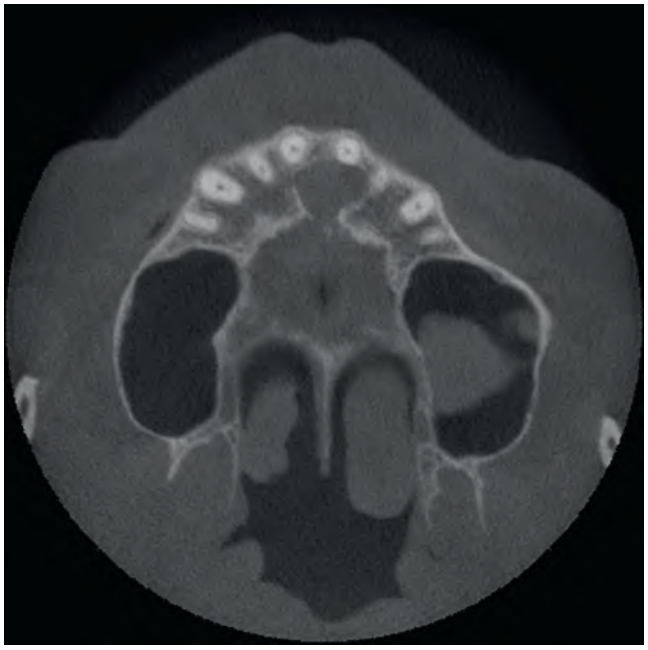

Figure 6-34 Nasopalatine canal (duct) cyst. Axial cone beam computed tomographic image shows a histologically proven nasopalatine canal (duct) cyst arising within the nasopalatine canal.

The nasoalveolar cyst is a soft tissue cyst of uncertain pathogenesis with no alveolar bone involvement. The cyst is observed in older adults, with a 4:1 female predilection. Clinically, the cyst presents as a swelling in the mucolabial fold. The cyst lining varies from squamous to respiratory (pseudostratified ciliated columnar) epithelium. Treatment is surgical excision, and recurrence is rare.

Pseudocysts

Simple (Traumatic, Hemorrhagic) Bone Cyst

The simple bone cyst is a pathologic cavity in bone that is not lined with epithelium. The cause is uncertain, although traditionally an association with trauma has been suggested. The

lesion is found most often in young patients, with an equal distribution between males and females. The lesion presents radiographically as a well-defined radiolucency that characteristically demonstrates a scalloping pattern around the roots of teeth. The lesion is usually asymptomatic and discovered on routine radiographs. Surgical intervention reveals a void within the bone, and healing generally follows intervention.

ODONTOGENIC TUMORS

The classification of odontogenic tumors that is most commonly used divides these tumors into three categories based on the type of cell that forms the tumor: epithelial, mesenchymal, and mixed epithelial and mesenchymal. Odontogenic tumors are derived from tooth-forming tissues, and the developmental stages of tooth formation are emulated in the various odontogenic tumors.

Epithelial Odontogenic Tumors

Ameloblastoma

Etiology and Pathogenesis

The ameloblastoma is the best known of the epithelial odontogenic tumors. The microscopic appearance of this tumor includes tumor cells resembling ameloblasts, with no formation of calcified material. *BRAF* (B-raf proto-oncogene serine/threonine kinase) gene mutations have been identified in ameloblastoma, as have a number of other mutations.[42] The efficacy of therapy targeted to these tumors is still being investigated, but may be helpful in cases where surgery is not an option.

Epidemiology

The ameloblastoma is most commonly seen in the posterior mandible, but may also arise in the maxilla and anterior aspect of the jaws. The radiographic appearance ranges from a unilocular to a multilocular radiolucency (Figure 6-35). Ameloblastomas are rare in children, with most cases occurring in patients between 20 and 50 years of age. A unicystic variant of the ameloblastoma tends to occur during teenage years and has been reported to exhibit a less aggressive behavior.

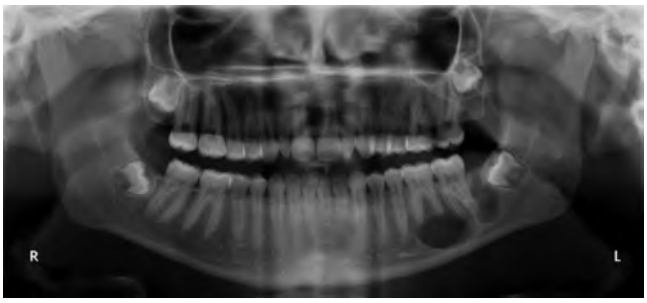

Figure 6-35 Ameloblastoma. Panoramic image shows a multilocular presentation of a histologically proven ameloblastoma.

Clinical, Radiographic, and Histologic Manifestations

Ameloblastoma is typically asymptomatic when small and shows up as an incidental finding on routine imaging. It is often associated with impacted teeth. Larger lesions can cause jaw expansion, perforation of the cortical plate, and even invasion into surrounding soft tissue. If left untreated ameloblastoma can lead to significant facial deformity. Microscopically, all ameloblastomas show a fibrous stroma, with islands or masses of proliferating epithelium that resemble the odontogenic epithelium of the enamel organ (i.e., palisading of cells around proliferating nests of odontogenic epithelium in a pattern similar to ameloblasts). Follicular, plexiform, and acanthomatous histologic variants of this tumor show basal cells, stellate reticulum, and squamous metaplasia. These histologic variants show no correlation with either the clinical appearance of the lesion or its behavior, and variation may be seen between different sections of the same tumor.[42]

Differential Diagnosis

Unilocular ameloblastoma may present like radicular cysts or resemble a dentigerous cyst, especially those lesions associated with an impacted tooth. For multilocular lesions odontogenic keratocyst, central giant cell granuloma, and odontogenic myxoma, among others, are include in the differential.

Management

Complete removal of the tumor is required to prevent recurrence; the plan for reconstruction often influences the extent of surgery. Rare examples of metastatic foci of an ameloblastoma in lungs or regional lymph nodes have been reported. Fewer than 20% of unicystic ameloblastomas have been reported to recur after curettage, whereas over 75% of solid ameloblastomas will recur unless treated by resection. Attempts have been made to marsupialize unicystic tumors. Recurrence is associated with incomplete removal of the tumor.

Adenomatoid Odontogenic Tumor

Etiology and Pathogenesis

Adenomatoid odontogenic tumor (AOT) is a benign tumor of odontogenic epithelium that exhibits behavior very different from the ameloblastoma. This tumor is characterized histologically by a very distinct capsule surrounding the tumor and structures resembling ducts ("adenomatoid") within the epithelium.[43]

Epidemiology

Approximately 70% of AOTs occur in females younger than 20 years and 70% involve the anterior jaw. Association with an impacted canine is common and the maxilla is affected more often than the mandible.

Clinical, Radiographic, and Histologic Manifestations

Early lesion can appear radiolucent, but as the lesion grows calcification arises within the lucency, leading to a mixed radiolucent-radiopaque lesion.[43] While often associated with impacted teeth, adenomatous odontogenic tumors may also present between the roots of teeth and may cause divergence of the roots as the lesion expands.

Differential Diagnosis

Early lesions without calcifications may resemble dentigerous cysts or lateral periodontal cysts. Once calcification is observed, calcifying odontogenic cyst and calcifying epithelial odontogenic tumor can present with a similar radiographic appearance.

Management

Adenomatoid odontogenic tumors often have a fibrous capsule, which means they are easily separated from the bone and rarely recur even with conservative curettage.

Calcifying Epithelial Odontogenic Tumor (Pindborg Tumor)

Etiology and Pathogenesis

The rare calcifying epithelial odontogenic tumor (CEOT) was first described by Dr. J. J. Pindborg in the 1950s. Since then only about 350 cases have been reported in the literature.[44] The lesion is thought to arise from rests of odontogenic epithelium.

Epidemiology

The CEOT has a presentation similar, in location and age of the patient, to ameloblastoma. The average age of presentation is in the fourth to fifth decades.

Clinical, Radiographic, and Histologic Manifestations

CEOT differs from other epithelial odontogenic tumors in that the epithelium does not resemble the epithelium of the tooth-forming apparatus.[44] It is composed of sheets of polyhedral epithelial cells with very little stroma. The cells of this tumor may be quite pleomorphic, with large nuclei. Foci of hyalin amyloid material and calcifications exhibiting concentric rings are frequently seen in this tumor. It is important for the pathologist to recognize this distinctive tumor so that it is not misdiagnosed as a squamous carcinoma. It is locally invasive and may present as a unilocular or multilocular swelling in the molar–ramus region. Larger lesions may expand the cortical bone.

Differential Diagnosis

Early lesions may present as small unilocular radiolucencies such as radicular cyst or lateral periodontal cyst. Multilocular radiolucent lesions would be in the differential with ameloblastoma, central giant cell granuloma, and odontogenic myxoma. For those lesions with calcifications, calcifying odontogenic cyst and AOT should be in the differential.

Management

Treatment is by enucleation or local block excision; the recurrence rate is reported to be 20%.

Squamous Odontogenic Tumor

The squamous odontogenic tumor is a rare lesion composed of multiple islands of squamous epithelium. The squamous epithelium does not exhibit the ameloblast-like features seen in the ameloblastoma. It is reported to occur equally within the maxilla and mandible. Radiographically, this tumor does not have distinctive features. The radiolucent area may resemble periodontal bone loss or periapical inflammatory disease. Conservative surgical excision is the treatment of choice for this tumor.

Mesenchymal Odontogenic Tumors

Odontogenic Myxoma

Etiology and Pathogenesis

Odontogenic myxoma is a benign tumor thought to arise from odontogenic ectomesenchyme.

Epidemiology

The mandible is the most common location (particularly the posterior mandible) of odontogenic myxomas and there is a slight female predilection. The mean age at presentation is in the third decade.[45]

Clinical, Radiographic, and Histologic Manifestations

Myxomas are slow-growing and invasive tumors that can become very large and distend the maxilla or mandible. Characteristically, a myxoma appears radiographically as a unilocular or multilocular lesion and is clinically and radiographically indistinguishable from other lesions that present with a similar radiographic appearance (Figure 6-36). Myxomas are tumors composed of very loose cellular connective tissue containing little collagen and large amounts of an intercellular substance that is rich in acid mucopolysaccharide. This lesion usually consists of very small rounded and angular cells lying in an abundant mucoid stroma that is reminiscent of dental pulp. Since similar lesions are very rare in other bones and since some oral myxomas contain tiny epithelial remnants that resemble inactive odontogenic epithelium, tumors with this histologic appearance that occur in the jaw bone are assumed to be odontogenic in origin.[45]

Differential Diagnosis

Ameloblastoma, odontogenic keratocyst, central giant cell granuloma, and central hemangioma are all included in the differential.

Management

Treatment is similar to that recommended for ameloblastoma.

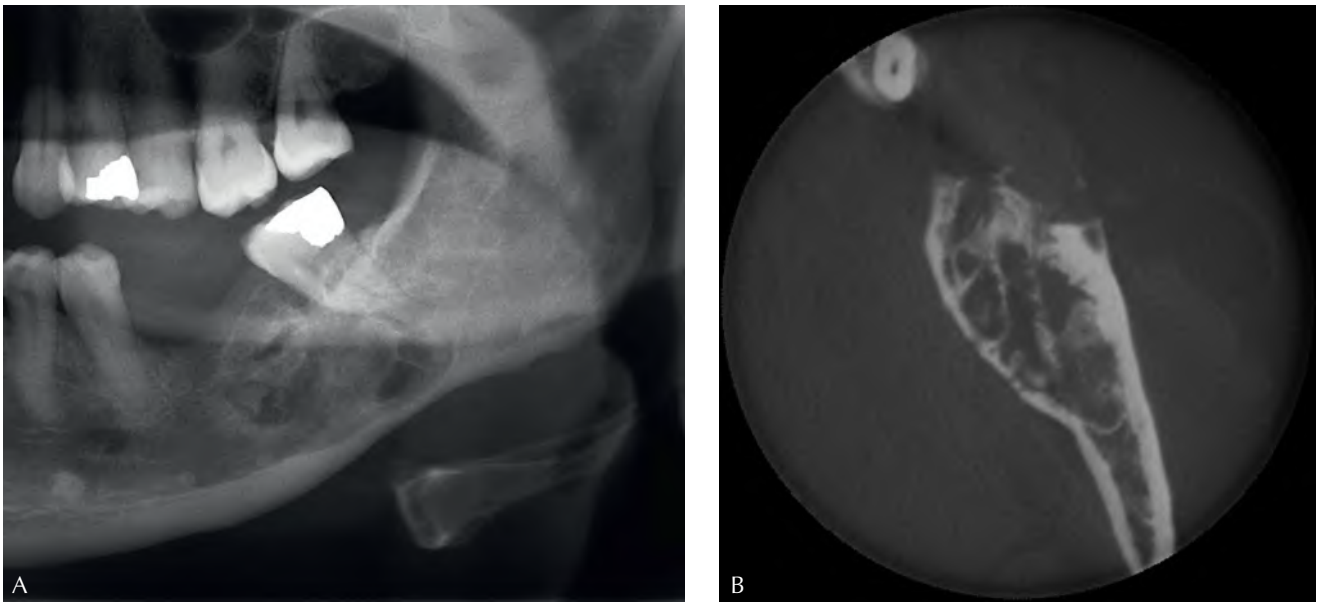

Figure 6-36 Odontogenic myxoma. (A) Cropped panoramic and (B) axial cone beam computed tomographic images show a well-defined multilocular radiolucency with long straight septa, characteristic of odontogenic myxoma.

Central Odontogenic Fibroma

The central odontogenic fibroma is a tumor composed of mature fibroblastic tissue admixed with nests and strands of odontogenic epithelium in varying amounts. It is an uncommon, slow-growing, and nonaggressive lesion. These tumors are usually well-defined unilocular radiolucencies. They are generally small, yet they may cause root resorption. Treatment is conservative excision.

Cementoblastoma

The cementoblastoma is a cementum-producing lesion that is fused to the roots of a vital tooth. The tumor often occurs in young adults and is associated with a mandibular molar or premolar.[46] Pain is a frequent complaint. Early in its development, this tumor presents as a periapical radiolucency that may be indistinguishable from a periapical inflammatory lesion. Later, the cementoblastoma demonstrates a pathognomonic appearance, a well-defined radiopaque mass surrounded by a radiolucent halo that incorporates the root of the tooth (Figure 6-37). Treatment involves removing both the tooth and the attached cementoblastoma. The cementoblastoma does not recur.

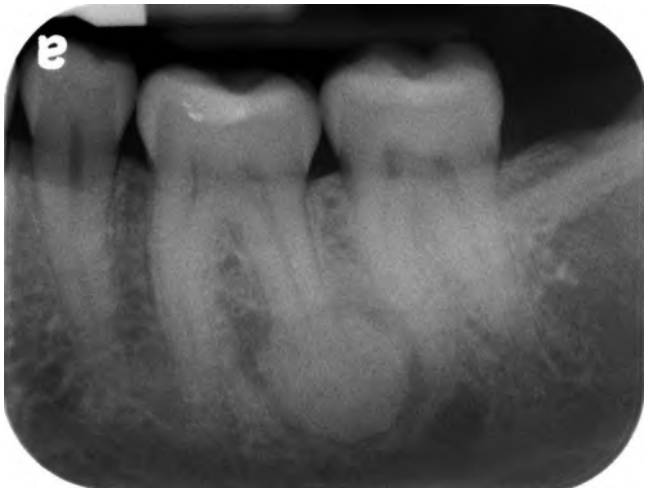

Figure 6-37 Cementoblastoma. Periapical image shows classic radiographic presentation of cementoblastoma fused to the root of the mandibular left first molar.

Mixed Odontogenic Tumors

Ameloblastic Fibroma

Etiology and Pathogenesis

The ameloblastic fibroma is a well-circumscribed tumor that is composed of mesenchymal tissue resembling dental papillae and small islands of odontogenic epithelium resembling dental lamina. A defined capsule may or may not be present with this tumor.

Epidemiology

Most cases of this tumor are in patients under 20 years of age, particularly very young children, and congenital cases have been reported. The most common location is the mandibular premolar and molar region.

Clinical, Radiographic, and Histologic Manifestations

Radiographically, an ameloblastic fibroma presents as a radiolucency that may be well defined, poorly defined, unilocular, or multilocular. When tooth-like formations are associated with this tumor, it is called an ameloblastic fibro-odontoma.

Management

The tumor is treated by surgical excision, and the recurrence rate is low.

Compound and Complex Odontomas

Etiology and Pathogenesis

Compound and complex odontomas are nonaggressive lesions that are more likely to be hamartomatous than neoplastic. Odontogenic cysts and other tumors may also be associated with odontomas.

Epidemiology

Most odontomas are identified in adolescents and young adults. The compound odontoma is most commonly seen in the anterior maxilla and the complex odontoma in the posterior mandible. A compound odontoma consists of a collection of numerous small teeth. Complex odontomas appear as radiopaque masses of varying radiodensity. Despite its designation as a hamartoma, the compound odontoma is considered the most common of the odontogenic tumors.

Clinical, Radiographic, and Histologic Manifestations

It is usually diagnosed by the radiographic identification of multiple small tooth structures. The complex odontoma appears radiographically as a radiopaque mass. It consists of a mass of enamel, dentin, cementum, and pulp that does not morphologically resemble a tooth. Histologic examination of the tissue is generally needed to establish the diagnosis.

Differential Diagnosis

Depending on the appearance of the odontoma, radiopaque lesions such as osteoblastoma, osteoid osteoma, enostosis, and idiopathic osteosclerosis may be included in the differential.

Management

Treatment of the compound or complex odontoma requires surgical excision. These lesions are not expected to recur.

BENIGN NONODONTOGENIC TUMORS OF THE JAWS

Osteomas and Gardner Syndrome

Etiology and Pathogenesis

Osteomas are benign tumors of bone that are composed of mature cancellous or cortical bone.

Epidemiology

Most are initially diagnosed in young adults.

Clinical, Radiographic, and Histologic Manifestations

They can form within the bone as a well-circumscribed radiopacity or on the surface of bone as either a sessile or polypoid bony-hard mass. Osteomas are asymptomatic and are generally undetected unless they are discovered on routine radiographic evaluation or cause facial asymmetry.

Differential Diagnosis

Dense bone island/idiopathic osteosclerosis and complex odontomas may mimic the radiographic appearance of osteomas. If the location is adjacent to teeth, condensing osteitis could also be considered.

Management

Osteomas can be followed with periodic radiographic evaluation to look for any alterations in size or shape. If multiple osteomas are identified in a child or young adult, evaluation for Gardner's syndrome (see below) should be considered.

Maxillary and mandibular tori were described earlier in this chapter. Although they are histologically identical to osteomas, they do not have unlimited growth potential and are not considered neoplasms.

The most significant feature of osteomas of the jaw is the association with Gardner's syndrome.[47] Gardner's syndrome is caused by mutations of the *APC* gene and inherited as an autosomal dominant trait with nearly 100% penetrance. A specific gene mutation responsible for Gardner's syndrome has been identified. Adenomatous polyps of the colon develop in the second and third decades in individuals with Gardner's syndrome. These polyps ultimately exhibit malignant transformation to adenocarcinoma. Patients with Gardner's syndrome develop multiple osteomas of the maxilla and mandible (Figure 6-38) that precede the diagnosis of colonic polyps. Other components of Gardner's syndrome include supernumerary teeth, impacted teeth, skin cysts, and fibrous tumors of the skin.[47]

Osteoblastoma and Osteoid Osteoma

Etiology and Pathogenesis

Benign tumor of osteoblasts.

Epidemiology

Osteoblastoma and osteoid osteoma occur much more commonly in other bones than the jaws. In the jaws, more than two-thirds of lesions are seen before the age of 30 years and there is a higher prevalence in males. The mandible is the most common site of occurrence.[48]

Clinical, Radiographic, and Histologic Manifestations

They are clinically, radiographically, and histologically very similar lesions. The size of the lesion is a distinguishing feature (Table 6-2). The pain associated with an osteoid osteoma

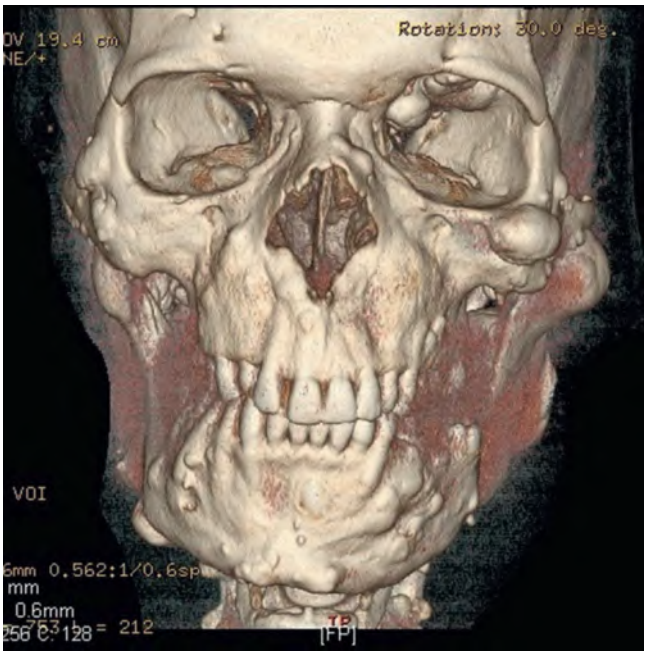

Figure 6-38 Osteomas in Gardner syndrome. Three-dimensional computed tomographic reconstructed image shows multiple craniofacial osteomas in a 30-year-old male diagnosed with Gardner syndrome.

Table 6-2 Distinguishing between osteoid osteoma and osteoblastoma.

	Osteoid Osteoma	Osteoblastoma
Size	Less than 2 cm	More than 2 cm
Symptoms	Nocturnal pain alleviated by aspirin	Dull, localizable ache not relieved by aspirin
Radiographic	Often central radiopaque nidus with a sclerotic border (target appearance)	Twice as common in mandible as maxilla
Most common location	Femur and tibia	Vertebrae

responds to aspirin and other nonsteroidal anti-inflammatory drugs,[48] whereas the pain associated with an osteoblastoma does not. Radiographically, the osteoblastoma presents as a radiolucency that may be either well or poorly defined, with patchy areas of radiopacity within the lesion. The osteoid osteoma is more likely to present with a surrounding zone of sclerosis. Histologically, they both resemble the cementoblastoma, but are not attached to a tooth. They are composed of sheets or irregular trabeculae of bone that exhibit prominent reversal lines. The bone is lined by osteoblast and osteoclast-like cells that contain multiple and large hyperchromatic nuclei. The central portion of the osteoid osteoma contains a concentration of nerve tissue.[48] These tumors are generally treated by conservative excision.

Differential Diagnosis

Depending on the location of the lesion and the amount of calcification, ossifying fibroma, dense bone island/idiopathic osteosclerosis, and complex odontomas may be considered in the differential diagnosis.

Management

Curettage or surgical excision is the most common therapy, with low risk of recurrence.

Chondroma and Chondromyxoid Fibroma

Cartilaginous tumors of the jaws are very rare. Any tumor-containing cartilage in the oral cavity and jaws must be evaluated very carefully by the pathologist to exclude malignancy. However, benign tumors of cartilage occurring in the jaws have been reported rarely. The chondromyxoid fibroma is composed of spindle-shaped and stellate-shaped cells in a myxoid and cartilaginous stroma.[49] The major concern with cartilaginous tumors in the jaws is to ensure that the diagnosis is correct. Benign cartilaginous tumors are treated by conservative excision. Multiple chondromas are components of Ollier's disease (multiple enchondromas) and Maffucci's syndrome (multiple enchondromas with soft tissue hemangiomas).

Desmoplastic Fibroma

Etiology and Pathogenesis

The desmoplastic fibroma of bone is a rare tumor that has been reported to occur in the jaws.[50] It is composed of uniform-appearing fibroblasts and abundant collagen fibers. The degree of cellularity may vary, but the cells of the desmoplastic fibroma do not show atypia and mitoses are not present.

Epidemiology

Most tumors have occurred in the mandible in patients under 30 years of age.

Clinical and Radiographic Manifestations

Painless enlargement of the mandible with an associated unilocular radiolucency is the most common presentation. Radiographically, the tumor may be well or poorly defined and occasionally multilocular.

Differential Diagnosis

Due to the wide range of radiographic appearances, a differential diagnosis is very broad.

Management

This tumor can behave in an aggressive fashion; accordingly, treatment is based on the extent and rate of tumor growth.

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7

Head and Neck Cancer

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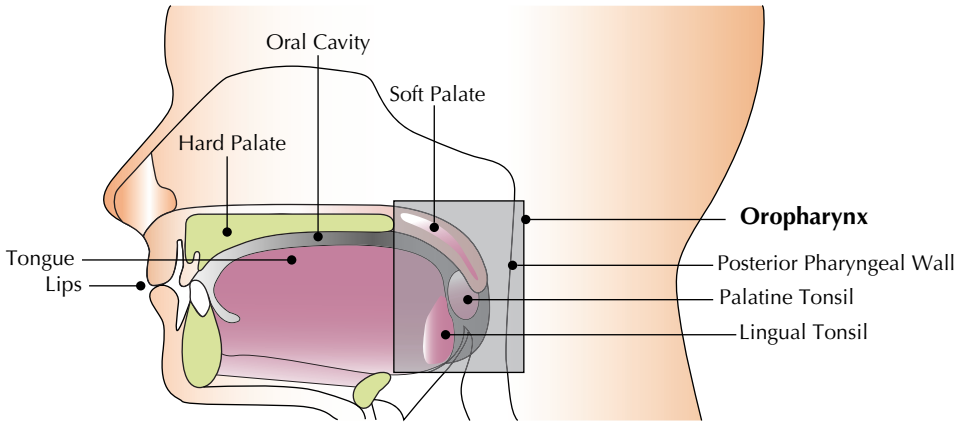


Figure 7-1 The oral cavity and oropharynx. *Source:* Copyright © 2011 American Dental Association. All rights reserved. Reproduced with permission of Elsevier.

Oral cancer is a broad term that includes a number of malignant diagnoses that present in the oral region. Even though the management and prognosis may be different among types and stages of oral cancer, the condition always has a dramatic impact on the patient's life. The cancer and its therapy are associated with morbidities that may negatively affect quality of life, both during cancer therapy, in the immediate period after treatment, and continuing throughout the life of the patient.

Older literature often combines oral squamous cell carcinoma (OSCC) and oropharyngeal carcinoma (OPC), making the evaluation of epidemiology, pathogenesis, and outcomes difficult to assess between the two diseases, and it is now recognized that OSCC and OPC must be evaluated individually. To develop a uniform baseline for discussion, the anatomic domains are presented in Figure 7-1. The oral cavity includes the lips, the labial and buccal mucosa, the anterior two-thirds of the tongue, the retromolar pad, the floor of the mouth, the gingiva, and the hard palate. The oropharynx includes the palatine and lingual tonsils, the posterior one-third (base) of the tongue, the soft palate, and the posterior pharyngeal wall. The nasopharynx extends above the oropharynx and the glottis and larynx below.

This chapter will provide a review of various types of oral and oropharyngeal malignant diseases, with a focus on OSCC and OPC. It will also review other cancers in the head and neck, including nasopharyngeal cancer, paraneoplastic syndromes, and head and neck malignant disease in AIDS. This is a topic that is highly relevant to all healthcare professionals caring for patients during all phases of cancer treatment, from detection to diagnosis, precancer treatment dental care and prevention, and managing oral and dental care for cancer survivors.

EPIDEMIOLOGY

OSCC and OPC represent the sixth most common cancer worldwide.[1] The global incidence of OSCC and OPC is 4.2% of all cancers (754,252) per year, which is expected to increase by 62% to 856,000 by 2035.[2] Worldwide over 354,864 new cases and 177,384 deaths were attributed to OSCC in 2018.[3]

In the United States, OSCC and OPC affect 10.8 of every 100,000 individuals, and 7.2 of every 100,000 individuals will have oral cancer.[2] The estimated new oral and oropharyngeal cancer cases in the United States for 2019 were calculated to be 53,000, with estimated deaths of 10,860.[4] During their lifetime 1.1% of the US population will be diagnosed with oral cavity and oropharyngeal cancer. The American Cancer Society (Cancer.Net) reports that 5-year survival in the United States is now over 62%.[5] This is an improvement in the relative survival compared to 1950–1954, during which relative survival was calculated to be 46%.[6]

The statistics are similar throughout North America but vary around the world; for example, in Hungary the incidence is up to 21.1 cases per 100,000 population.[7] In Southeast Asia the prevalence of oral cancer is high. Oral cancer is ranked one of the sixth most frequent malignancies in Asia, where nearly 274,300 new cases occur annually. The incidence rate is more than 10 per 100,000[8] and it may reach an annual incidence rate of 21.4 per 100,000 individuals in some districts of India.[9,10] Cultural habits, including betel quid chewing, alcohol consumption, and reverse smoking, as well as low socioeconomic status and low consumption of fruits and vegetables, contribute to this high prevalence. The trend differs among countries in this region (it increases in Pakistan and decreases in the Philippines and Sri Lanka) and even varies among provinces of the same country (Thailand).[8]

The majority of oral cancers are squamous cell cancers. Other malignant diseases that can occur in the oral cavity include tumors of the salivary glands, lymph nodes, bone, and soft tissue.

Approximately 95% of oral cancer occurs in people older than 40 years, with an average age at diagnosis of approximately 60 years.[11] OSCC at a young age and even in pediatric patients has however been reported.[12]

The majority of oral cancers involve the lateral borders and base of the tongue. The lips, gingiva, dorsal tongue, palate,

and salivary glands are less common sites. Primary squamous cell carcinoma (SCC) of bone is rare; however, a tumor may develop from epithelial rests and from epithelium of odontogenic lesions, including cysts and benign lesions. Individuals who have had a previous cancer are at high risk of developing a second primary oral cancer. African Americans in the United States have a lower risk of developing OSCC and OPC than Caucasians (9.6 vs. 11.2 per 100,000 population).[13]

Data published specifically for OPC associated with human papillomavirus (HPV) infection showed increased incidence, most of which is related to a rise in incidence in Caucasian males.[14,15] In contrast, the incidence in black males has not increased.[2] Analysis of tissues in national registries during the years 1984–2004 showed that the increase in the population-level incidence of oropharyngeal cancers in the United States since 1984 is caused by HPV infection.[16,17] HPV is primarily associated with OPC, with many fewer HPV-positive tumors in the oral cavity, nasopharynx, and larynx. Despite the changing risk factors for OPC, there is no evidence that detection of high-risk HPV can predict the development of oropharyngeal cancer accurately, as the majority of individuals clear the virus. Interesting findings suggest that tonsillectomy may reduce the incidence of OPC, and decreasing tonsillectomies conducted between 1970 and 2009 may also reflect the period of increasing HPV infection and OPC.[18]

A risk prediction model incorporating OSCC/OPC risk factors, including age, sex, race, smoking, alcohol, lifetime sexual partners, and HPV infection, predicted the following 1-year risks: 21.1/100,000 for older individuals (65–69-year-olds), 13.9/100,000 for men, 10.4/100,000 for Caucasians, 18.0/100,000 for smokers >20 pack years, 18.4/100,000 for heavy alcohol users, and 140.4/100,000 for oncogenic HPV, showing the relative risks of each component of the model.[19] Risk of oral cancer is moderately increased in immunocompromised patients (transplants and HIV infection), was associated with duration of immunosuppression, and was highest in those HIV infected.[20]

Tumors of the salivary glands, the majority of which involve the parotid glands, represent less than 5% of all head and neck tumors. Approximately two-thirds of these are benign mixed tumors (pleomorphic adenomas). In order of decreasing frequency, malignant salivary gland tumors are mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma, SCC, malignant pleomorphic adenoma, undifferentiated carcinoma, lymphoma, melanoma, and a mixed group of sarcomas. Malignant salivary gland tumors are more common in the submandibular, sublingual, and minor salivary glands than in the parotid glands.[21]

ORAL CANCER CLASSIFICATION

Oral cancer nomenclature reflects the histopathologic characteristics of the lesion. In order to facilitate communication between healthcare providers, a classification system was established by the World Health Organization/International Agency for Research on Cancer (WHO/IARC).[22] The classification system was most recently updated in 2017 based on advances in technology and outcome data.

According to the WHO/IARC classification of tumors, the morphology of the cells and the tissue architecture as seen in light microscopy are used to define the neoplasm, which may correlate with the biology and behavior of the cancer.

Publications within the WHO/IARC classification of tumors reference books ("Blue Books," 4th edition) refer to cancer of the oral cavity, oropharynx, cancer of the salivary glands, and odontogenic tumors. Notable changes in this 2017 update underscore the distinct pathologic differences between OSCC and OPC. Tumors of the oropharynx (base of tongue, tonsils, and adenoids) are further delineated into HPV-positive and HPV-negative SCC. HPV-positive tumors are no longer graded histologically. These changes underscore the epidemiologic trends demonstrated by the changing demographics, anatomic site, and prognostic outcomes that make up the current landscape of head and neck cancer.

SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY AND OROPHARYNX

Etiology and Risk Factors

The incidence of oral cancer is age related, which may reflect time for the accumulation of genetic changes and duration of exposure to initiators and promoters. These include chemical and physical irritants, viruses, and hormonal effects. In addition, decreased immunologic surveillance over time may be another explanation for the age relation. Furthermore, immunosuppressed patients following solid organ and hematopoietic stem cell transplantations, patients treated with chemotherapy, and HIV patients have an increased risk.

Tobacco and Alcohol

Tobacco products and alcohol are acknowledged risk factors for oral and oropharyngeal cancer. Tobacco contains potent carcinogens, including nitrosamines, polycyclic aromatic hydrocarbons, nitrosodiethanolamine, nitrosoproline, and polonium. Tobacco smoke contains carbon monoxide, thiocyanate, hydrogen cyanide, nicotine, and metabolites of these constituents. Nicotine is a powerful and addictive drug. Epidemiologic studies have shown that up to 80% of oral cancer patients were smokers.[11] In addition to the risk of primary cancers, the risk of recurrent and second primary oral cancers is related to continuing smoking after cancer treatment. Of patients who were observed for 1 year, 18% developed a recurrence or a second primary oral cancer, and those who

continued to smoke had a 30% risk.[23] The effect of smoking on cancer risk diminishes 5–10 years after quitting.

Most studies have focused on cigarette use; however, other forms of tobacco use have been associated with oral cancers. Benign hyperkeratosis and epithelial dysplasia have been documented after short-term use of smokeless tobacco products, and it is implied that chronic use will be associated with an increasing incidence of malignant lesions.[11,24] The potential risk of oral cancer with cannabis is unclear as data are inconsistent, with some reports suggesting decreased risk of cancer associated with the anti-inflammatory and antioxidant properties of cannabinoids. Route of ingestion (smoking, vaping, or edible formulation) and potential contaminants along with confounding variables make the relationship between cannabis and head and neck cancer currently indeterminate.[25,26]

All forms of alcohol, including "hard" liquor, wine, and beer, have been implicated in the etiology of oral cancer. While this topic is difficult to study for many reasons, several studies identified subpopulations in which alcohol is not a risk factor for oral cancer, such as nonsmoking, non-betel-chewing participants or those with the MTHFR TT genotype in Asians.[27,28] In contrast, other studies identified subpopulations at a higher risk for oral cancer following high-dose long-lasting exposure to alcohol, such as participants with ADH1C*1/*2 (Caucasians), ADH1C*1/*2 or ADHA1C*2/*2 (Asians), and ALDH2*2 (Asians).[29] The combined effects of tobacco and alcohol result in a synergistic effect on the development of oral cancer. The mechanisms by which alcohol and tobacco act synergistically may include dehydrating effects of alcohol on the mucosa, increasing mucosal permeability, and the effects of potential carcinogens in alcohol or tobacco. Various enzymatic pathways were suggested as having a role in the mechanism of the synergistic effect of smoking and alcohol on the oral mucosa. Alcohol in small amounts has been shown to have cardioprotective effects and increases high-density lipoprotein levels. The definition of moderate alcohol intake is likely related to individual factors, therefore making population-level recommendations for safe intake not possible.[24]

Areca Nut and Betel Leaf

People who use betel quid, pa(a)n masala, Gutk(ha)a, Catechu gum, or Supari, with or without added tobacco, are at a higher risk for developing oral cancer. In parts of Asia and Southeast Asia (e.g., India, Taiwan), use is historically widespread and accounts for the higher incidence of oral cancer. This habit is often continued in immigrant communities in the United States and Canada and providers outside of India and Asia should be familiar with the effects of this carcinogen: oral submucous fibrosis of the buccal mucosa and periodontium may develop secondary to alkaloid damage to fibroblasts. The resulting fibrosis may cause a decreased intraoral aperture, interfering with speech, swallowing, and oral care, which may lead to an increase in periodontal disease risk. Submucous fibrosis is considered a premalignant condition and other deleterious health effects including increased risk of non-head and neck primary cancers have been reported.[30]

Human Papillomavirus

HPVs are DNA viruses that infect various epithelial surfaces. There are more than 120 types of HPV. HPV 16, 18, 31, 33, and 35 are considered high-risk subtypes due to their association with malignant tumors. HPV 16 alone is associated with about 90% of HPV-positive oropharyngeal cancers. The virus penetrates the host cell and integrates into the host cell genome, where it can replicate. Malignant transformation occurs through the expression of two HPV viral oncogenes, E6 and E7, which downregulate p53 and Rb, two critical cell regulators of cell cycle progression. HPV-related head and neck squamous cell carcinoma (HNSCC) continue to express p16, unlike HPV-negative tumors, which makes p16 a marker for HPV infection.[31] There are many unanswered questions about the biology of HPV infection, which include clearance versus persistence of virus, latency and carcinogenesis, site localization, recurrence, and second primary cancers. This is discussed further in the section on oncoviruses.

HPV is transmitted by direct contact, primarily by means of vaginal, anal, and oral sex. Risk of developing HPV-positive oropharyngeal cancer increases with an increasing number of self-reported lifetime sexual partners (oral and vaginal), younger age at first sexual activity, and history of having a same-sex partner; in addition, the level of risk can vary according to tumor site.[32] It is important to note that these findings are related to oropharyngeal carcinoma, whereas in oral cancer HPV is not well defined as a risk factor.

Nutritional Factors

Low consumption of fruits and vegetables and high consumption of meat, tobacco, and alcohol is associated with an increased risk of cancer. Foods high in vitamins A, C, E, and selenium have antioxidant protective effects, particularly for epithelial cancers. High abdominal adipose composition combined with low consumption of nutritionally dense foods is a concern for increased cancer rates in Western countries.[33]

Lycopene and beta carotene may play a role in reducing the risk of premalignant lesions of the oral cavity. This hypothesis is based on population studies in which deficiency was associated with a risk of SCC, and on studies of vitamin A and carotenoid supplementation, as well as on studies of reduction in carcinogenesis in animal models.

Some reports have demonstrated that vitamin A may cause regression of premalignant leukoplakia.[34]

Other Risk Factors

There is conflicting evidence on the causality of other risk factors related to oral health, including alcohol-based mouthwashes, poor dental status, denture use, chronic mucosal trauma, and microorganisms. These factors combined with exposure to known carcinogens likely work in a synergistic fashion. The role of local trauma in the development of oral cancer remains controversial.[35,36] It is possible that chronic trauma, in the presence of other risk factors and carcinogens, may promote the transformation of epithelial cells, as has been demonstrated in animal studies.

In lip cancer, sun exposure, fair skin, pipe smoking, and alcohol are identified risk factors.[37] Recurrent herpes simplex virus of the lip has not been associated with increased cancer risk.

Environmental exposure to indoor and outdoor pollution from wood smoke and coal combustion, leading to inhaled toxins such as mercury, lead, sulfur dioxide, nitrogen, and other particulates, is related to numerous deleterious health effects globally. The IARC has classified air pollution as a carcinogen and it is a leading environmental cause of cancer deaths.[38]

Certain inherited cancer syndromes show an increased risk for oral cancer. For example, oral cancer is one of the cancers that are typical for patients with Fanconi anemia. Cowden syndrome, xeroderma pigmentosum, and dyskeratosis congenita were reported in association with oral cancer as well.[39]

Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are at increased risk of developing secondary neoplasms, particularly leukemias and lymphomas, which may manifest in the oral tissues. Likewise, OSCC has been reported as having up to a 20-fold increase in risk in these patient populations.[40–42] OSCC after an extended period of immunosuppression post transplantation is documented as having similar molecular changes as seen in nonmedically induced immunosuppression.[43] Oral cancer may behave more aggressively in patients post HSCT with chronic graft-versus-host disease and associated immunosuppression. Other immunosuppressed patients show increased risk for oral cancer as well, such as patients after liver transplantation.[44]

Oral Potentially Malignant Disorders

The WHO listed several oral conditions as having the potential to transform into oral cancer, including lichen planus, leukoplakia, discoid lupus erythematosus, inherited disorders, tobacco-related lesions, erythroplakia, actinic cheilitis, and submucous fibrosis.[23] Under the term "leukoplakia," it is worthwhile mentioning proliferative verrucous leukoplakia, which behaves more aggressively than other leukoplakias and has a high risk of progression to SCC.[45] Within the oral cavity, leukoplakia, erythroleukoplakia, and speckled leukoplakic lesions may have dysplastic elements within the clinically identifiable lesion. Keratotic epithelium with dysplasia has a 3–5 times increased risk of malignant transformation with severe dysplasia.[46]

The classification of oral potentially malignant disorders (OPMDs) takes into account that a field change in clinically normal-appearing tissues may occur in a patient with a diagnosed OPMD. Most patients will not have a specific diagnosis and many may have an isolated lesion. Clinical and histologic features may help the oral medicine provider stratify risk for malignant progression. These high-risk factors include large size, nonhomogeneous texture, red or speckled in color, tongue or floor of mouth location, tobacco use, and histologic severe dysplasia.

Pathogenesis

Carcinogenesis is a genetic process that leads to a change in molecular function, cell morphology, and, ultimately, cellular behavior. Carcinogenesis is not limited to the epithelium but involves a complex epithelial, connective tissue, and immune function interaction.

Major genes involved in OSCC include oncogenes and tumor suppressor genes (TSGs). Regulatory genetic molecules may be involved as well.[47] The genetic changes may be reflected in allelic loss or addition at chromosome regions corresponding to proto-oncogenes and TSGs, or epigenetic changes such as deoxyribonucleic acid (DNA) methylation or histone deacetylation. Extracellular enzymes, cell surface molecules, and immune function play a role in the development and spread of oral cancer; viruses and carcinogens are involved as well.[48]

While the principal studies have been related to epithelial changes, some of the components listed can constitute a complex environment that suggests an epithelium-connective tissue theoretical model. For example, the interplay of extracellular enzymes, cell surface molecules, growth factors, and the immune system leads to epithelial–connective tissue interaction. According to this model, mucosal differentiation and maturation of epithelial cells represent an epithelial and connective tissue bidirectional process that may be involved in carcinogenesis.

Oncogenes

Oncogenes may encode for growth factors, growth factor receptors, protein kinases, signal transducers, nuclear phosphoproteins, and transcription factors. Although proto-oncogenes increase cell growth and effect differentiation and are likely involved in carcinogenesis, few have been

consistently reported in HNSCC. Proto-oncogenes associated with HNSCC include ras (rat sarcoma), cyclins, myc (myelocytomatosis), erb-b (erythroblastosis), bcl (B-cell lymphoma), int-2, CK8, CK19, and epidermal growth factor receptor (EGFR).[47,49] Each of these oncogene families has several genes and isoforms with potential roles in carcinogenesis. For example, the ras family has three genes (Hras, Kras, Nras) and represents one of the most mutated oncogenes in human cancer, including oral cancer.[50]

Tumor Suppressor Genes

TSGs negatively regulate cell growth and differentiation. Functional loss of TSGs is common in carcinogenesis and in OSCC. Both copies of a TSG must be inactivated or lost for loss of function (the "two-hit" hypothesis). Chromosomes are numbered (1 to 23), and the arms of each chromosome are divided by the centromere into a short arm (designated P) and a long arm (designated Q). TSGs have been associated with sites of chromosome abnormalities where loss of genetic nucleic segments has been reported to commonly involve chromosome arms 3p, 4q, 8p, 9p, 11q, 13q, and 17p. TSGs involved in HNSCC are P53, Rb (retinoblastoma), and p16INK4A. Other candidates include FHIT (fragile histidine triad), APC (adenomatous polyposis coli), DOC1 VHL (gene for von Hippel-Lindau syndrome), and TGF-R-II (gene for transforming growth factor type II receptor).[47]

Gene-Regulating Proteins

Part of the oncogenic gene regulation is performed by transcription factors. These are proteins binding to DNA sequences to permit or inhibit co-binding to RNA polymerase, which in turn regulates the activation of the DNA-segment respective gene. Transcription factors that were identified from oral tumors and their potential contribution to oral cancer are listed in Table 7-1.[50]

Table 7-1 Commonly involved oncogenic transcription factors propelling oral cancer.

OTF	Oncogenic potential in OSCC
AP-1	Overexpression, nuclear expression increased according to degree of dysplasia, lymph node metastasis, increased transcriptional activity
NF-κB	Differential expression, activation, proliferation, malignant transformation, invasion
c-Myc	Overexpression, DNA amplification, DNA binding activity, progression of oral cancer
STAT	Early overexpression and activated form of transcription factor, active in OSCC
β-catenin	Nuclear overexpression, oral cancer progression, metastasis
Snail	Overexpression, activation, invasion, correlated with EMT
HIF1α	Overexpression, progression, expression correlates with poor prognosis, invasion
Mutated p53 (GOF)	Inactivated protein, GOF of mutant p53 propel mitosis by expressing cyclin A and cyclin B, GOF leads to shorter disease-free survival, prevention apoptosis after DNA damage, chemoresistance, disease progression

EMT, epithelial–mesenchymal transition; GOF, gain of function; OSCC, oral squamous cell carcinoma; OTF, oncogenic transcription factor.

Source: Adapted with permission from Yedida GR, Nagini S, Mishra R. The importance of oncogenic transcription factors for oral cancer pathogenesis and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;116(2):179–188.

Loss of Heterozygosity

Loss of heterozygosity (LOH) or allelic loss has been studied in oral premalignant lesions and predicts the malignant risk of low-grade dysplastic oral epithelial lesions.[51] The importance of allelic loss has been shown in retrospective and cross-sectional studies and confirmed in a prospective study of patents with dysplasia, where lesions with allelic loss at 3p, 9p, and 17p predict risk of progression to SCC, even in histologically benign tissue or tissue with mild dysplasia. This is of importance, as the majority of potentially malignant oral lesions (hyperplasia, mild and moderate dysplasia) do not progress to cancer. Lesions that progress to SCC appear to differ genetically from nonprogressing lesions, even though they may not demonstrate different histomorphologic findings.

Molecular analysis therefore may become necessary in diagnosis. LOH on 3p and/or 9p is seen in virtually all progressing cases. LOH on 3p and/or 9p has a 3.8 times relative risk of developing SCC, and if additional sites of LOH are present (4q, 8p, 11q, 13q, or 17p), there is a 33-fold increase in risk of progression to cancer. Accumulation of allelic loss is seen in progressing lesions, and the majority of progressing dysplasias have LOH on more than one arm (91% vs. 31% of nonprogressing dysplasias); 57% have loss on more than two arms (vs. 20% of dysplasias without progression). LOH on 4q, 8p, 11q, 13q, and 17p is common in severe dysplasia and carcinoma in situ as well as SCC.[52,53]

Hypermethylation

The role of promoter hypermethylation of CpG islands is being investigated in OSCC, as methylation of epigenetic DNA has been shown to result in a loss of function in some genes involved in cell cycle regulation and DNA repair that may lead to loss or change in TSGs involved in carcinogenesis. Changes in DNA methylation of six genes and a significantly higher frequency of methylation in a number of TSGs, including cyclin A1 and p16 promoter sequences, have been seen. Mitochondrial DNA (mtDNA) content increases with oxidative damage as possible compensation to mitochondrial dysfunction. MtDNA as assessed by polymerase chain reaction for specific mitochondrial genes was

shown to increase with severity of dysplasia and in SCC. These findings support the model of accumulation of genetic alterations as mucosal disease progresses from benign to dysplasia and potentially to SCC, and the contention that mtDNA increases with histologic grade.[54,55]

MicroRNA

MicroRNAs are small segments of nonencoding single-stranded RNAs that mediate gene expression at the post-transcriptional level by mRNA degradation or translational repression. Aberrant microRNA may disrupt the normal regulation and lead to malignancy. MicroRNAs function either as oncogenes or as tumor suppressors and are suggested to play a role in oral cancer.[56]

Extracellular Enzymes

SCC primarily spreads by direct local extension and by regional extension, primarily via the lymphatics. Regional spread in the oral mucosa may occur by direct extension and possibly by submucosal spread and results in wide areas of involvement. Production of type I collagenase, heparanase, prostaglandin E_2, and interleukin-1 and connective tissue growth factor (CTGF) may affect the extracellular matrix, and motility of epithelial cells may allow invasion.[57,58] Changes in the basement membrane, such as the breakdown of laminin and collagen, occur with invasion. Matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase play a role in cancer initiation and development and have prognostic significance.[59] The initiation or progression of oral cancer may also be associated with polymorphism of the vascular endothelial growth factor (VEGF) gene.[60,61] Understanding the biology of invasion by malignant cells may lead to additional approaches to diagnosis and management.

Cell Surface Changes

Changes in cell surface receptors and major histocompatibility class I and class II antigens have been seen and may indicate that immune surveillance and immune function may be affected in patients with oral cancer. Other cell surface changes include a loss of cytoplasmic membrane binding of lectins, which has been shown to correlate with the degree of cellular atypia.

Intercellular adhesion molecules may play a role in tumorigenesis and perineural invasion. Integrin is a cell adhesion receptor and is often associated with altered expression in tumors as well as with malignant transformation. Alterations in cell-bound immunoglobulins and circulating immune complexes are detectable, but the importance of these changes is unclear.

Immunosuppression

The development of malignant disease at a higher rate in immunosuppressed patients indicates the importance of an intact immune response. Mononuclear cell infiltration correlates with prognosis, and more aggressive disease is associated with limited inflammatory response. Total numbers of T cells may be decreased in patients with head and neck cancer. In addition, the mixed lymphocyte reaction is reduced in some patients, and a diminished migration of macrophages has been demonstrated. Clusters of differentiation 8 (CD8) lymphocytes (T-suppressor cells) predominate tumor infiltrates, suggesting that immunosuppression is associated with progression of disease. Programmed cell death-1 (PD-1) is currently the target of many cancer immunotherapy agents aimed at interference with specific immune checkpoints. This immunoinhibitory receptor is part of the cytotoxic T-lymphocyte antigen family.[62]

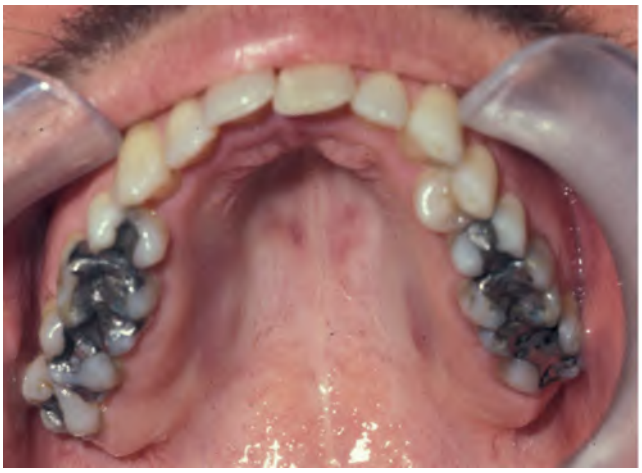
Oncoviruses

An estimated 12% of cancers can be caused by an oncovirus, including Epstein–Barr virus (EBV), HPV, human T-cell lymphotropic virus-1 (HTLV-1), Merkel cell polyomavirus (MCPyV), hepatitis B and C viruses (HBV and HCV), and Kaposi sarcoma (KS) herpesvirus (HHV8). As discussed previously, HPV is the most critical oncovirus in the pathogenesis of head and neck cancer and has dramatically changed the demographics and treatment approach as well as outcomes of OPC. HPV-related lesions are increasingly reported at other head and neck sites, including the oral cavity.[63] Up to 80% of OPC and 26% of OSCC have been associated with high-risk HPV, showing a continuing trend to increasing HPV in SCC.[64] HPV prevalence in the OSCC group was higher than in potentially malignant disorder participants or the control group. The most common HPV subtypes detected in OPC are HPV 16 and 18 (68% and 34%, respectively). Other types of HPV detected in OSCC were HPV 6, 11, 31, 33, 35, and 56.[65]

EBV and HHV8 are of particular importance to understanding head and neck cancer. EBV infection is noted in malignant transformation of nasopharynx and specific salivary gland cancers. This is discussed further in the section on nasopharyngeal carcinoma. HHV8 or KS herpesvirus, which historically affected older European males, became a global concern during the AIDS epidemic of the 1980s. KS continues to impact immunosuppressed individuals and can occur in the oral cavity. (Figures 7-2 and 7-3).

PRESENTING SIGNS AND SYMPTOMS

Unfortunately, patients are most often identified after the development of symptoms associated with advanced stages of disease. Discomfort is the most common symptom that leads a patient to seek care and may be present at the time of diagnosis in oral cavity tumors. However, oropharynx cancers



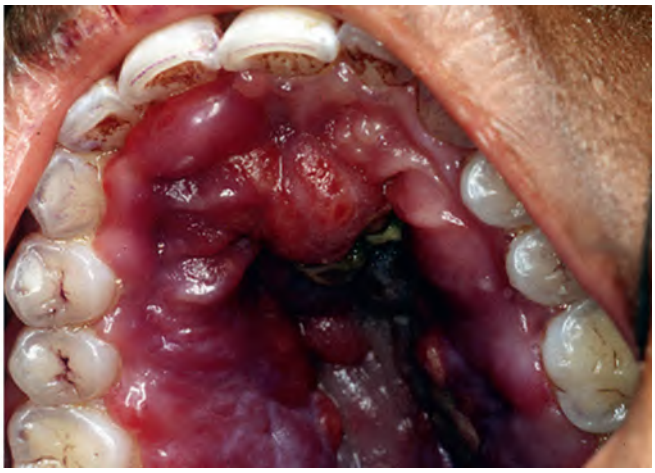


Figure 7-2 Bilateral involvement of the anterior and posterior hard palate with purple discolorations consistent with Kaposi sarcoma.

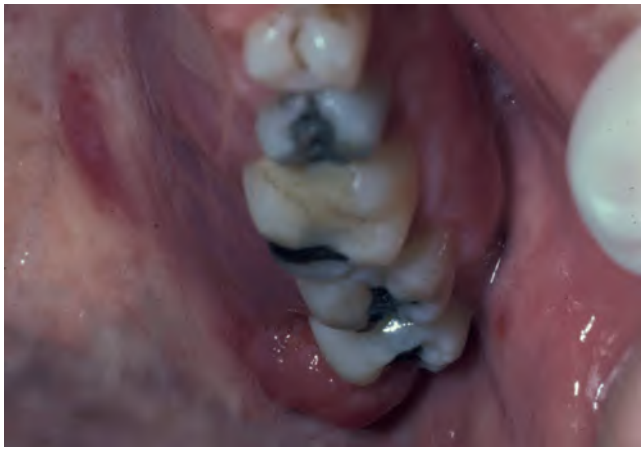


Figure 7-3 Gingival involvement by Kaposi sarcoma, with discoloration and enlargement and soft tissue mass on the maxillary tuberosity.

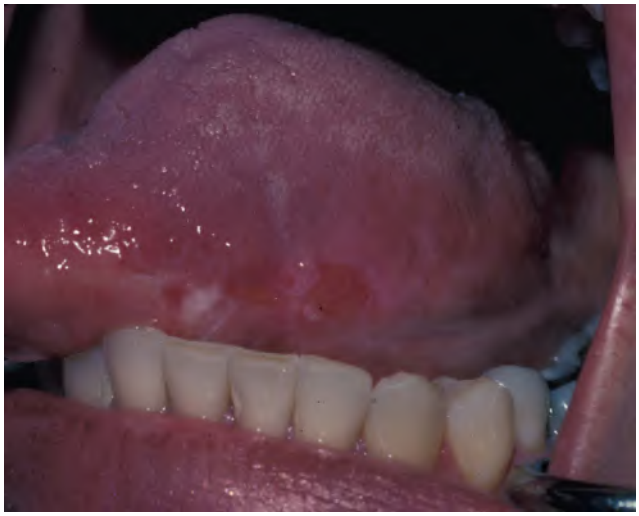


Figure 7-4 Irregular erythroleukoplakia of the left lateral border of the tongue.

often present with an awareness of a mass in the neck.[66] Dysphagia, odynophagia, otalgia, limited movement, oral bleeding, neck masses, and weight loss may occur with advanced disease.[67] Paresthesia or dysesthesia, especially when it is unilateral, is a red flag that may indicate neural involvement and requires that cancer be ruled out. Loss of function involving the tongue can affect speech, swallowing, and diet.

Possible tissue changes may include a red, white, or mixed red and white lesion; a change in the surface texture producing a smooth, granular, rough, or crusted lesion; or the presence of a mass or ulceration (Figures 7-4, 7-5, 7-6, 7-7, 7-8, and 7-9). The lesion may be flat or elevated and may be minimally palpable or indurated. The high-risk sites for oral carcinoma include the lower lip, the anterior floor of the mouth, and the lateral borders of the tongue.

The clinical presentation may take a different shape in verrucous carcinoma, a subtype of OSCC with characteristic clinical findings. It can be described clinically as grainy, papillary, verruciform, fungating, or cauliflower-like. Verrucous carcinoma may develop from the progression of proliferative verrucous leukoplakia and develop into carcinoma.[45,68,69]

Lymphatic spread of oral carcinoma most commonly involves the submandibular and digastric nodes and the upper cervical nodes, and can involve the remaining nodes of the cervical chain. The nodes most commonly involved are those that are ipsilateral to the primary tumor, although the closer the tumor is to the midline and the more posterior in the oral cavity or oropharynx, the more common is the involvement of the bilateral and contralateral nodes.

Lymph node involvement may not occur in an orderly fashion. Lymph nodes associated with cancer become enlarged and firm to hard in texture, and with progression may become fixed. The fixation of nodes to adjacent tissue due to invasion of cells through the capsule is a late occurrence and evidence

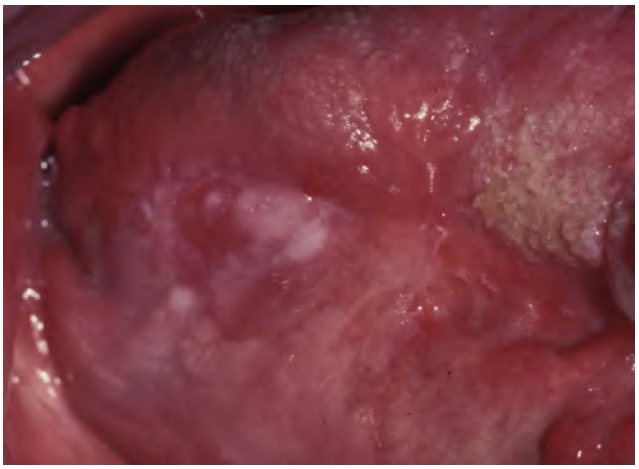


Figure 7-5 Previously treated squamous cell carcinomas are at risk of recurrent squamous cell carcinoma. This case was treated with surgery and postoperative radiation therapy and presented with an area of erythroleukoplakia that was diagnosed as recurrent squamous cell carcinoma.

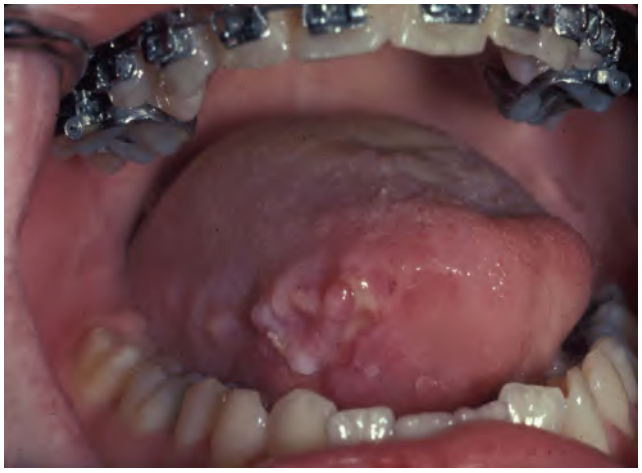


Figure 7-6 Indurated and ulcerated lesion of the right anterior tongue in a 15-year-old girl, persisting after removal of orthodontic appliances, proven to be squamous cell carcinoma on biopsy.

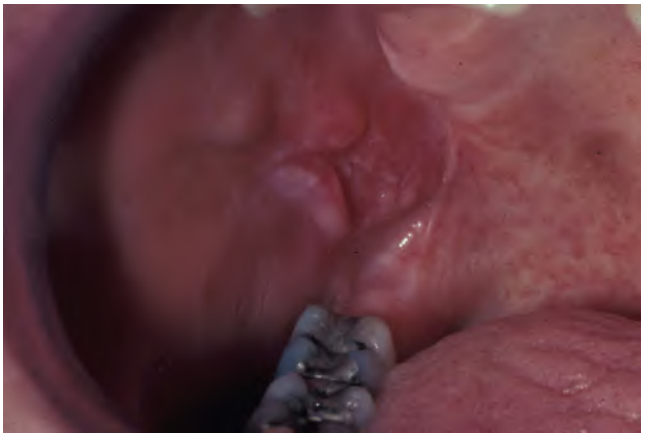


Figure 7-7 Nonpainful, irregular indurated exophytic and ulcerated buccal mass; histopathology revealed squamous cell carcinoma.

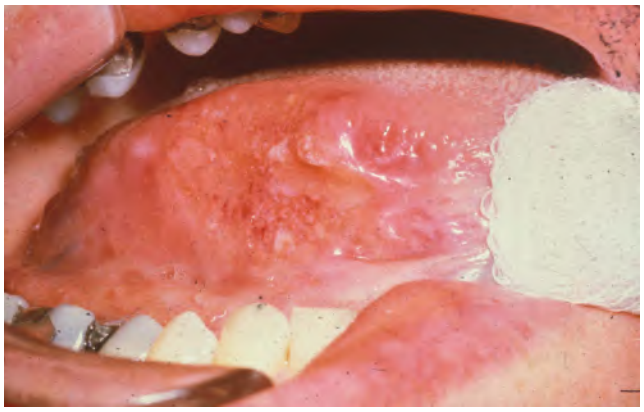


Figure 7-8 Eroded, erythroleukoplakic, indurated lesion in the right posterior third of the lateral border of the tongue, diagnosed as squamous cell carcinoma.

of aggressive disease. The fixation of the primary tumor to adjacent tissue overlying bone suggests the involvement of the periosteum and possible spread to bone. Nodes are not tender unless they are associated with secondary infection or an inflammatory response is present, which may occur after a biopsy. Spread of tumor is critical for prognosis and for selection of treatment. The understaging of nodes by cursory assessment or the overstaging of nodes following a biopsy, when an inflammatory component may be present, impacts the selection of treatment. Therefore, accurate node examination is needed before biopsy.

It is essential to have an understanding of the differentiation between OSCC and OPC with respect to cervical nodal metastasis. Staging by the AJCC 8th edition (see later) takes into account the high rate of nodal metastasis in HPV-related OPC. Tonsillar and oropharyngeal SCC is more likely to be diagnosed after regional metastasis has occurred, with 12% localized and 67.5% regional metastasis at diagnosis. Metastasis of OSCC at diagnosis is localized in 31.7% or regional in 45.2%. The stage at initial diagnosis is similar across all sexes and ethnic backgrounds for OPC and is related to the molecular behavior of HPV-related tumors, rather than delayed diagnosis or racial or socioeconomic barriers to care.[70]

DIAGNOSIS AND HISTOPATHOLOGY

Diagnosis is primarily based on histopathology. Within the epithelial tumors, SCC is the most prevalent oral malignancy. It has several subtypes based on histopathology. Some of the variants may have a unique clinical presentation.

For the diagnosis of OSCC, dysplasia involves the full thickness of the epithelium and the basement membrane is violated. Dysplasia describes a range of cellular abnormalities that

include changes in cell size and morphology, increased mitotic figures, hyperchromatism, changes in nuclear size and the nuclear–cytoplasmic ratio, and alteration in normal cellular orientation and maturation. Well-differentiated carcinoma retains some anatomic features of epithelial cells, including their ability to produce keratin, whereas poorly differentiated carcinoma involves a loss of the anatomic pattern and function of epithelium. Tumors may be associated with a mixed inflammatory infiltrate. Inflammatory and reactive lesions can be difficult to differentiate from dysplasia, and the experience of the pathologist becomes important with a need for clinical reassessment and repeat investigation. Invasion of lymphatics, blood vessels, and perineural spaces is of critical importance, but is difficult to determine.[71]

Histologically, verrucous carcinoma is characterized by piling up of keratin on the surface, with downgrowth of club-shaped fingers of hyperplastic epithelium with a pushing front rather than infiltration into the connective tissue. Dysplasia may be mild. Usually, a dense infiltrate of lymphocytes and plasma cells is present. Verrucous carcinoma rarely spreads to lymph nodes and typically remains locally destructive.[72,73] The difficulty in diagnosis and treatment is due to a benign histology or mild dysplastic changes that may be seen despite progressive and recurrent disease.

The term basaloid squamous carcinoma (BSC) has been introduced for tumors of which the major portion is composed of a solid growth of basaloid cells with small cystic spaces containing periodic acid–Schiff– and alcian blue–positive material. The histologic hallmark of the neoplasm is that of an OSCC in intimate relationship with a basaloid component. Immunohistochemical findings may be helpful in distinguishing BSC from histopathologically similar tumors.[74] HPV-associated cancers of the oral cavity are more likely to have basaloid features.[75]

Spindle cell carcinoma, also referred to as sarcomatoid SCC, is a rare variant of SCC. The histologic criteria of spindle cell carcinoma is the demonstration of epithelial changes ranging from prominent dysplasia to frank OSCC in conjunction with a dysplastic spindle cell element or evidence of direct transition of epithelial cells to dysplastic spindle cells. Osteoid-appearing material within the spindle cell component can be found.[76]

A few cases of adenoid SCC of the oral mucosa have been reported, also known as acantholytic SCC. This is mostly seen in the skin and very rarely in the oral cavity. The adenoid structure results from loss of cohesion of the epidermoid tumor cells. It may show pseudovascular morphology.[77] Other variants such as carcinoma cuniculatum and intraoral sebaceous carcinoma have been reported and may be confused with more common variants such as mucoepidermoid carcinoma.

While histopathology is the gold standard in diagnosis, it is a subjective assessment of tissue, with inter- and intrarater variability. However, phenotypic changes appear following molecular change, and it is expected that as molecular markers become defined, they will provide additional information and may ultimately become the gold standard in diagnosis.

Staging and Grading of Oral Cancer: Tumor–Nodes–Metastasis System

The American Joint Committee on Cancer (AJCC) Tumor–Nodes–Metastasis (TNM) staging system is the most widely used system for clinical and pathologic staging of cancer. Staging reflects prognosis, and is therefore a determinant of treatment strategy.[78] T describes the primary tumor, N indicates the presence of regional lymph node metastasis, and M indicates distant metastasis. The staging system for oral and oropharyngeal cancer combines the T, N, and M categories to classify lesions as stages I through IV and IVA though IVC. The AJCC classification is currently in its 8th edition, which has made significant changes to the TNM staging of head and neck cancers with the aim of improving the reproducible differentiation between stage groups. Major changes from AJCC 7 include newly added staging algorithms for nasopharynx cancer and HPV-mediated oropharynx cancer that reflect the unique biology of these diseases. Changes have also been made to the staging of oral cancer, taking depth of invasion (DOI) and extranodal extension (ENE) into consideration.

There are separate TNM classifications for cancer of the mucosal lip and oral cavity (Table 7-2), HPV-positive and -negative oropharyngeal carcinoma (Table 7-3), and salivary gland carcinomas. The classifications use the same principles with adjustment to the specific anatomic regions.

Adjunctive Diagnostic Aids and Screening Tools

Early detection of potentially malignant and malignant lesions is associated with improved treatment outcomes and a reduction in morbidity of treatment. Patient history and thorough head and neck and intraoral examinations are prerequisites. The definitive test for diagnosis remains tissue biopsy. Several aids to the oral examination were suggested in the past, including light technologies, vital tissue staining using toluidine blue (TB), and computer-assisted cytology of oral brush biopsy specimens.[79] Additional markers based on blood and saliva samples are under investigation for use in early detection, diagnosis, and surveillance for recurrence. There is no consensus regarding the standardization of collection, storage, processing, and analysis of salivary biomarkers and this is not currently a feasible clinical tool.[80] It is imperative to

Table 7-2 Staging of cancer of the mucosal lip and oral cavity.

Primary Tumor (T)		
TX	Primary tumor cannot be assessed	
Tis	Carcinoma in situ	
T1	Tumor ≤2 cm with depth of invasion (DOI*) ≤5 mm	
T2	Tumor ≤2 cm with DOI* >5 mm and ≤10 mm; or Tumor >2 cm and ≤4 cm, with DOI* ≤10 mm	
T3	Tumor >2 cm and ≤4 cm with DOI* >10 mm; or Tumor >4 cm with DOI* ≤10 mm	
T4	Moderately advanced or very advanced local disease	
T4a	Moderately advanced local disease Tumor >4 cm with DOI* > 10mm; or Tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face) NOTE: Superficial erosion of bone/tooth socket (alone) by gingival primary is not sufficient to classify a tumor as T4	
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery	
*DOI is depth of invasion and not tumor thickness.		
Regional Lymph Nodes (N)		
Clinical N (cN)		**Pathological N (pN)**
NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension, extranodal extension (ENE)(-)	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension, ENE(-)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(-)	Metastasis in a single ipsilateral node, 3 cm or smaller in greatest dimension and ENE(+); or Larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, and ENE(-)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension, and ENE(-)	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); or A single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension, and ENE(-)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension, and ENE(-)	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension, and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, and ENE(-)	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, and ENE(-)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or Metastasis in any node(s) and clinically overt ENE(+)	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); or Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or A single contralateral node of any size and ENE(+)

(*Continued*)

Table 7-2 (Continued)

N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)
N3b	Metastasis in any node(s) and clinically overt ENE(+)	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or Multiple ipsilateral, contralateral, or bilateral nodes with any ENE(+); or A single contralateral node of any size and ENE(+)
Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+).		
Distant Metastasis (M)		
M0	No distant metastasis	
M1	Distant metastasis	
Prognostic Stage Groups		
Stage 0	Tis N0 M0	
Stage I	T1 N0 M0	
Stage II	T2 N0 M0	
Stage III	T3 N0 M0	
	T1 N1 M0	
	T2 N1 M0	
	T3 N1 M0	
Stage IVA	T4a NO M0	
	T4a N1 M0	
	T1 N2 M0	
	T2 N2 M0	
	T3 N2 M0	
	T4a N2 M0	
Stage IVB	Any T N3 M0	
	T4b Any N M0	
Stage IVC	Any T Any N M1	

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Table 7-3 Staging of oropharyngeal cancer.

	Staging of HPV-Mediated (p16+) Oropharyngeal Carcinoma	Staging of Oropharyngeal (p16-) Cancer
Primary Tumor (T)		
TX		Primary tumor cannot be assessed
T0	No primary identified	
Tis		Carcinoma in situ
T1	Tumor 2 cm or smaller in greatest dimension	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible or beyond*	Moderate advanced or very advanced local disease

T4a			Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*	
T4b			Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery	
*Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue does not constitute invasion of the larynx				
Regional Lymph Nodes (N)				
	Clinical N (cN)	**Pathological N (pN)**	**Clinical N (cN)**	**Pathological N (pN)**
NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm	Metastasis in four or fewer lymph nodes	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm	Metastasis in more than four lymph nodes	Metastasis in a single ipsilateral lymph node larger than 3 cm but not more than 6 cm in greatest dimension and ENE(-); or Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE(-); or Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE(-)	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or Larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)
N2a			Metastasis in a single ipsilateral lymph node larger than 3 cm but not more than 6 cm in greatest dimension and ENE(-)	Metastasis in a single ipsilateral lymph node 3 cm or smaller in greatest dimension and ENE(+); or A single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
N2b			Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
N2c			Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3	Lymph node(s) larger than 6 cm		Metastasis in a lymph node more than 6 cm in greatest dimension and ENE(-); or Metastasis in any node(s) and clinically overt ENE(+)	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE(-); or Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); or A single contralateral node of any size and ENE(+)
N3a			Metastasis in a lymph node more than 6 cm in greatest dimension and ENE(-)	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE(-)

(*Continued*)

Table 7-3 (Continued)

N3b		Metastasis in any node(s) and clinically overt ENE(+)	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); or A single contralateral node of any size and ENE(+)
Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+).			
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Prognostic Stage Groups			
	Clinical Stage Groups	**Pathological Stage Groups**	**Clinical and Pathological Stage Groups**
Stage 0			Tis N0 M0
Stage I	T0-2 N0-1 M0	T0-2 N0-1 M0	T1 N0 M0
Stage II	T0-2 N2 M0 T3 N0-2 M0	T0-2 N2 M0 T3-4 N0-1 M0	T2 N0 M0
Stage III	T0-4 N3 M0 T4 N0-3 M0	T3-4 N2 M0	T3 N0 M0
			T1 N1 M0
			T2 N1 M0
			T3 N1 M0
Stage IV	Any T Any N M1	Any T Any N M1	
Stage IVA			T4a N0 M0
			T4a N1 M0
			T1 N2 M0
			T2 N2 M0
			T3 N2 M0
			T4a N2 M0
Stage IVB			Any T N3 M0
			T4b Any N M0
Stage IVC			Any T Any N M1

Source: Reproduced with permission from AJCC: HPV-Mediated (p16+) Oropharyngeal Cancer and Oropharynx (p16-) and Hypopharynx. In Amin MB, Edge SB, Greene FL, et al. (Eds.). *AJCC Cancer Staging Manual*, 8th edn. New York: Springer; 2017: 113–136.

note that these techniques are adjunctive aids for screening and tools for early detection, and are not a replacement for surgical tissue sample collection and histopathologic diagnosis. The development of noninvasive screening techniques may have impact at the population level with regard to cancer control and detection. Providers implementing these aids in clinical practice should be aware of the utility and limitations of each test in their clinical setting.[81]

Vital Tissue Staining with Toluidine Blue

Vital staining with TB may be used as an adjunctive aid in the assessment of potentially malignant oral mucosal lesions. TB is a metachromatic dye that has an affinity to binding with DNA. TB staining has been correlated with LOH profiles in tissue biopsy. TB can be applied directly to suspicious lesions or used as an oral rinse. The assessment of dye uptake depends on clinical judgment and experience (Figure 7-10). Positive retention of TB, particularly in areas

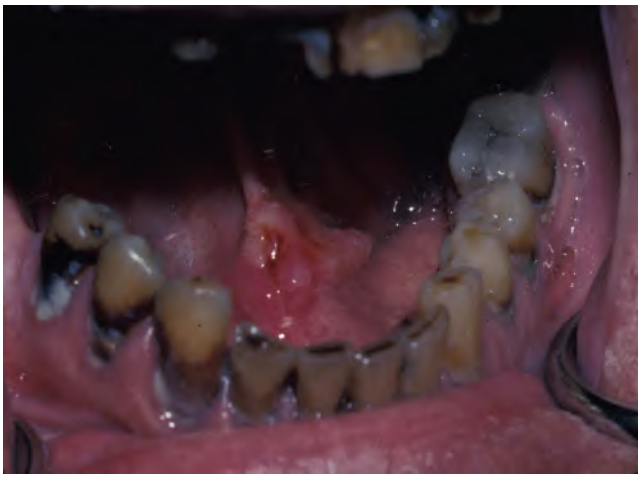


Figure 7-9 Asymptomatic erythroplakia in the floor of the mouth in a patient presenting due to toothache, diagnosed on biopsy as squamous cell carcinoma.

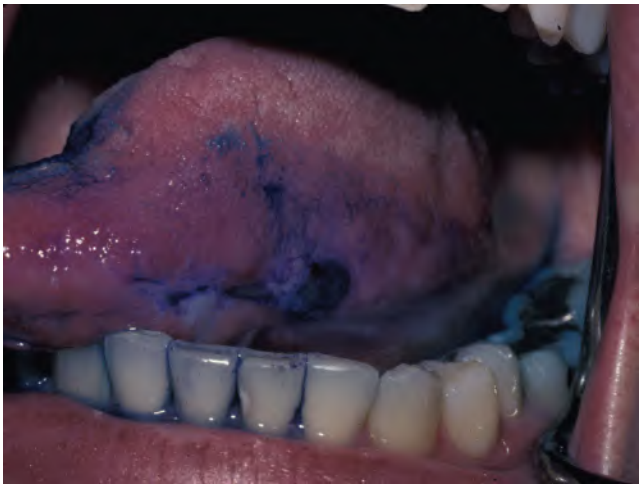


Figure 7-10 Irregular erythroleukoplakia, following application by toluidine blue. Inferior of lesion and superior stained site were biopsy-proven squamous cell carcinoma.

of leukoplakia, erythroplakia, and uptake in a peripheral pattern of an ulcer, may indicate the need for biopsy or assist in identifying the site of biopsy. False-positive dye retention may occur in inflammatory and ulcerative lesions, but false-negative retention is uncommon.

TB is currently cleared by the US Food and Drug Administration (FDA) as an adjunctive marking aid to a chemiluminescence light device, and not marketed as a stand-alone diagnostic tool. TB has been suggested by the Council on Scientific Affairs of the American Dental Association for use in high-risk patients and high-risk clinical settings by experienced providers, but no guidance was possible for use in the general practice setting due to the lack of clinical study in these settings.[82]

Visualization Adjunctive Tools

Chemiluminescent devices such as ViziLite® (Den-Mat Holdings, Lompoc, CA, USA) generate light based on chemical reaction. The suspected area of mucosa appears brightly lit. Other products like VELscope® (Apteryx Imaging, Akron, OH, USA) generate fluorescent light using an LED source, sometimes combined with optical filtration of the viewfinder to enhance natural tissue fluorescence. These products are promoted to assist the practitioner in discovering mucosal abnormalities, specifically OPMDs, and to evaluate the margins of a resection site. There is no consensus regarding the sensitivity and specificity of these devices and their ability to detect early disease.

There is an increasing interest in the use of confocal microscopy and optical coherent tomography systems to provide tissue diagnosis in real time, noninvasively, and in situ. Such a diagnostic approach is available in dermatology and is anticipated to be developed for oral mucosal application in the future. Other imaging modalities are being studied due to the need for improved detection and to assist in diagnosis and treatment.[83]

Cytopathology

Brush cytology, such as the OralCDx® system (OralScan Laboratories, Suffern, NY, USA), combines the cytobrush with a computer-assisted analysis of the cytologic sample, assessing the cell morphology and keratinization. The final diagnosis is made by an examining pathologist on the basis of standard histomorphologic criteria. Further developments in cytology include molecular evaluation of exfoliated cells for molecular markers of dysplasia or carcinoma to improve the diagnostic and prognostic value. Liquid-based cytology has renewed some interest in this noninvasive technique, as it may improve its sensitivity and specificity. This may be combined with biomarkers to improve accuracy, but validated and standardized methods of interpretation have not been established.[84]

Molecular Analysis

Improved technological advances allow for expeditious and cost-effective molecular analysis of HNSCC tumors and have led to the development and implementation of novel molecular targets for therapeutic suppression and/or enhancement.[85] Molecular markers from tissue specimens have elucidated HNSCC HPV-negative and HPV-positive cancers arising from different anatomic locations as well as genomic profiles, molecular characteristics, and therefore clinical prognosis.[86] The Cancer Genome Atlas Network (TCGA) and Hammerman et al. (2015) collated the molecular landscape of HPV-positive and HPV-negative HNSCC. HPV-positive tumors often demonstrate mutations in genes E6 and E7, TP53/RB1, TRAF3, FGFR2/3, CD8, DC56, ICOS, LAG3,

HLA-DR. Alterations in HPV-negative tumor genes commonly noted were TP53, CDKN2A/RB1, HRAS, CASP8, EGFR, ERBB2, FGF1, FAT1, AJUBA, NOTCH1, TP63, NFE2L2, and KEAP1.[87,88]

Imaging

Routine radiology, computed tomography (CT), nuclear scintiscanning, magnetic resonance imaging (MRI), and ultrasonography can provide evidence of bone involvement or can indicate the extent of some soft tissue lesions. The selection of the appropriate imaging modality is dependent on the type and location of the suspected tumor. Positron emission therapy (PET) using the radiolabeled glucose analogue 18-fluorodeoxyglucose (^{18}FDG) offers a functional imaging approach for the entire body (Figures 7-11 to 7-17).

Acquisition of a Tissue Specimen

In addition to standard surgical biopsy techniques, tissue can be acquired for histopathology by using fine-needle aspiration (FNA) or core needle biopsy (CNB). Open biopsy of enlarged lymph nodes is not recommended; in such cases, FNA biopsy should be considered. FNA/CNB also may aid in the evaluation of suspicious masses in other areas of the head and neck, including masses that involve the salivary glands, tongue, and palate, or when there is a contraindication to conventional biopsy (e.g., thrombocytopenia). Ultrasound may assist in guiding FNA/CNB.

Treatment

The principal objective of treatment is to cure the patient of cancer with the least possible morbidity of care and maintaining quality of life. The choice of treatment depends upon tumor-specific factors, the site and size of the primary lesion, the presence or absence of metastases, and generalized prognostic data. Current trends in treatment plan recommendations are grounded in fundamentals of patient-centered care, which take into account the patient's personal preference, current performance status, and ability and willingness to tolerate therapeutic modalities based on cultural, individual, and biopsychosocial-motivated beliefs and attitudes.

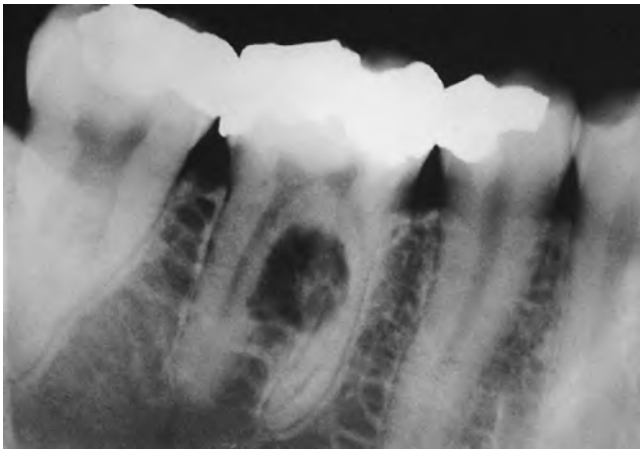


Figure 7-11 Periapical radiograph demonstrating bone destruction in the furcation of the first molar tooth and associated resorption of the root. A subsequent biopsy specimen demonstrated squamous cell carcinoma, which was diagnosed as a primary intra-alveolar lesion.

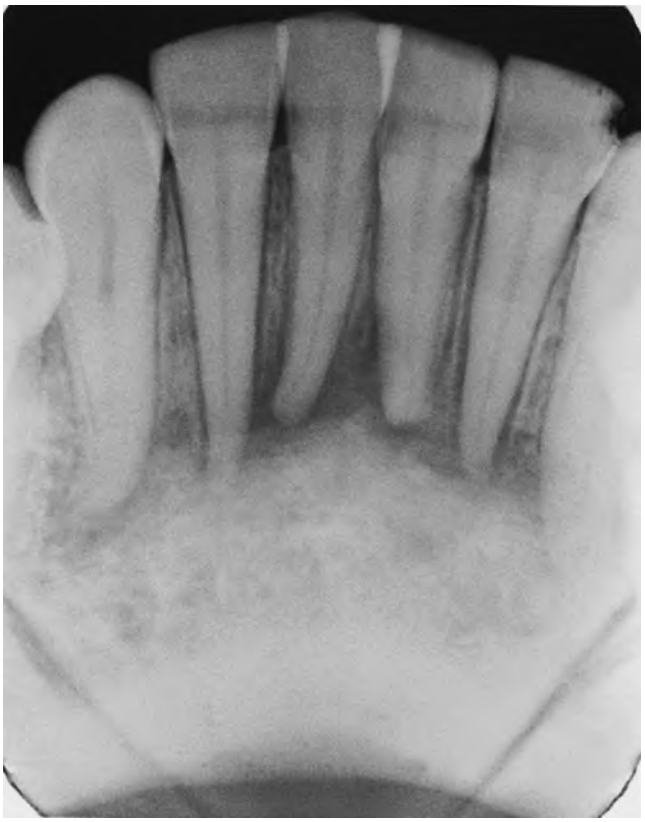


Figure 7-12 Periapical radiograph demonstrating an irregular radiolucency involving the bone of the apical region of the mandibular anterior teeth, without a change in root anatomy. The teeth tested vital. The radiographic finding was the first indication of involvement of the bony squamous cell carcinoma.

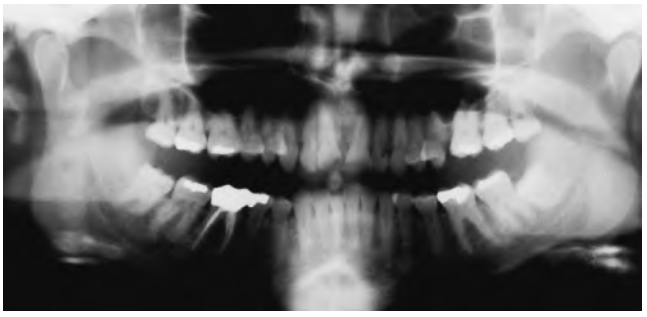


Figure 7-13 Panoramic radiograph taken at the time of diagnosis of squamous cell carcinoma.

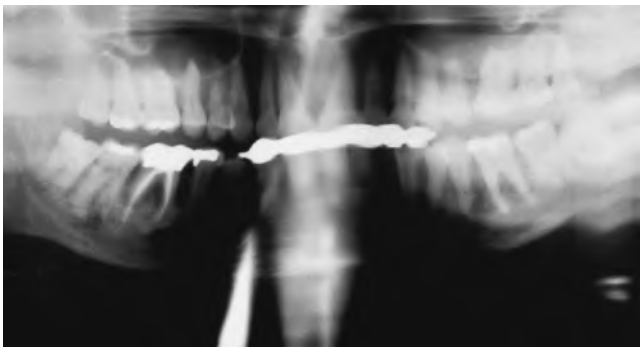


Figure 7-14 Massive bone destruction of the mandible, shown after five years of follow-up in a case of squamous cell carcinoma (see Figures 7-11 and 7-12) extending to the molar regions bilaterally. The anterior teeth had been lost due to progressive destruction of the anterior mandible and floor of the mouth.

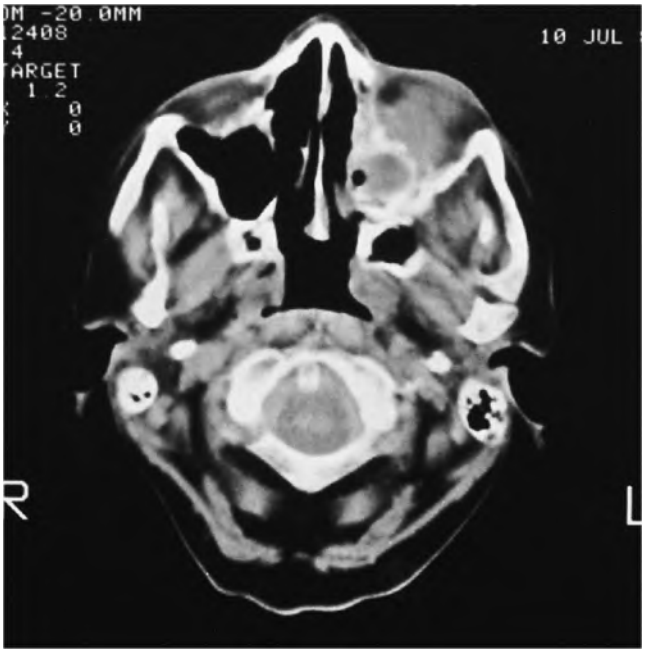


Figure 7-15 Computed tomographic scan demonstrating destruction of the medial wall of the antrum and opacification of the antrum. Additional views suggested that the opacification represented a tissue mass that was consistent with tumor.

First-line definitive therapy may include surgery, radiation therapy, with or without chemotherapy/targeted therapy, for curative intent for oral and oropharyngeal carcinoma. Immunotherapy as an adjunct to principal therapeutic modalities of surgery, radiation, and chemoradiotherapy is now included in treatment options. In general, the larger the primary tumor and the more advanced the disease, the more multimodality treatment is recommended for upfront, initial therapy. Often the combined treatment includes all three modalities: radiotherapy, surgery, and chemotherapy.

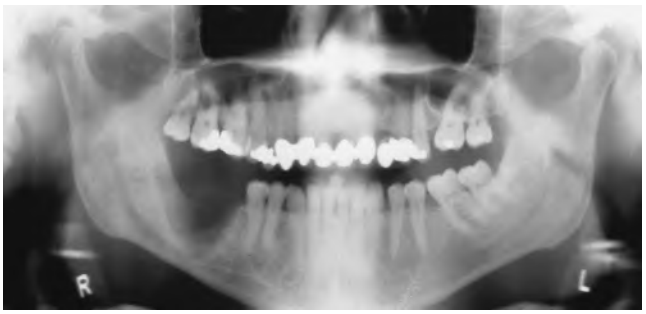


Figure 7-16 Panoramic radiograph showing bony destruction of the molar region of the right mandible due to invasion of contiguous tumor. Paresthesia of the right lip was present at the time of diagnosis.

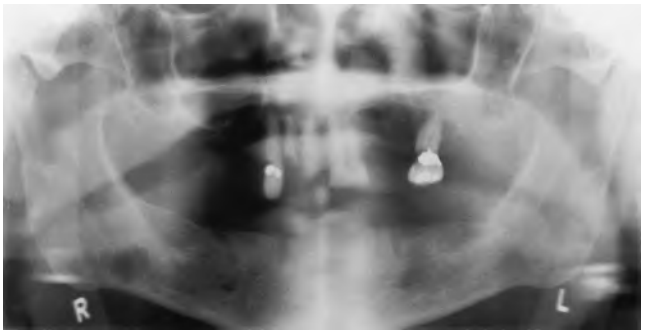


Figure 7-17 Panoramic radiograph demonstrating a destructive lesion of the right mandible overlying the mandibular canal. Anesthesia of the mandibular nerve and jaw pain were present. The bone biopsy specimen was consistent with metastatic colon carcinoma, which was subsequently diagnosed.

Continuing study of clinical outcomes, both survival and survivorship, will shed new light on the preferred combined treatment protocol.

Treatment recommendations are also impacted by the ability to preserve oropharyngeal function including speech, swallowing, and esthetics. Furthermore, the support available to the patient throughout therapy, a thorough assessment of the potential complications of each therapy, and the experience of the oncologic team may influence multidisciplinary treatment planning decisions. Initial therapy provides the best chance of curative therapy; if the patient experiences a recurrence or metastasis after first-line therapy, the options for treatment may be limited, and the likelihood of cure is reduced. However, in the era of immunotherapy, novel options for improving overall survival for recurrent and metastatic head and neck cancer are emerging.[89]

Targeted therapies for use in HNSCC have been limited to cetuximab in the definitive setting and have a low response rate in the metastatic setting. Limited development of available targeted therapies has driven investigations of tumors'

ability to evade innate immunosurveillance, and many researchers and institutions have shifted resources to immunotherapy pathways such as checkpoint inhibitors and immune effectors.

Multidisciplinary Care Model

National Comprehensive Cancer Network (NCCN) 2019 guidelines for treating patients with head and neck cancer note that all patients need access to multidisciplinary team members who have expertise in providing disease- and treatment-specific care. These team members and support services include head and neck surgery, radiation oncology, medical oncology, plastic and reconstructive surgery, specialized nursing care, dentistry/prosthodontics, physical medicine, speech and swallowing therapy, social work, clinical nutrition, pathology, diagnostic and interventional radiology, and additional adjunctive services. Cancers of the labial mucosa, oral cavity, oropharynx, hypopharynx, nasopharynx, glottic larynx, supraglottic larynx, ethmoid sinus, maxillary sinus, and salivary gland tumors all require dental evaluation as part of their initial work-up, which includes history and physical, biopsy, clinically indicated imaging and multidisciplinary consultation as indicated.[90]

Oral Complications

NCCN guidelines note that outcomes are improved when patients are treated at high-volume centers by providers with expertise in head and neck cancer management and prevention of complications. The oral medicine/dental provider with specific and comprehensive training and experience plays an integral role in the planning of post-treatment reconstruction along with the head and neck surgeon. In addition to prosthetic reconstruction, the oncologic dentist's role in the multidisciplinary treatment team includes diagnosing and treating existing dental conditions and providing patient-centered education and preventive care strategies. Complications from cancer treatment can be secondary to direct tissue damage, as well as to the surgical resection and reconstruction of the resulting defect, and can be in the form of both short- and long-term complications. Oral hard and soft tissues experience both transient and permanent changes from head and neck radiation, including mucositis, xerostomia/hyposalivation, dysgeusia and ageusia, trismus, delayed healing, osteoradionecrosis, and an increase in the risk of dental decay and periodontitis. The frequency of tissue necrosis is related to the treated volume, fraction size, and total dose of radiation therapy, the proximity of the radioactive implant to bone, and the presence of comorbid risk factors including dental status.[91]

SURGICAL ONCOLOGY

Though the principles and tenets of surgical oncology for head and neck cancers have not changed dramatically in the last two decades, advancements in technology, surgical approaches, and science have led to improved patient outcomes, particularly in respect to quality of life, surgical candidacy, and post-treatment function. As there is increasing histopathologic, genomic, and immunologic data to help characterize and predict the behavior of head and neck cancers, there has been a paradigm shift toward personalized medicine and tailoring cancer treatment and therapies to each individual patient and their particular cancer. Despite advances in radiation therapy, chemotherapy, targeted therapy, and immunotherapy, the backbone of treatment for resectable malignant tumors of the oral cavity remains upfront surgery with tailored adjuvant therapy.

Robotic Surgery

Perhaps the most important technological advances in ablative head and neck cancer surgery within the last decade has been the advent of robotic-assisted surgery for the treatment of oropharynx cancer. Historically, SCC of the oropharynx was treated via open approaches including lip split mandibulotomy, lateral pharyngotomy, transhyoid pharyngotomy, or transoral oropharyngectomy. There was a paradigm shift toward organ preservation for the treatment of oropharynx cancer in the mid-1990s after data from the Veterans Affairs Laryngeal Cancer Study Group trial emerged demonstrating efficacy of radiotherapy and chemoradiotherapy in patients with T1–T3 SCC of the larynx.[92] These data were quickly extrapolated and radiation or concurrent chemoradiotherapy was widely used for the treatment of SCC of the oropharynx. Unfortunately, full-dose radiation to the oropharynx (66–70 Gy) used in the definitive setting substantially increased the risk of long-term dysphagia, xerostomia, and osteoradionecrosis of the mandible.

In the early 2000s it was noted that long, stable demographic trends shifted and the incidence of oropharynx SCC increased.[93] It was not until 2010 when this particular subset of oropharyngeal SCC driven by HPV was described and contrasted to HPV-negative oropharyngeal SCC. These data from the Radiation Therapy Oncology Group (RTOG) 0129 study demonstrated a significant survival benefit in patients with HPV-positive oropharynx SCC (84.2% 3-year survival) compared to patients with HPV-negative oropharynx SCC (57.1% 3-year survival).[94] The majority of these cases present with small primary tumors in the lymphoid-bearing tissue of the base of the tongue or palatine tonsil and cervical metastasis to level II. Despite the high incidence of nodal metastasis, the prognosis and response to treatment are dramatically

better than the HPV-negative counterpart. In 2019, the incidence of HPV-associated head and neck cancer has surpassed the incidence of HPV-associated gynecologic/cervical cancers.

Since patients with HPV-positive oropharynx cancer are generally younger and respond more favorably to treatment, there has been an ongoing effort to de-escalate and de-intensify therapy for this subgroup of patients to reduce the late radiation-induced toxicity and morbidity. In 2008, the FDA approved the use of the da Vinci surgical robot (Intuitive, Sunnyvale, CA, USA) for the treatment of oropharynx SCC. This is well suited to HPV-positive oropharynx cancers of the base of the tongue or palatine tonsils, as traditional surgical access generally required open approaches including lip split and mandibulotomy.[95,96] The surgical robot is introduced through the oral cavity with the aid of a suspended retractor. Just like endoscopic techniques, robotic-assisted surgery allows for minimally invasive approaches and "wristedness." The da Vinci robot allows for 7 degrees of freedom and 90 degrees of articulation, which enable movements that are not possible with conventional endoscopic or traditional surgery. This allows for access to the oropharynx with the use of high-definition angled endoscopes for surgical removal of malignant tumors via a strictly transoral approach (Figures 7-18, 7-19, 7-20, 7-21, and 7-22). The major benefit to this approach is to de-intensify or eliminate radiotherapy and improve short- and long-term swallowing

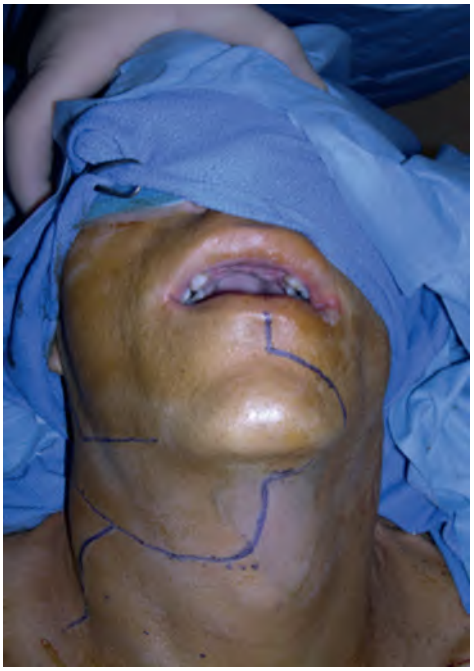


Figure 7-18 Traditional lip split mandibulotomy for right base of tongue cancer. This requires pharyngeal reconstruction with a vascularized flap.

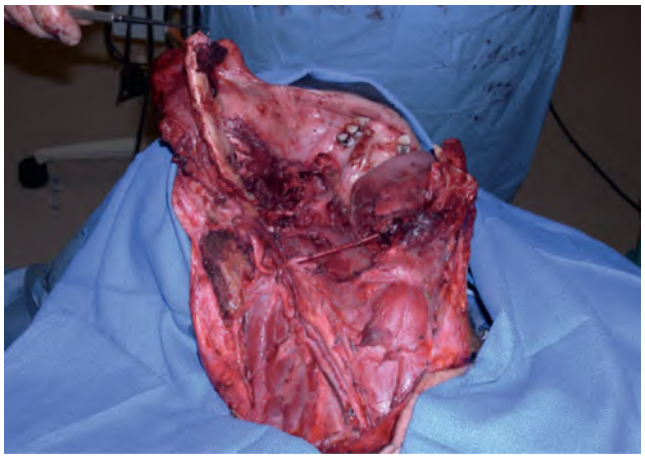


Figure 7-19 Neck dissection for right base of tongue cancer, as in Figure 7-18.

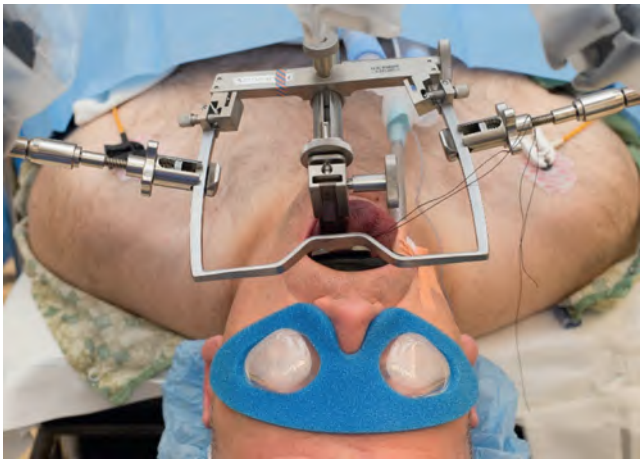


Figure 7-20 Initial set-up for FK-WO TORS retractor (Olympus Medical, Center Valley, PA, USA) in place with patient oroendotracheally intubated.

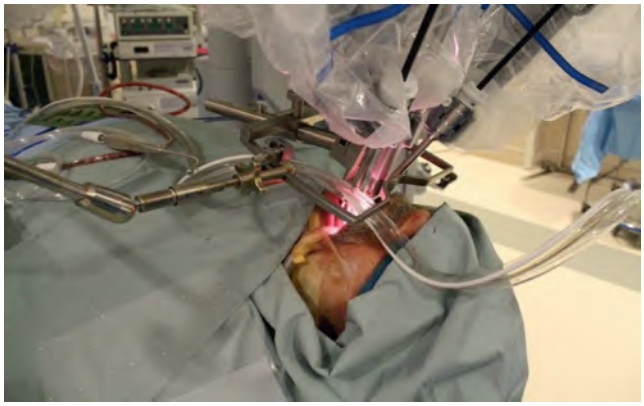


Figure 7-21 The da Vinci surgical robot (Intuitive, Sunnyvale, CA, USA) is docked and all three arms (endoscope, monopolar cautery, and Maryland forceps) are advanced into the oral cavity.

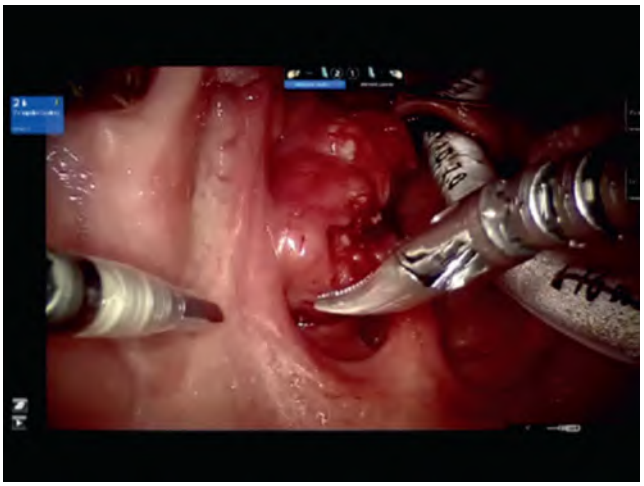


Figure 7-22 Robotic console view of left tonsil cancer immediately prior to resection.

outcomes. In addition, transoral robotic surgery (TORS) for the treatment of early-stage oropharynx SCC has shown superiority in functional outcomes, including less dysphagia and significantly lower rates of feeding tube dependence, when compared to concurrent definitive chemoradiation. TORS is considered first-line treatment for many patients with HPV-associated oropharynx cancer, and 5-year overall survival rates are greater than 91%.

Advances in Ablative Oral Cavity Surgery

Since its inception in head and neck surgical oncology, the use of computer-assisted surgery has not only revolutionized maxillofacial reconstruction, it has allowed for more precise surgical ablation with less invasive approaches. The earliest iteration of this was three-dimensional (3D) printing and stereolithography using CT scans and associated Digital Imaging and Communications in Medicine (DICOM) data to 3D print models of a patient's anatomy in 1998 (Medical Modeling, Golden, CO, USA). This can be used as a 3D reference when planning ablative surgeries for oral head and neck cancers. 3D models are particularly helpful in T4 oral cavity cancers of the maxilla or mandible that encroach on the skull base, infratemporal fossa, or masticator space, as these house essential neurovascular structures and are traditionally difficult to visualize. Surgical ablative plans can be digitally created in a virtual environment, usually via web meeting with a biomedical engineer who can effectively manipulate the DICOM data. The computer surgical plan can also be exported into intraoperative navigation software to allow for precise replication of the digital surgical design and osteotomies.[97] More commonly, the virtually and digitally planned resection is processed to design 3D-printed cutting jigs that are patient specific and allow for guided bony cuts and osteotomies for cancer resection. These have been shown to be highly accurate and reproducible.[98] The use of 3D-printed, virtually designed, patient-specific cutting jigs and implants allows for predictable osteotomies and osteosynthesis without wide access.[99] Maxillectomy and mandibulectomy can often be carried out via a transoral approach without the need for transcervical or transfacial skin access when computer-assisted surgery and design are utilized.

Microvascular Reconstruction

Undoubtedly, the most important advance in surgery in regard to the treatment of oral head and neck cancer has been the advent and refinement of microvascular reconstructive techniques. Microvascular free flap, or free tissue transfer, is best described as an autogenous transplant that is harvested from the patient's own body and may include bone, muscle, skin, fascia, or any combination of these paired with its perfusing artery and draining vein. This is transplanted to the head and neck and used to reconstruct acquired oncologic defects and re-vascularized by anastomosing its vessels to those in the head and neck. Prior to the 1990s, the majority of surgical reconstruction of oral cavity defects was limited to skin grafts, healing by secondary intention, and local-regional flap reconstruction. In most cases, these were not adequate reconstructions by modern standards, as they were only partially effective in restoring form and function. Prior to the advent of microvascular surgery, a patient undergoing composite resection for a floor-of-mouth SCC would almost certainly be severely deformed, tracheostomy and gastrostomy tube dependent, and functionally debilitated. Primary reconstruction of oncologic defects at the time of ablative surgery is routinely carried out with the use of microvascular free flaps. As these techniques have been refined, flap reconstruction success rates at high-volume centers are greater than 95%. Free tissue transfers are inherently robust and resistant to infection, necrosis, fistula, and devitalization due to the active blood supply and drainage. The importance of radiotherapy in the adjuvant setting for oral cavity cancers cannot be understated, and with the use of free tissue transfer patients are sufficiently healed to start radiotherapy within the six-week postoperative window, which seems to be maximally beneficial.

Although free flaps may be harvested from almost every part of the human body, several are used most commonly for reconstruction of oral cavity defects. The radial forearm free flap, a fasciocutaneous flap based on the radial artery and its venae comitantes, is the most frequently used soft tissue free flap for oral reconstruction. This is thin, pliable, and easy to harvest, with a long robust vascular pedicle for microvascular anastomosis. In most cases, it is the flap of choice for reconstruction of partial or hemiglossectomy defects due to its size match. The volar aspect of the forearm generally cannot be closed primarily, so a skin graft is required to reconstruct the donor site defect on the wrist. Alternatively, the flap can be taken as an ulnar forearm free flap based on the ulnar vessels (Figures 7-23, 7-24, 7-25, and 7-26).

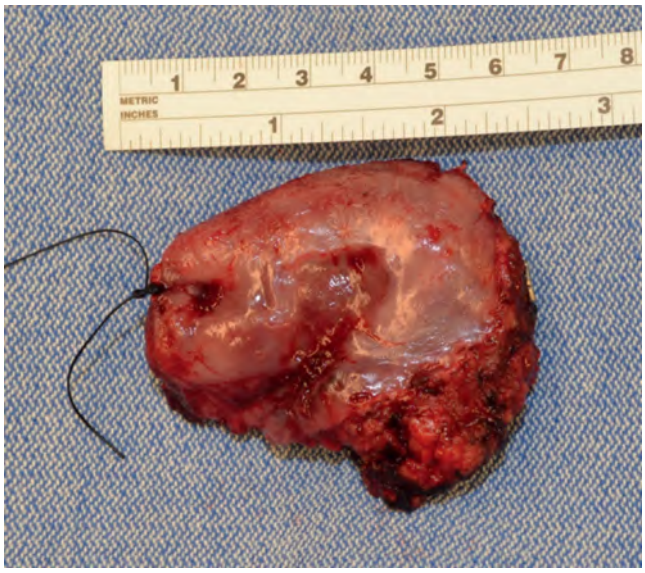


Figure 7-23 Hemiglossectomy specimen for tongue squamous cell carcinoma.

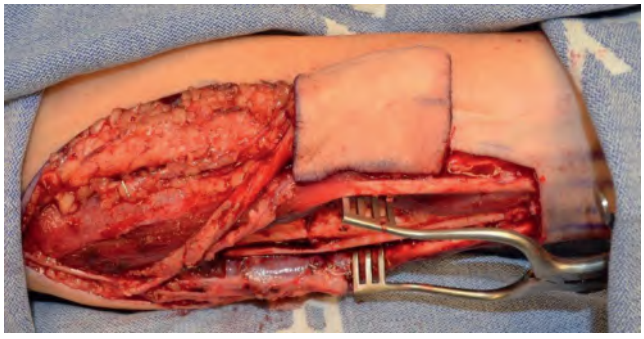


Figure 7-24 Ulnar forearm flap harvest.

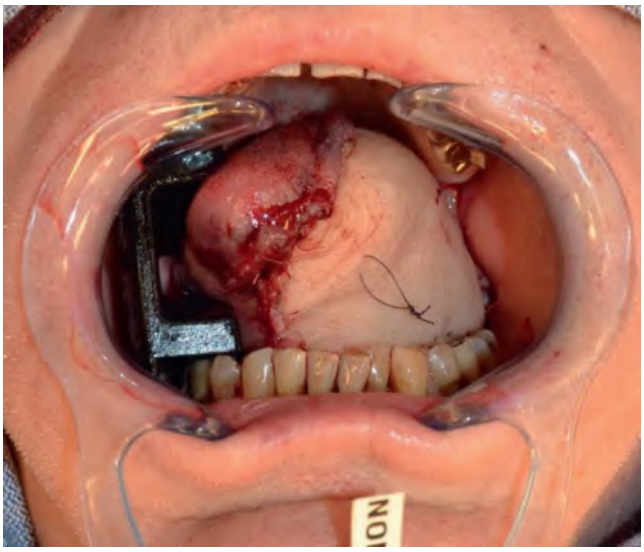


Figure 7-25 Flap inset after microvascular anastomosis.

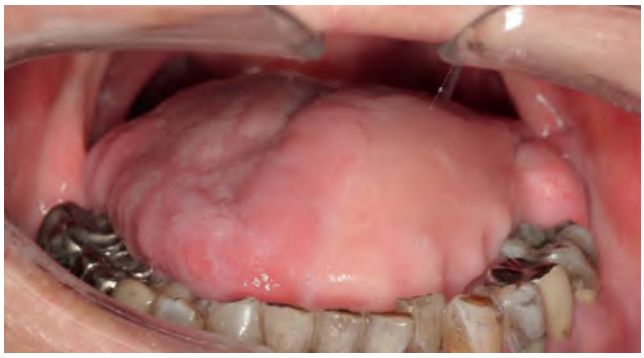


Figure 7-26 Six months after radiation with excellent speech and deglutition.

Alternatively, when a larger volume of tissue is required, such as for those undergoing total glossectomy, an anterolateral thigh free flap may be favored. This is based on the descending branch of the lateral femoral circumflex artery and its venae comitantes. A large volume of skin, subcutaneous tissue and fat, and vastus lateralis muscle may be harvested and vascularized on its pedicle. One major advantage of this flap over the radial forearm flap, other than the size, is the ability to close the donor site primarily without the use of a skin graft (Figures 7-27, 7-28, and 7-29).

The workhorse of oromandibular and palatomaxillary hard and soft tissue reconstruction since the 1990s has remained the microvascular fibula free flap. The long bony length, long vascular pedicle of the peroneal arteries and veins, plasticity, and sufficient bone stock for dental implantation have made this the first-line composite hard and soft tissue flap for reconstruction of the jaws at most centers.[99] The fibula flap was also the first to be used in computer-assisted design and reconstruction.[100] The fibula can be harvested with or without a vascularized skin paddle or muscle, depending on the reconstructive need. The skin that is harvested with the fibula in most patients is thin and pliable and readily movable along the long axis of the bone. Like the radial forearm flap, the lateral calf skin defect from osteocutaneous fibula flap harvest generally requires a split-thickness skin graft to close (Figures 7-30, 7-31, 7-32, 7-33, and 7-34).

The subscapular system free flap is the most versatile flap used for head and neck reconstruction. As the subscapular artery and vein traverse the axilla, they give rise to multiple branches that supply the lateral border of the scapula bone, the scapular tip, the latissimus dorsi muscle, the serratus anterior muscle, the skin of the back overlying the scapula, and segments of the ribs. Any combination of these tissues can be harvested, all connected to the subscapular artery and vein. Large volumes of skin and latissimus muscle are available for harvest to reconstruct massive oral, head, and neck defects. Though the scapula bone is not as robust or long as the fibula, it still provides excellent bone stock for maxillomandibular reconstruction, and in some cases suitable for

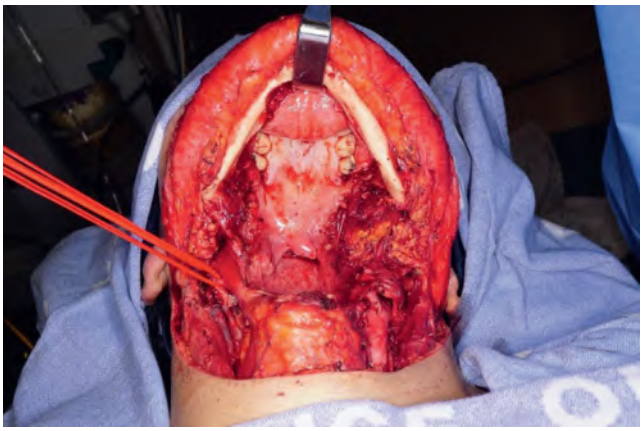


Figure 7-27 Total glossectomy defect viewed from the neck.

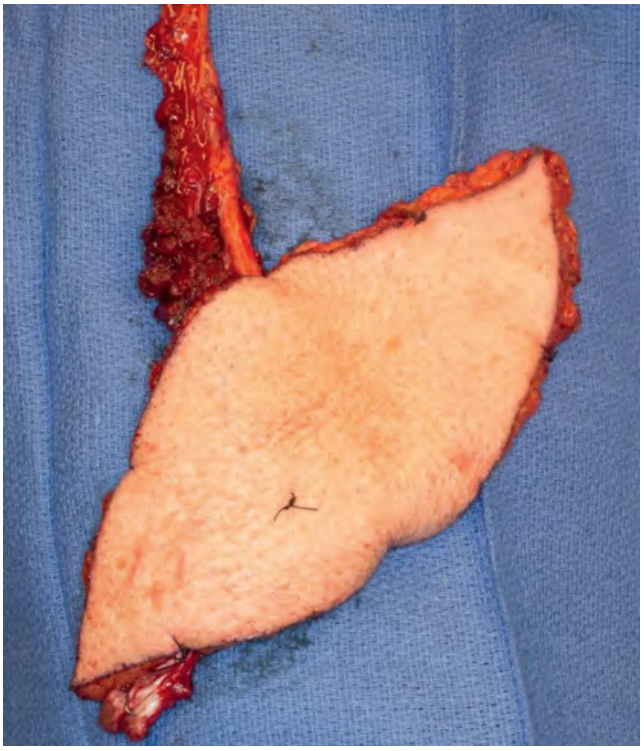


Figure 7-28 8 × 20 cm anterolateral thigh flap harvested.

future dental implantation. Unlike the fibula, the scapula donor site can be closed, primarily because the skin of the back has laxity and may be widely undermined when needed. Its major disadvantage is its location on the body, as scapula harvest requires a patient to be positioned on their side in a lateral decubitus position, which can be cumbersome and time consuming to set up in the operating room. In addition, it is incredibly difficult and awkward for both the ablative and reconstructive surgeons to work simultaneously. In most cases, the patient is repositioned mid-case after the ablative surgery is complete, increasing overall surgical time. Due to

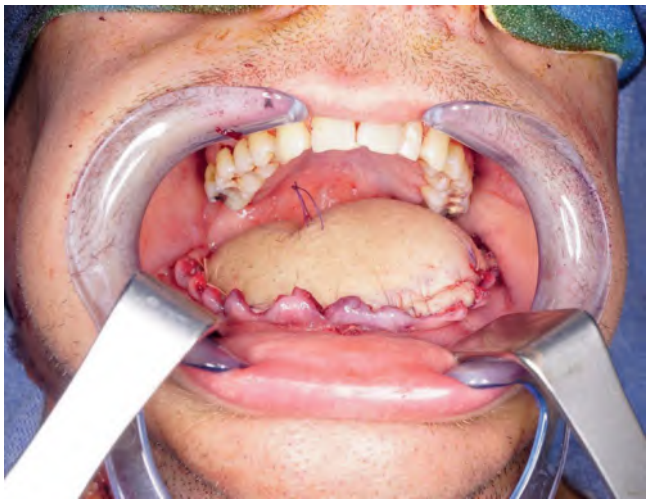


Figure 7-29 Reconstruction of tongue and floor of mouth with anterolateral thigh free flap.

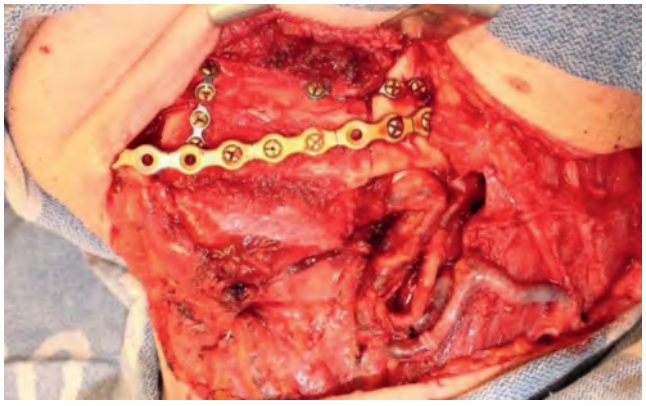


Figure 7-30 Fibula flap to reconstruct lateral mandibular defect with completed arterial and venous anastomosis to the neck.

these considerations, the subscapular system/scapula flap is used in cases where massive soft tissue volume is needed, or in patients with severe peripheral vascular disease of the lower extremities where fibula flap harvest is not possible (Figures 7-35, 7-36, and 7-37).

Management of the Neck

Imaging

OSCC has a high propensity for regional lymph node metastasis. Approximately 20–45% of patients with early-stage oral cancer who present without clinical or radiographic evidence of regional disease will, in fact, harbor occult cervical metastasis.[101] The presence of a pathologically positive metastatic cervical lymph node in patients with oral head and neck cancer is a significant negative prognostic factor with up to a 50% reduction in 5-year survival rates. Work-up

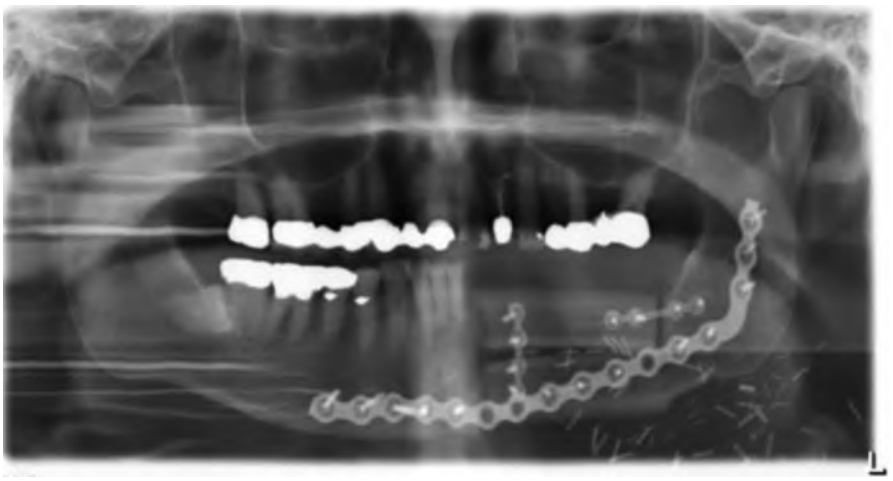


Figure 7-31 Postoperative orthopantomogram.

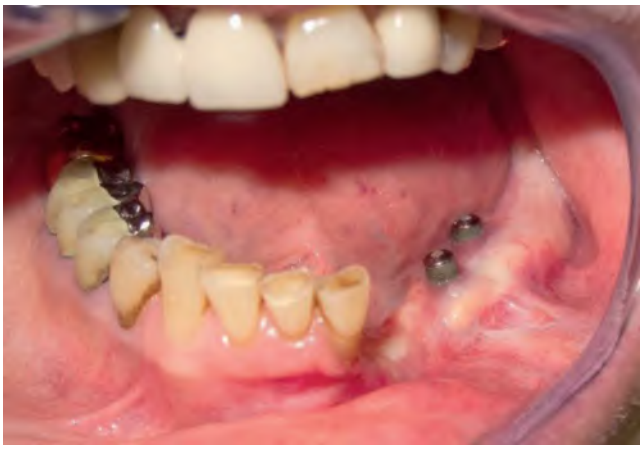


Figure 7-32 Delayed implant placement into the fibula prior to restoration.

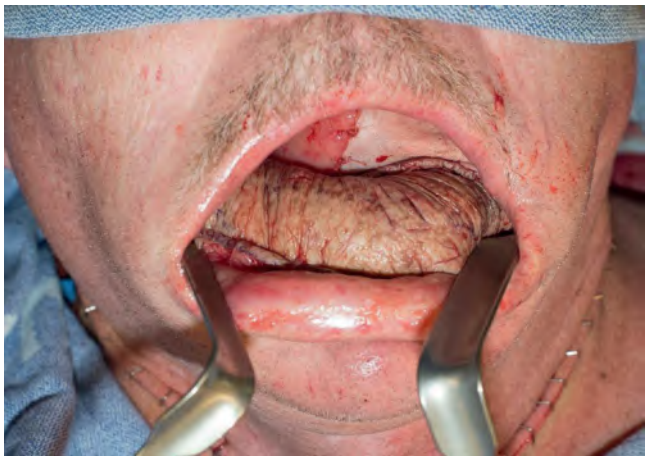


Figure 7-34 Immediate postoperative view of flap inset into oral cavity.

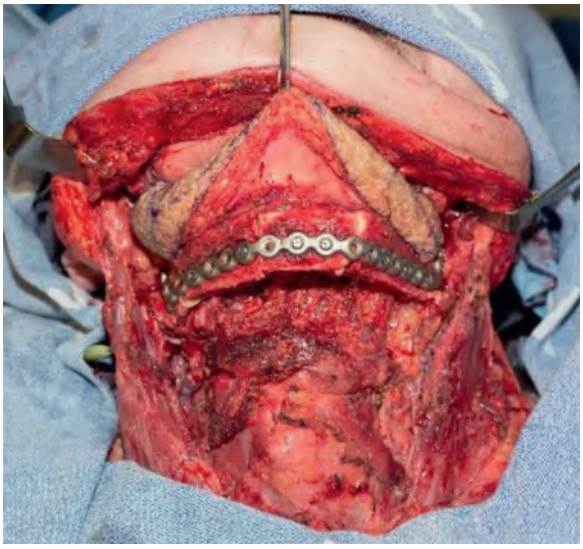


Figure 7-33 Total mandibulectomy defect for T4 floor-of-mouth squamous cell carcinoma with three-segment fibula reconstruction.

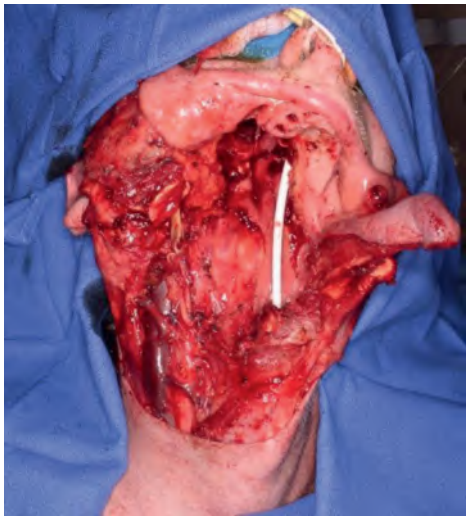


Figure 7-35 Floor-of-mouth squamous cell carcinoma necessitating mandibulectomy, pharyngectomy, and maxillectomy. Note the massive soft tissue and bone defect.

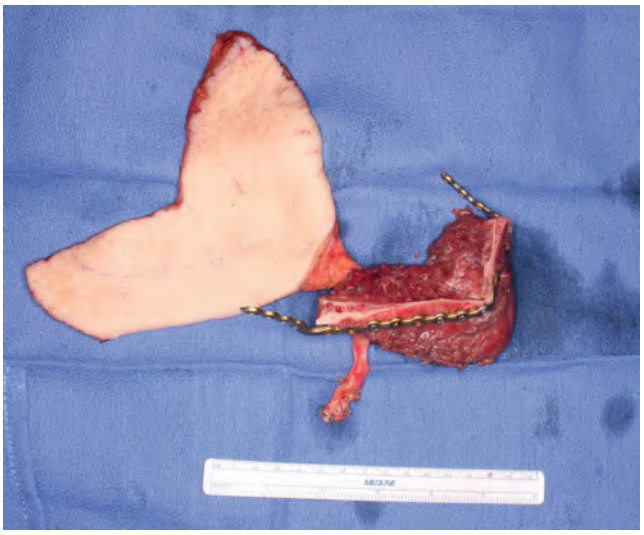


Figure 7-36 Scapula flap harvested and shaped for mandibular and soft tissue reconstruction. This includes the scapular lateral border, scapular skin, and infraspinatus muscle, all pedicled on the subscapular vessels.

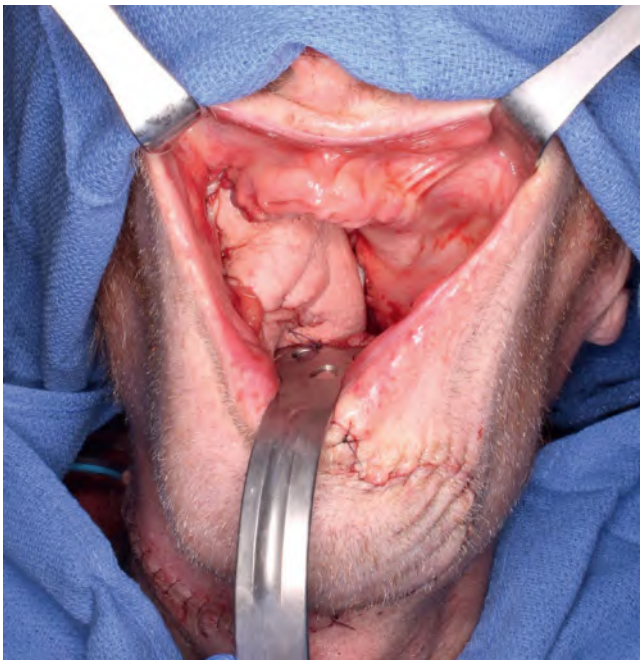


Figure 7-37 Flap inset providing excellent mandibular bony reconstruction as well as closure of the massive soft tissue oral/pharyngeal defect.

and staging of the cervical lymphatics in patients with biopsy-proven oral cavity SCC are necessary. Clinical neck examination is an important tool; however, it is limited by low sensitivity in ruling out cervical metastasis. Contrast-enhanced CT scan is the most widely used imaging modality in the United States, as it has high sensitivity, specificity, reproducibility, and transferability. MRI has similar specificity and sensitivity; however, it can be more difficult to read and harder to tolerate, as image acquisition times are significantly longer than for a CT scan. The most specific technique for interrogation of the cervical lymphatics preoperatively is ultrasound-guided FNA biopsy, but this requires technical proficiency from the ultrasonographer and interventional radiologist and may not always be reproducible.

Patients with clinically positive cervical metastasis (cN+) found on clinical exam, CT, MRI, PET, or ultrasound who are undergoing surgery for oral cavity carcinoma should receive a therapeutic neck dissection to remove the affected nodes and at-risk nodes for cervical metastasis in an en bloc fashion. This generally necessitates a modified radical neck dissection with removal of cervical basins I–V. Care should be taken particularly with oral cavity cancers to completely remove all level I lymph nodes and perifacial nodes around the marginal mandibular nerve and facial artery as it crosses the mandible. In contrast to the radical neck dissection described by George Crile in the early 1900s, the modified radical neck dissection initially described by Suarez and Bocca in 1967 preserves the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle in the majority of cases. The structures sometimes require sacrifice if there is gross tumor invasion from a lymph node with extranodal tumor extension. The oncologic outcomes are similar; however, there is a significant decrease in morbidity associated with the preservation of critical neurovascular and muscular structures.

The more difficult treatment dilemma is how to manage patients with oral cavity cancer and a clinically negative neck (cN0). Decisions regarding the treatment approaches for these patients have been debated extensively, which has produced numerous investigations. Fortunately, in the last five years evidence has emerged demonstrating a survival benefit when the cN0 is treated with elective selective neck dissection in patients with OSCC. Two prospective clinical trials demonstrated decreased risk of death or cancer recurrence in patients with T1 and T2 oral cavity cancer with cN0 necks undergoing elective neck dissection. A critical histopathologic factor in determining the risk of cervical recurrence in both studies was tumor DOI, thickness of tumor cells past the basement membrane. In 2015, D'Cruz et al. found, in post-hoc analysis, that the protective effect of elective neck dissection on recurrence and death was lost when tumor DOI from the primary site was 3 mm or less.[102] Similar analysis was undertaken in 2019 by Hutchinson et al. in a prospective multicenter study. The outcomes confirmed previous reports, but also demonstrated a positive survival benefit even in patients with tumor DOI of 3 mm or less (hazard ratio of 0.81).[103]

It is evident that elective neck dissection is beneficial from an oncologic and survival standpoint in the treatment of cN0 early-stage OSCC, particularly when the tumor DOI is 3 mm or greater. This should be carried out as a selective neck dissection, selecting the highest at-risk nodal basins for dissection, in an en bloc fashion. For oral cavity cancers, the highest risk of cervical metastasis is in levels I, II, and III. There is some evidence to support the phenomenon of "skip metastasis," or isolated metastatic lymph nodes in level IV, in tongue cancer. Lymphadenectomy of levels I, II, III (supra-omohyoid), and possibly level IV with preservation of the spinal accessory nerve, sternocleidomastoid, and internal jugular vein is standard practice for elective selective neck dissection.

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy is a minimally invasive technique to interrogate cervical lymphatics in patients with OSCC and offers the potential of reduced morbidity compared to selective neck dissection. Outcomes from investigations within the last decade have supported its use for early-stage OSCC, but consensus among surgeons has yet to be achieved. The concept of sentinel lymph node and lymphatic mapping was first used reliably and accurately to predict regional cancer spread by Morton et al. in 1992 in patients with stage I cutaneous melanoma. Since then, sentinel lymph node biopsy has been a critical part of the treatment of melanoma with clinically negative regional disease. Multiple single-center pathologic validation studies on sentinel lymph node biopsy suggest that it is efficacious for the identification of sentinel lymph nodes, may detect occult metastasis, and accurately predicts a status of lymphatic basins with negative predictive values ranging between 90 and 98%.[101,104] Results of the American College of Surgeons Oncology Group validation trial Z0360 demonstrated a negative predictive value of 96%.[105] Sentinel lymph node biopsy is an excellent alternative to observation of the clinically negative neck; however, it is unclear whether or not a negative sentinel lymph node biopsy results in the same survival benefit as elective neck dissection for early-stage OSCC.

Indications for sentinel lymph node biopsy of the oral cavity are biopsy-confirmed T1 or T2 oral SCC with clinically negative neck disease based on physical exam and advanced imaging. Estimation of tumor thickness and DOI is also critical in selecting these patients, since thicker tumors as previously described would benefit more from an elective neck dissection. A punch biopsy taking a tangential core of the primary tumor is sometimes helpful in identifying DOI on biopsy prior to surgery, in order to decide between a sentinel lymph node biopsy or elective neck dissection for the cN0 neck.

Patients undergoing this procedure will have the tumor injected with a nuclear radio tracer, usually technetium 99-m labeled sulfur colloid. This may be done by the surgeon or the nuclear medicine physician hours prior to surgery. Multiple planar images are taken in the nuclear medicine suite via a gamma camera to complete the lymphoscintigraphy as the tracer descends through the lymphatics. Single photon-emission CT (SPECT) can also be used, as this provides a 3D anatomic image combined with nuclear imaging to localize the draining lymph nodes. Radiotracer will accumulate in the first draining echelon of lymph nodes, or the sentinel node, and be evident on the SPECT scan or lymphoscintigram. This can then be targeted for removal during surgery with the use of an intraoperative gamma probe. Once the lymph node is confirmed to be the sentinel node intraoperatively, it is sent for histopathology and serial step sectioning to identify metastasis or micrometastasis. In patients with a positive sentinel lymph node, further treatment is usually necessary in the form of a neck dissection and/or postoperative radiotherapy.

Computer-Assisted Surgical Planning

Since 2009, oral and maxillofacial surgeons have been at the forefront of developing technology for computer-aided head and neck ablative surgery and reconstructive surgery.[100] Improvements in imaging technology, imaging software, and biomedical engineering have allowed for surgeons to virtually and digitally carry out procedures and transfer those plans to the operating room. Ongoing evolution of this technology allows for precise and accurate surgical ablation and reconstruction, aiding surgeons to achieve results that were previously difficult or impossible. Perhaps the greatest impact of this technology is the ability to preplan, visualize, and pre-navigate a complex operation prior to entering the operating room. Surgeons without years of clinical experience can achieve reconstructive success, since much of the trial and error may be done in the virtual environment during the web meeting.

Data is acquired using high-resolution medical-grade or cone-beam CT scans with 1 mm cuts or finer. These DICOM images are uploaded to a third-party digital planning company. The DICOM data are segmented and rebuilt in a 3D fashion by biomedical engineers. A web meeting between the surgeon and biomedical engineer with shared viewing screens demonstrates the patient anatomy based on the high-resolution CT data. 3D anatomy can be easily manipulated in the virtual environment and appropriate surgical planning is carried out, including osteotomies for resection, mapping the position of nerves and teeth, and reconstruction of defects using bone flaps such as a fibula, scapula, or iliac crest flap. Since all the data are patient specific, the final surgical plan can be exported as a stereolithography (STL) file used to design patient-specific cutting jigs to carry out

osteotomies, or patient-specific permanent titanium 3D-printed surgical plates and implants. These data may then be exported into surgical navigation software in order to facilitate and confirm adequate osseous positioning in the intraoperative setting.

Multiple validation studies have demonstrated the accuracy, precision, and effectiveness of computer-aided surgical planning.[106,107] It allows surgeons to achieve extremely complex reconstructive designs while decreasing operating room time. As with most technology, there is a learning curve required to effectively use these methods to achieve the desired outcomes. 3D-printed cutting guides and jigs that are patient specific must be adapted to the mandible or maxilla precisely. If one portion of the operation is misguided or poorly executed, there may be compounding error as the reconstructive portion is based on accurate surgical ablation. If the virtual design plan is aborted, modifications must be made intraoperatively (Figures 7-38, 7-39, 7-40, and 7-41).

Dental Reconstruction

As previously mentioned, one major benefit of computer-assisted surgery and computer-aided surgical simulation is the ability to create complex reconstructions as well as incorporate guided dental implant placement into osseous free flaps. Historically, the goal of head and neck reconstruction of cancer defects with microvascular free flaps was simple: to keep the flap perfused and the patient alive. As technology and science evolve, the goal of the surgeon and patient has become to return to as close to the precancer state as possible. The use of endosseous dental implants plays an integral role in the comprehensive treatment and reconstruction of head and neck cancer patients. With computer-assisted design and planning, as well as advances in microvascular reconstruction, immediate dental implant placement into bone flaps at the time of ablative and reconstructive surgery

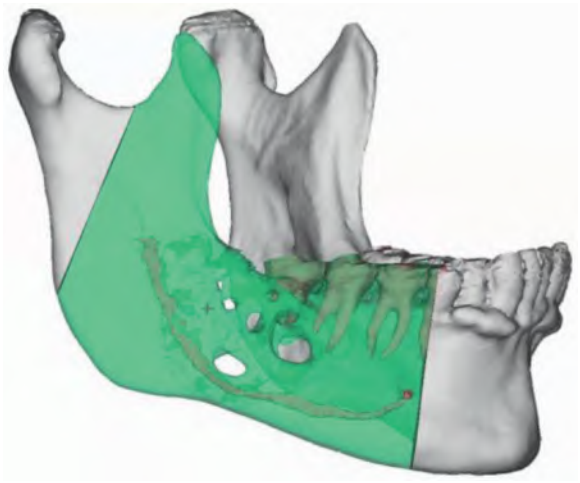


Figure 7-38 Squamous cell carcinoma of the right mandible with highlighted virtual mandibulectomy in green. The patient-specific fibula computed tomographic scan is being used to start the virtual reconstruction.

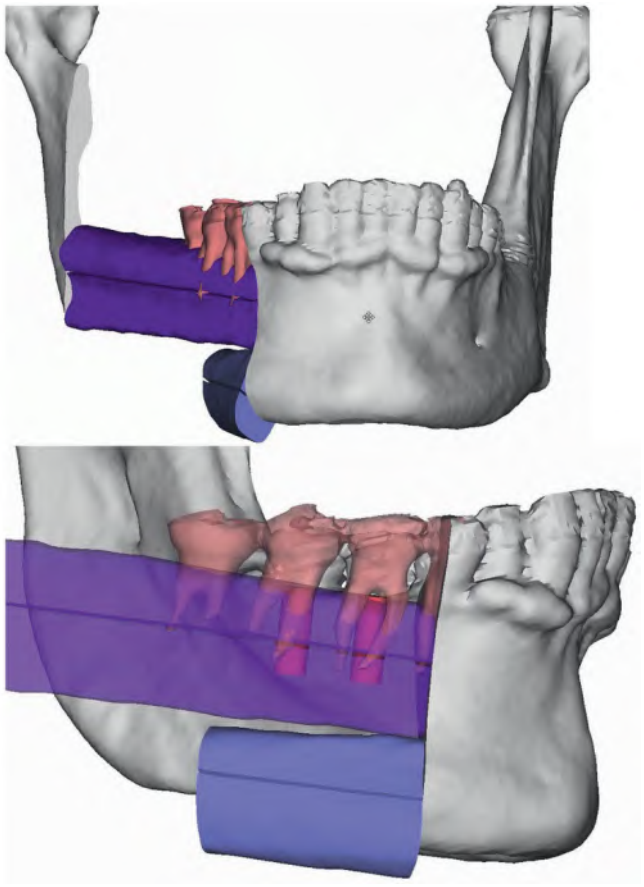


Figure 7-39 Two fibula segments are used to reconstruct the alveolus and basal mandible, with planned endosseous dental implants into the fibula.

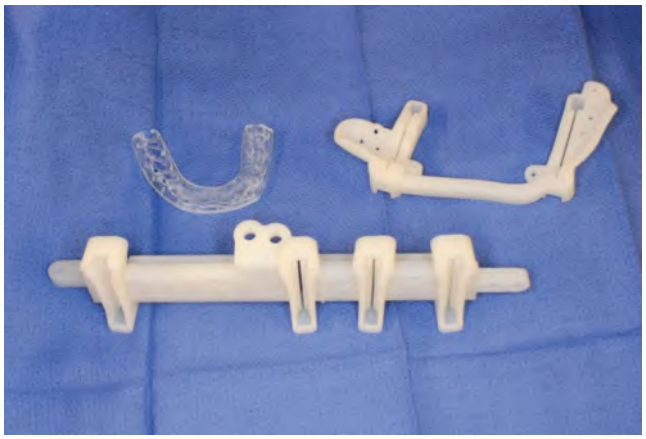


Figure 7-40 Once the plan is finalized, patient-specific 3D-printed occlusal splints, mandible cutting guides, and fibula cutting jigs are manufactured.

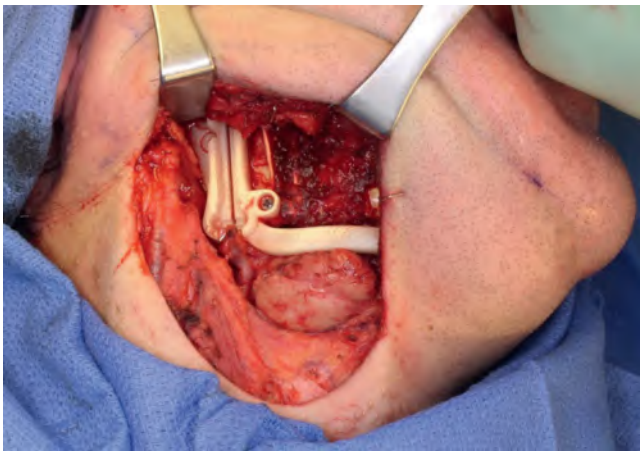


Figure 7-41 Mandibular cutting jig in place prior to osteotomy.

is possible. Traditionally, dental implants have been placed six months to a year after the patient has completed cancer therapy. More recently, placement of dental implants into the fibula flap at the time of mandibular or maxillary reconstruction has been shown to be as successful and safe (94% implant success, 98% restorability success).[108] The fibula is an extremely dense cortical bone with little to no marrow space and most analogous to type I mandibular bone with a predominantly periosteal blood supply. Unlike traditional dental implant placement into the jaws, implants in a fibula should be placed through both cortices and care should be taken to slightly overprepare and screw-tap the bone to prevent fracture or pressure necrosis.

A major advantage of simultaneous dental implant placement during ablative and reconstructive surgery is that it can be done while still pedicled to the leg, working outside of the confines and constraints of the oral cavity. With computer-aided surgical simulation, implants can be planned at precise positions and angulations for optimal restorability in the virtual environment. The fibula bone flap can be planned and adjusted to support those implants for a dentally and occlusally driven reconstruction. This plan is carried out in the operating room using the fibula cutting guide and cutting jig with implant guide sleeves prior to the segmentation of the fibula flap and transfer to the head neck region. Often, the implants are buried and then exposed 4–6 months later to ensure complete osseointegration for prosthetic fabrication.

A comprehensive surgical reconstruction for OSCC is not complete until both the tissue and dentition resected with cancer surgery are replaced. Without the definitive restorative approach, including dental prosthetics, patients may feel psychologically and socially debilitated. In most cases, it may take up to 18 months and multiple procedures for a patient to undergo complete dental restoration after mandibulectomy or maxillectomy. In 2012, surgeons first described the "jaw in a day" technique that addresses exactly this problem.[109] Planning in a fully digital workflow, the patient can undergo mandibulectomy or maxillectomy and reconstruction with a fibular free flap, along with immediately loaded dental implants and a hybrid prosthesis. This eliminates the multiple interim procedures and lag time to dental reconstruction. Currently, this technique is used primarily in patients that do not require a skin paddle transplant with their fibula, as the thickness of the skin may prevent complete seating of the prosthesis. In order to circumvent this, an osseous fibula flap is harvested and used to reconstruct the jaw. The native soft tissue and gingiva are closed over the fibula flap and around the immediately loaded dental implants. This technique offers patients a single-stage solution to reconstruct bone, soft tissue, and teeth during a mandibulectomy or maxillectomy, and hopefully represents a preview into the advances and direction of future oncologic surgical approaches (Figures 7-42, 7-43, 7-44, 7-45, 7-46, 7-47, and 7-48).

RADIATION ONCOLOGY

Radiation oncologists work closely with a multidisciplinary team of physicists, dosimetrists, radiation therapists, nurses, dietitians, dentists, and social workers. Radiation therapy may be administered with intent to cure, as a single modality, as part of combined radiation–surgery and/or chemotherapy management, or for palliation.[110] Radiotherapy with intent to cure causes early and late toxicities. In palliative care, radiation may provide symptomatic relief from pain, bleeding, ulceration, and oropharyngeal obstruction.

Radiation kills cells by interaction with water molecules in the cells, producing charged molecules that interact with

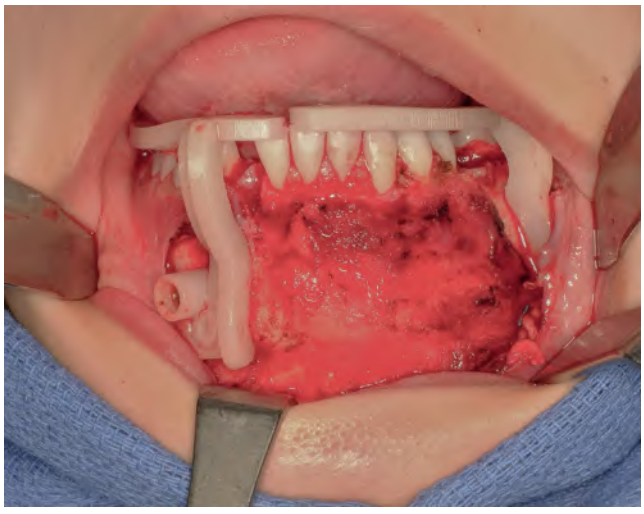


Figure 7-42 Transoral mandibulectomy with custom cutting jigs in place.

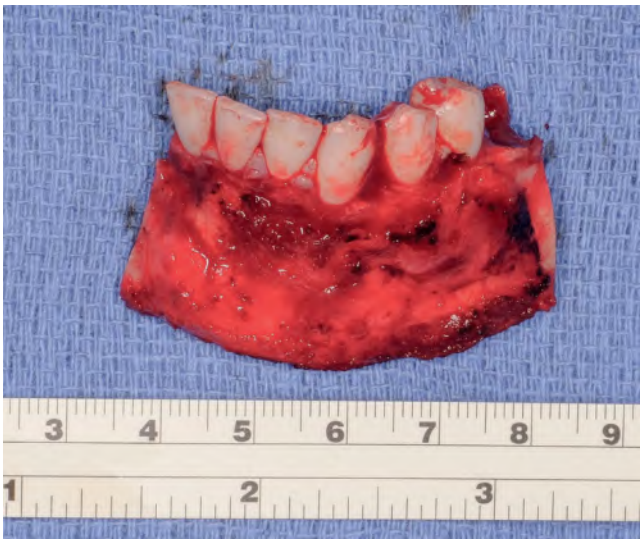


Figure 7-43 Mandibulectomy specimen.

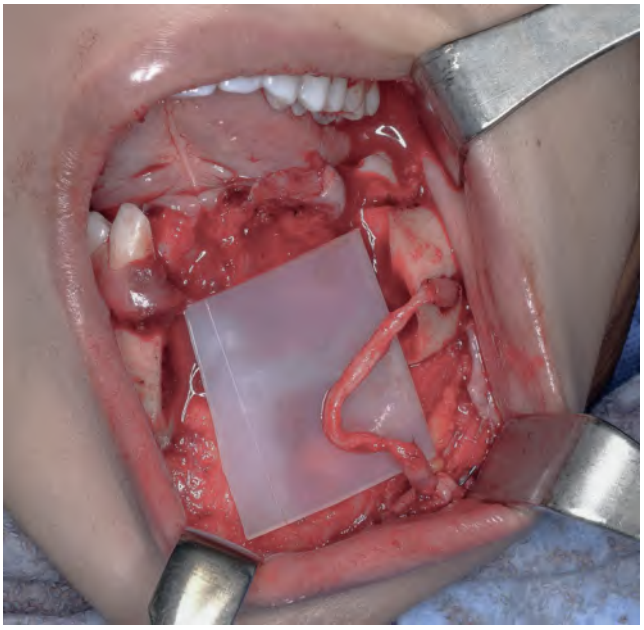


Figure 7-44 Reconstruction of mental nerve with nerve graft.

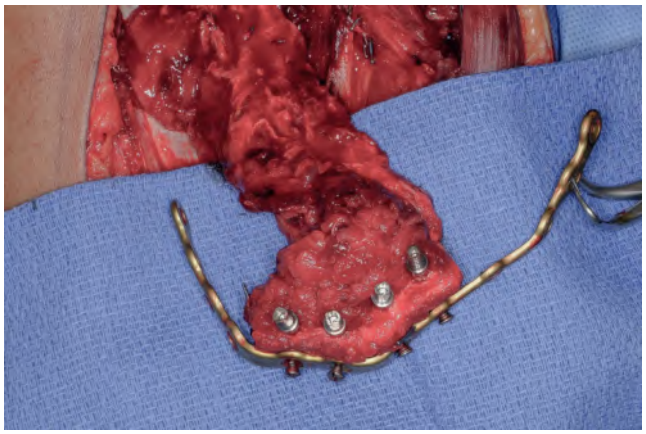


Figure 7-45 Fibula bone flap harvested and segmented while pedicled to leg.

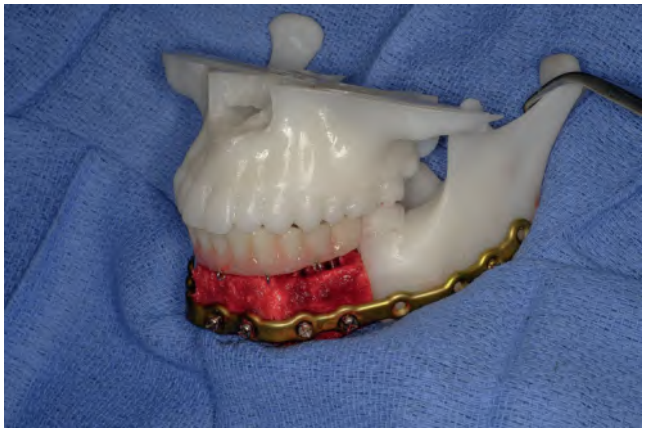


Figure 7-46 Implants loaded with fixed hybrid prosthesis and tried in to countermodel while still on leg.

biochemical processes in the cells and by causing direct damage to DNA. The affected cells may die or remain incapable of division. Due to a greater potential for cell repair in normal tissue than in malignant cells and a greater susceptibility to radiation due to the higher growth fraction of cancer cells, a differential effect is achieved. To achieve therapeutic effects, radiation therapy is delivered in daily fractions for a planned number of days. The relatively hypoxic central tumor cells are less susceptible to radiotherapy, but may become better oxygenated as peripheral cells are affected by radiation and thus become more susceptible to subsequent fractions of radiation. In general, the more differentiated the tumor, the less rapid will be the response to radiotherapy. Exophytic and well-oxygenated tumors are more radiosensitive, whereas large invasive tumors with small growth fractions are generally less responsive. Radiotherapy fractionation can be used to improve oncologic outcomes by intensifying treatment with altered fractionation or by combining systemic therapy, which may sensitize certain tumors to radiotherapy.

The biologic effect of radiation depends on the dose per fraction, the number of fractions over time, the total treatment time, the total dose of radiation, and the type of radiation used (e.g., electron, neutron, proton).[111] Methods for representing the factors of dose, fraction size, and time of radiation with a single calculation using the time–dose fraction (TDF) and the nominal standard dose (NSD) calculations have been described. When comparing studies of radiation effect and when describing the results of studies of cancer patients treated with radiotherapy, reporting the total

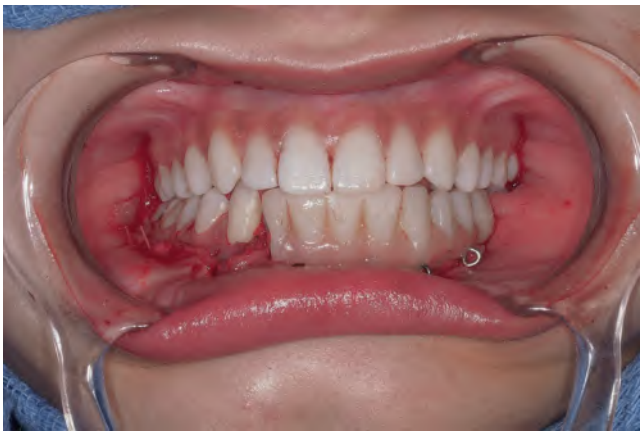


Figure 7-47 Immediate postoperative reconstruction.

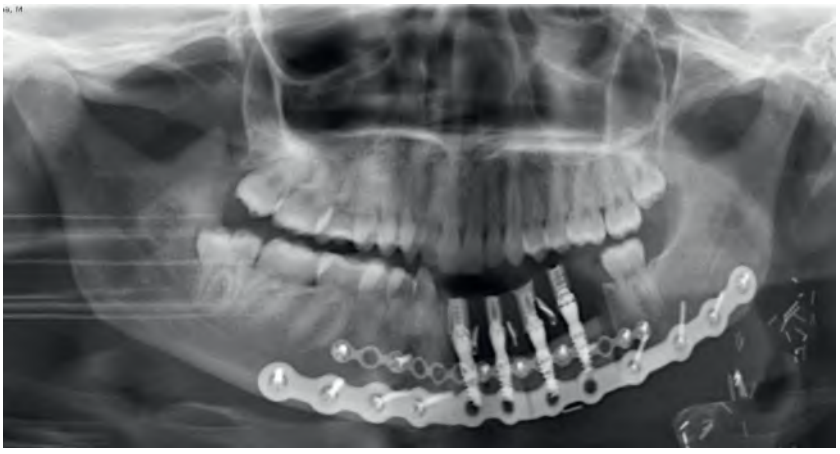
dose is inadequate because of the importance of fraction size and the time of therapy (which are not available for comparison). The use of the TDF or the NSD will facilitate the understanding of the relative biologic effect (RBE). The tolerance of the vascular, neurologic, and connective tissues to radiation influences both the success of tumor control and the development of treatment complications. The late complications of radiotherapy are due to effects on vascular, connective, and slowly proliferating parenchymal tissues. Late effects are related to the number of fractions, fraction size, total dose, tissue type, and volume of tissue irradiated and whether combined with chemotherapy. An increase in fraction size or a reduction in the number of fractions with the same total dose results in increased late complications, including tissue fibrosis and soft tissue and bone necrosis. As specificity of treatment planning improves, doses can be minimized. High-risk primary treatment sites may receive a dose of 72 Gy, while postoperative radiotherapy doses may be de-escalated to 66 Gy for high-risk sites and as low as 50 Gy for low-risk sites such as negative margins and cervical lymph nodes without extranodal extension.[110]

Radiation can be used preoperatively, postoperatively, or with a planned split-course approach, although there is controversy on the best approach. The advantages of preoperative radiation are the destruction of peripheral tumor cells, the potential control of subclinical disease, and the possibility of converting inoperable lesions into operable lesions. The disadvantages include delayed surgery and delayed postsurgical healing. The addition of chemotherapy following a combination of radiotherapy and surgery is used to treat cells that remain at the margin of resection and to reduce the potential for regional and systemic spread. Local control of the primary disease appears to be similar with preoperative or postoperative radiotherapy, but in some series the incidence of metastases was lower in the postoperative group.

Intensity-modulated radiotherapy (IMRT) uses radiation beams of varying intensity, which provides the ability to conform the prescription dose to the shape of the target tissues in three dimensions, reducing the dose to surrounding normal tissues. During the optimization process, each beam is divided into small "beamlets" whose intensity can be varied so that the optimal dose and distribution are obtained. The resultant intensity profile of each beam is complex. Rapid dose gradients outside the target result in sparing of normal tissues. IMRT and other advanced beam therapies are ideally suited for head and neck malignancies given the proximity of these tumors to critical structures, including the brainstem, optic chiasm, and salivary glands. IMRT has been shown to have comparable disease control to standard radiotherapy in head and neck oncology, with reduced acute and late toxicity. IMRT versus conventional radiotherapy has been demonstrated to improve quality of life and long-term severity of complications such as xerostomia in numerous studies and systematic reviews.[112,113]

Technical advances such as IMRT, newer faster forms of image-guided IMRT (IGRT), adaptive radiotherapy, and proton beam therapy reduce the size of the high-dose field of irradiation and limit the exposure of adjacent vital structures, including the salivary glands, but increase the

Figure 7-48 Postoperative panorex.



volume of tissue irradiated at low dose. Adaptive radiotherapy accounts for patient- and treatment-related morphologic changes such as severe weight loss or swelling to reduce an excessive dose to vital tissues. IMRT with meticulous treatment planning is recommended to reduce long-term treatment complications, in particular xerostomia, by reducing mean doses to less than 26 Gy to the parotid glands. Despite the improved outcomes for parotid function, most patients continue to experience xerostomia and salivary hypofunction post radiotherapy to some degree. This is likely a result of the difficulty in dose reduction in the region of the submandibular and sublingual glands.[114]

Radiation Sources

For treatment of superficial tumors, radiation with low penetration may be used. Low-kilovolt radiation (50–300 kV) can be used in the treatment of skin and lip lesions. Electron beam therapy provides superficial radiation and has largely replaced low-kilovolt x-ray machines because electrons produce a rapid dose build-up and fall-off of dose; thus, the depth of penetration can be relatively controlled. Electrons are useful in providing radiation to skin lesions, parotid tumors, and cervical nodes. Deep-seated tumors may be treated with heavy-particle irradiation, such as neutron beam radiation, which is considered for salivary gland tumors and central nervous system malignancies.

Proton Therapy

Protons are charged particles that can deliver a more concentrated and precise radiation dose to targeted tumor volumes, while minimizing exit doses to adjacent healthy tissue due to the heavy mass of protons. The homogeneous beam is more susceptible to artifact interference such as surgical hardware or metallic dental restorations. Intensity-modulated proton therapy (IMPT) with multifield optimization is often necessary in head and neck cancer treatment due to the inherent anatomic complexity of the region, which may lead to increased uncertainty of proton beam range.[115] Proton beam therapy is available at some centers, but a substantial upfront cost presents a barrier to widespread use and implementation. IMPT in head and neck cancer continues to be evaluated.[116] It is theorized that IMPT reduces damage to adjacent tissues and improves long-term sequelae such as xerostomia; however, early studies report mixed outcomes.[117]

Cancer Treatment Planning

Simulation is the first step in treatment planning, including immobilization via a thermoplastic face mask and CT, MRI, or PET scan to fabricate a radiotherapy treatment plan. Diagnostic-quality CT and MRI are used for computer-based treatment algorithms to target tumor volume and minimize critical normal adjacent structures. The radiation treatment plan is determined by the tumor site and size, relation to vital structures, volume to be radiated, radiation technology available, number of treatment fractions, total number of days of treatment, and tolerance of the patient. The dose to the eye, optic chiasm or spinal cord, salivary glands, alveolar bone, and soft tissue can be limited through the selection of the radiation source, field set-up, and shielding, and by moving the uninvolved tissue out of the field.

The current approach to treatment with the greatest potential to spare high-dose irradiation to vital tissue adjacent to the tumor includes IMRT, IGRT, or IMPT. For repeated doses of radiation to be applied to the site of treatment, the patient and the area of treatment are immobilized, using various techniques and materials, including head holders, bandages, laser positioning using head and neck "landmarks" or tattoos, and custom acrylic shells. Custom shells provide the best means of immobilization and positioning of patients that are critical in IMRT, IGRT, and proton beam therapy. These techniques may be combined with an oral device to position the mandible, allowing the maxilla or mandible to be moved into or out of the radiation field. An oral device can also position the tongue in or out of the treatment field.

Treatment planning requires localization of the tumor, and tumor margins can be marked with radiopaque gold seeds or lead wire, or based on real-time CT such as is incorporated into IGRT. If a shell is used, markings can be placed on the shell or by a marking on the skin (Figures 7-49 and 7-50). The 3D contours of the radiation field as planned by computer modeling and alterations can be made as needed. IGRT provides accurate and ongoing tumor contours and margin delineation during radiotherapy.

Modern radiation therapy is now using smaller margins around the tumor with the use of elaborate treatment algorithms. More complex set-ups include boost fields and sequential-field set-ups to maximize therapeutic effects and reduce complications (Figure 7-51).

CHEMOTHERAPY

Chemotherapy has been integrated into treatment algorithms for multiple types of head and neck cancer, including previously untreated locally advanced and recurrent or metastatic oral cavity and oropharynx cancer. Advances in systemic therapy have been made with the recognition of two distinct etiologies for HNSCC: environmental carcinogenesis (tobacco/alcohol/areca nut) and HPV. Three contexts are defined with regard to the chemotherapeutic management of HNSCC:

- Adjuvant postoperative concurrent chemoradiotherapy (CCRT).

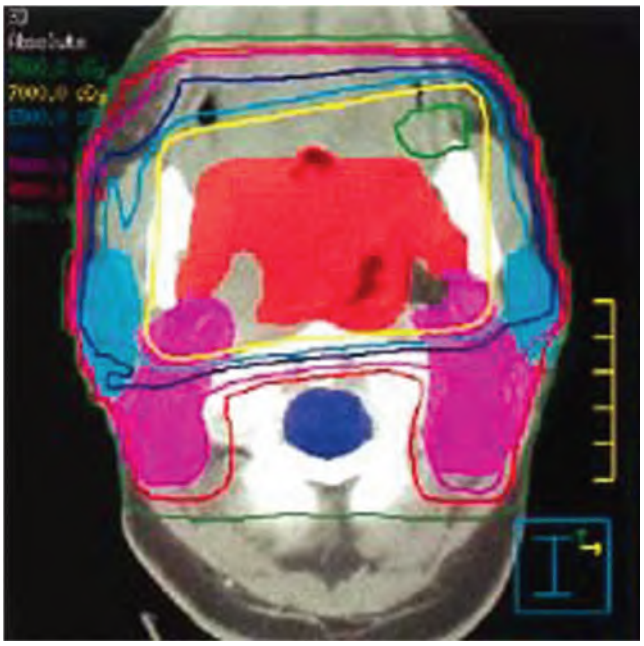


Figure 7-49 Conventional radiation is delivered in few fields and may result in high-dose exposure across the region of exposure. Exposure to vital structures such as midbrain, optic nerves, and salivary gland may be included in the high-dose volume.

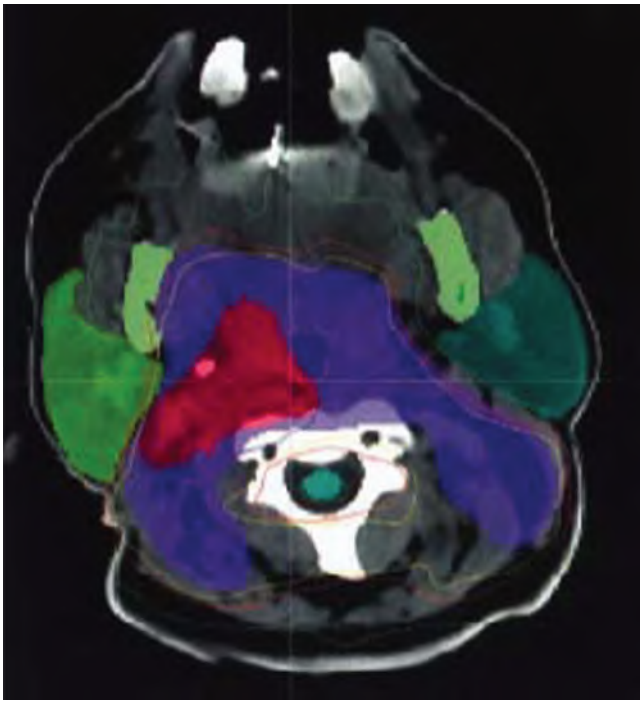


Figure 7-50 Intensity-modulated radiotherapy allows control of contours of radiation fields, tailoring of dose to enable high dose to tumor volumes, and shaping of fields to result in reduced dose to vital tissues such as brainstem, optic nerves, and salivary gland.

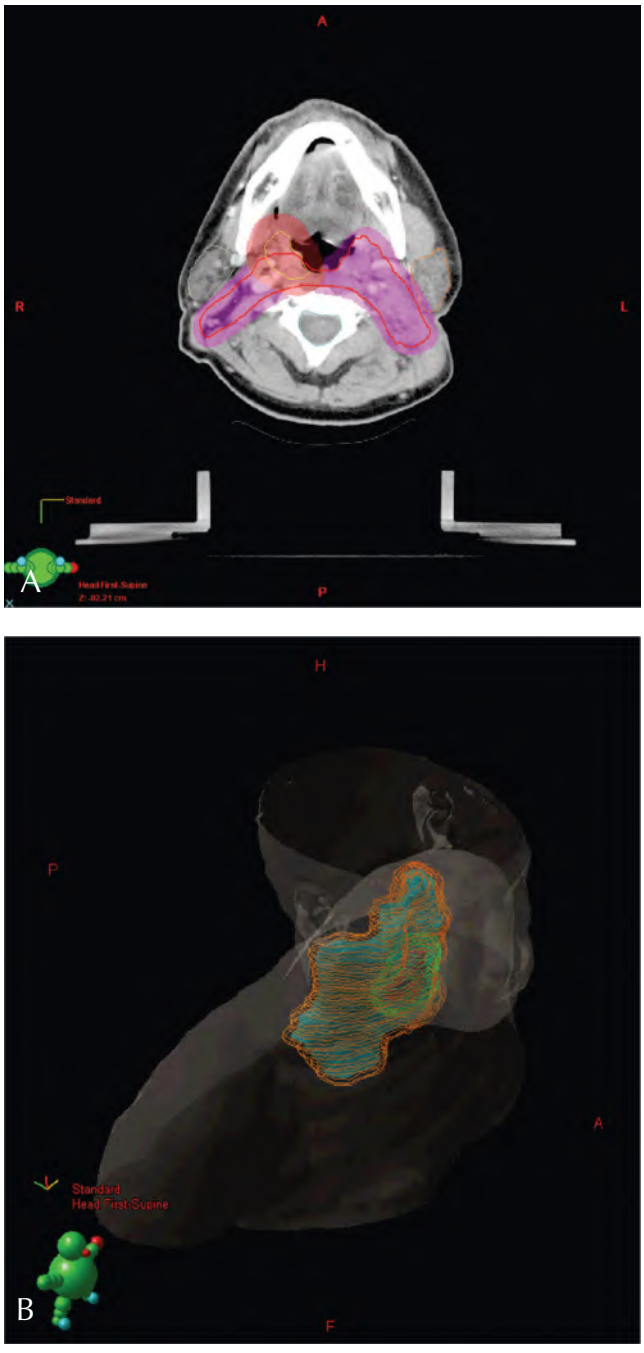


Figure 7-51 (A) Two-dimensional representation of intensity-modulated radiotherapy (IMRT) dosing to unilateral tumor, with minimal dose to salivary glands and spinal cord, and high-treatment dose to tumor and parapharyngeal lymph nodes. (B) Three-dimensional reconstruction of treatment fields using IMRT, where doses are contoured in three dimensions to maximize tumor dose and minimize dose to vital and uninvolved structures.

- Definitive CCRT, sometimes preceded by induction chemotherapy known as sequential therapy, for management of locally advanced or unresectable disease.
- Recurrent or metastatic disease.

The choice of treatment is determined by multiple factors, including the anatomic site of the primary tumor, disease stage at presentation (stage III and higher with positive surgical margins and ENE/extracapsular extension (ECE) being of importance), and the overall performance status of the patient, including their ability to tolerate various treatment modalities as well as their goals of therapy.

Systemic Therapy for Previously Untreated, Locally Advanced Head and Neck Squamous Cell Carcinoma

See Table 7-4.

Primary Definitive Concurrent Chemoradiotherapy

In patients with unresectable HNSCC, chemotherapy in addition to definitive radiotherapy has been shown to improve disease-free survival (DFS) and overall survival (OS). The Head and Neck Intergroup conducted a phase III randomized trial comparing radiotherapy alone, radiotherapy with concurrent bolus cisplatin every three weeks or a split course of single daily fractionated radiotherapy, and three cycles of concurrent fluorouracil and bolus cisplatin. The results established cisplatin–radiotherapy as the standard of care for this treatment group.[118] Cetuximab is a chimeric human/murine immunoglobulin (Ig) G1 and inhibitor of EGFR that is overexpressed in HNSCC, along with its ligand transforming growth factor-alpha (TGF-a). In combination with radiotherapy, cetuximab has been shown to be an alternative for patients unable to tolerate the toxicities of cisplatin.[119] Cetuximab is currently the only FDA-sanctioned targeted therapy for HNSCC.

Adjuvant Therapy

Treatment of advanced HNSCC with surgery and radiotherapy alone is often associated with a suboptimal outcome in terms of locoregional recurrence, distant metastasis, and DFS. Two trials, EORTC 22931 and RTOG 9501, have compared high-risk disease (ECE and positive surgical margins) treated with CCRT versus radiotherapy alone and have shown positive outcomes with regard to locoregional control (LRC) and DFS, highlighting the role of cisplatin in the treatment of advanced HNSCC.[120,121] Cisplatin is associated with exacerbation of the acute toxicities mucositis and

Table 7-4 Primary definitive chemotherapy

Squamous cell cancers of the lip, oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic larynx, ethmoid sinus, maxillary sinus, occult primary	
Primary systemic therapy + concurrent RT	
High-dose cisplatin (preferred) (category 1) Carboplatin/infusional 5-FU (category 1) 5-FU/hydroxyurea (category 2B) Carboplatin/paclitaxel (category 2B) Cetuximab (category 2B) Cisplatin/infusional 5-FU (category 2B) Cisplatin/paclitaxel (category 2B) Weekly cisplatin 40 mg/m^2 (category 2B)	The preferred chemoradiotherapy approach for fit patients with locally advanced disease remains concurrent cisplatin and radiotherapy
Postoperative chemoradiation	
Cisplatin (category 1 for high-risk (+ ENE and + margins) nonoropharyngeal cancers)	
Induction/sequential chemotherapy	
Docetaxel/cisplatin/5-FU (category 1 if induction is chosen) Paclitaxel/cisplatin/infusional 5-FU Following induction, agents used with concurrent chemoradiotherapy typically include weekly carboplatin, weekly cisplatin (category 2B), or weekly cetuximab	Cisplatin-based induction chemotherapy can be used, followed by radiation-based locoregional treatment (i.e., sequential chemoradiotherapy). However, an improvement in overall survival with the incorporation of induction chemotherapy compared to proceeding directly to state-of-the-art concurrent chemoradiotherapy (cisplatin preferred) has not been established in randomized studies After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy Radiotherapy alone vs. radiotherapy plus weekly carboplatin or cetuximab are among the options

Source: Adapted with permission from the National Comprehensive Care Network (NCCN) Guidelines Version 3.2019, 9/16/2019, Principles of Systemic Therapy. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

dermatitis as well as significant systemic toxicities, and therefore is not tolerated by all patients with HNSCC. Cetuximab is again an alternative treatment that has shown favorable DFS and OS in this treatment group.[119]

Deintensification

Current treatment paradigms were developed prior to the discovery of the role of HPV in the pathogenesis of OPC. Recognizing that HPV-associated OPC has a better prognosis, independent of treatment modality, than HPV-negative HNSCC has led to the development of de-intensification strategies for treatment with the goal of minimizing late toxicities of therapy. Fakhry and colleagues published a landmark study that documented the favorable prognosis of HPV-positive OPSCC, ECOG 2399, wherein HPV-positive patients had higher response rates and improved OS.[122]

Induction Therapy

Induction therapy (ICT) has a role in inducing rapid tumor shrinkage, eliminating distant metastases, and preservation of organs, but does not necessarily improve OS compared to CCRT. Sequential therapy (ST) combines ICT with CCRT and was examined in the DeCIDE and PARADIGM trials, which compared ST with docetaxel to CCRT. Neither showed a difference in OS.[123,124]

Systemic Therapy for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

See Table 7-5. The goals of therapy become palliative for patients who develop recurrent or metastatic disease that is not responsive to surgical salvage or reirradiation.

The EXTREME trial compared carboplatinum versus cisplatin and fluorouracil with or without cetuximab in patients with recurrent, metastatic HNSCC and demonstrated that adding cetuximab resulted in a benefit in OS and progression-free survival (PFS).[125] The addition of cetuximab to standard platinum-based chemotherapy has become the first-line standard of care for patients with recurrent, metastatic, platinum-sensitive HNSCC.

For patients with recurrent, metastatic HNSCC that are refractory to platinum-based regimens, the anti-PD1 monoclonal antibody nivolumab has been shown to significantly improve OS.[89] The safety and tolerability of pembrolizumab

Table 7-5 Chemotherapy for recurrent, unresectable, or metastatic, non-nasopharyngeal head and neck squamous cell carcinoma (with no surgery or radiotherapy option).

	Preferred Regimens	Other Recommended Regimens
First Line	Cisplatin/5-FU/cetuximab (category 1)*	*Combination therapy*
	Carboplatin/5-FU/cetuximab (category 1)*	Cisplatin/cetuximab
		Cisplatin or carboplatin/docetaxel or paclitaxel
	Immunotherapy	Cisplatin/5-FU
	Pembrolizumab/platinum (cisplatin or carboplatin)/5-FU*	Cisplatin or carboplatin/docetaxel/cetuximab
	Pembrolizumab (for PD-L1 positive tumors)	Cisplatin or carboplatin/paclitaxel/cetuximab
		Single agents
		Cisplatin
		Carboplatin
		Paclitaxel
		Docetaxel
		5-FU
		Methotrexate
		Cetuximab
		Capecitabine
Subsequent Line	*Immunotherapy*	*Combination therapy or single agents*
	Nivolumab if disease progression on or after platinum therapy (category 1)	See options listed for first-line therapy
	Pembrolizumab if disease progression on or after platinum therapy (category 1)	*Targeted therapy*
		Afatinib if disease progression on or after platinum therapy (category 2B)

*Data suggest an overall survival advantage for patients treated with pembrolizumab/platinum/5-FU when compared to cetuximab/platinum/5-FU for first-line treatment of recurrent metastatic squamous cell carcinoma.

Source: Adapted with permission from National Comprehensive Care Network (NCCN) Guidelines Version 3.2019, 9/16/2019, Principles of Systemic Therapy. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf

were demonstrated in the KEYNOTE-012 trial.[126] In 2016 the FDA approved nivolumab and pembrolizumab for second-line treatment of HNSCC.

Immunotherapy

Patients with HNSCC have a relatively poor prognosis despite major advancements in the standard of care therapies, surgery, and CCRT. Although the prognosis for HPV-positive HNSCC is better than for HPV-negative HNSCC, both have high relapse rates for locoregional and distant metastatic disease. Recurrent or metastatic HNSCC has limited treatment options and immunotherapy offers an intervention that may improve OS for these patients.

Checkpoint Inhibitors

Immune checkpoints are a system of receptor/ligand interactions between T cells and other cells in the body that distinguish self from non-self. A recognition of non-self triggers an immune response and tumor cells are able to express self-ligands to avoid such a response. Receptors in the immune checkpoint system include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1(PD-1), and programmed cell death receptor ligand 1 (PD-L1). Ipilimumab is anti-CTLA-4, is approved for metastatic melanoma, and is currently being tested for its efficacy in HNSCC. Nivolumab is anti-PD-1 and was investigated in the CheckMate 141 trial, showing improved survival compared with standard of care in recurrent/metastatic HNSCC patients with progression on platinum therapy.[127] Pembrolizumab showed encouraging results in the KEYNOTE-012 trial for recurrent or metastatic HNSCC.[126]

Immune System Agonists (Co-stimulatory Molecules)

Agonist antibodies to the co-stimulatory molecules OX-40 and 4-1BB can enhance T cell proliferation and function and thereby generate therapeutic antitumor responses. Anti-OX-40 and Anti-4-1BB are currently under investigation in the treatment of HNSCC.

Adoptive T Cell Therapy

Adoptive T cell therapy (ACT) is a process that starts with the harvesting of tumor-infiltrating T cells from autogenous tumor and expanding them with IL-2 to test for tumor specificity. They are then expanded for reinfusion in a lymphocyte-depleted patient. ACT has been used in the treatment of metastatic melanoma with promise and there have been successful reports of its use in HNSCC.[128]

Active Immunotherapy (Vaccines)

An optimal antitumor immune response is necessary to mediate the therapeutic effect of immunotherapies such as PD-1 inhibitors. Many types of vaccines are under investigation for their ability to promote an antitumor T cell response and thereby complement the effect of checkpoint inhibitors and immune system agonists. Examples are peptide and whole-protein vaccines, whole-cell vaccines, autophagosome-based vaccines, the HPV vaccine, and oncolytic virus vaccines.

PROGNOSIS

The most important factors influencing survival in patients with oral and oropharyngeal cancer are the presence of HPV and the stage of disease at diagnosis.[67] Unfortunately, the majority of oral cancers continue to be diagnosed at advanced stages, after becoming symptomatic. Cancers positive for HPV, particularly type 16, have a better prognosis compared to HPV-negative tumors.[94,122] This parameter is now critical to stratify the patient's risk; however, HPV testing must not be considered in isolation, as there are important interactions with other parameters, such as tobacco and alcohol exposure. Additional prognostic factors for oral cancer include DOI, perineural invasion, differentiation level, lymphocytic infiltrate at interface, status of surgical margins, and ENE of cervical metastases.[68]

There is rarely a second chance for a cure, as cure rates decline rapidly if the lesion is not successfully managed with initial therapy, and therefore the initial approach to therapy is critical. Locoregional causes of death from head and neck cancer may be due to erosion of major vessels, erosion of the cranial base, nutritional compromise, cachexia, and secondary infection of the respiratory tract. The fact that the OS in younger patients is better reflects that a more complex medical background and comorbidities in older patients expose them to additional systemic complications and poorer outcome.

PREVENTION

Primary prevention has focused on tobacco as a major cause of upper aerodigestive tract cancers, and attention has been paid to strategies of tobacco cessation. Diet has been studied, with evidence supporting a diet rich in fresh fruits and vegetables in developing countries, but with less support in the developed world. Vitamins or nutritional supplements have not been shown to be effective, including no definitive studies investigating antioxidant supplementation. Without vaccination, almost all adults who have been sexually active are exposed to HPV at some point in their lives, usually before age 26. Population-level intervention for preventing

associated oral/oropharyngeal cancer is aimed at elimination of HPV infection through vaccine.

Human Papillomavirus Vaccine

Human papillomavirus is known to have 19 different oncovirus strains. These are known to cause cervical, vaginal, vulvar, anal, penile, and head and neck cancers. Current vaccination is expected to prevent 90% of these cancers. The vaccine can be given to children (boys and girls) age 9 to adults age 45. Gardasil® 9 (Merck, West Point, PA, USA) can provide immunity to 9 of the 19 HPV strains known to cause cancer.

Vaccine recommendations have expanded to include both male and female adolescents. It has been estimated that effective sex-neutral sustained vaccination for HPV 16, 18, 6, and 11 of 80% of the population could result in elimination of these oncoviruses.[129] As there is no current treatment for HPV once a patient is infected, future therapies are aimed at enhancing the immune response to clear the virus once exposed. Pathways involve using therapeutic vaccines with live vector, protein, mRNA or DNA, or cell-based vaccines aimed at one or more oncoproteins (E6, E7) of the HPV virus.[130]

Early Diagnosis and Cancer Control

Head and neck and oral examinations have been shown in a large trial in India to result in earlier identification of OSCC and to translate into improved survival compared with a control group.[131] Furthermore, it is possible that this approach is cost-effective, as shown in this high-risk patient population.[132]

A position paper by the United States Preventive Services Task Force (USPSTF) noted that there is insufficient evidence to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults by nondental providers. This reflects the fact that OSCC is a rare disease and progress of disease once present is unpredictable. While the USPSTF's conclusion represents the available evidence in terms of cost-effective and risk–benefit analysis, it challenges guidance from a public health perspective and specifically excludes dental providers from the recommendations. It is thought that early detection based upon a visual and tactile examination performed in the dental care setting may be associated with improved survival with reduced costs. However, false-positive and false-negative findings and the potential for overtreatment are a concern in HNSCC, as they are in other malignancies such as breast and prostate cancer. Considering that oral cancer screening is an integral component of the overall routine comprehensive head and neck examination in the primary dental care setting (opportunistic screening), it is considered to be good practice.[82,133]

MALIGNANT TUMORS OF THE SALIVARY GLANDS

Salivary gland tumors represent approximately 6% of head and neck tumors and most commonly arise in the parotid glands, where the majority of tumors are benign adenomas; that is, pleomorphic adenoma, myoepithelioma, basal cell adenoma, Warthin's tumor, canalicular adenoma, duct papilloma, and cystadenoma. The parotids may be the site of transformation in a relatively small number of these cases (approximately 15–35% of salivary gland malignancies). Malignant tumors of the salivary glands develop most commonly in the submandibular, sublingual, and minor salivary glands (approximately 40%, 70–90%, and 45–80% of salivary gland malignancies, respectively). Major salivary gland carcinomas, unlike most head and neck carcinomas that are squamous in origin, are classified into over 20 histologic subtypes.[22] The most common of these are mucoepidermoid carcinoma, adenoid cystic carcinoma, and acinic cell carcinoma. The cause of salivary gland tumors remains obscure, but ionizing radiation has been identified as a risk factor. Many chromosomal events and oncogenes are postulated in the pathogenesis of salivary gland cancer.

Clinical Presentation and Diagnosis

Malignant salivary gland tumors most commonly present as a painless mass. When the mass is superficial or large, it may cause intraoral or extraoral asymmetry. When the mass is intraoral, it may be ulcerated. Neurologic involvement may lead to discomfort and numbness, and with parotid gland tumors involvement of the facial nerve may cause facial paralysis. In the floor of the mouth, salivary gland malignancies may cause ankyloglossia.[134] Most small malignant lesions are clinically indistinguishable from benign lesions. The most common site of minor salivary gland cancer is the posterior hard palate, but other sites in the oral cavity or upper respiratory tract may be involved. Most salivary gland tumors spread by local infiltration, by perineural or hematogenous spread, or less commonly via lymphatics.[78]

Biopsy of masses in the major glands may be accomplished by FNA or CNB, and diagnosis may be made without open biopsy; however, surgical biopsy may be necessary if FNA is not diagnostic. In masses involving minor glands, biopsy can be performed with routine techniques.[134]

Treatment and Prognosis

Studies assessing treatment and prognosis are complicated by the large variety of histologic subtypes, and the small numbers seen of each type of salivary gland cancer. Therefore, treatment trials provide limited guidance. Surgery is the principal treatment of the primary tumor. Despite the

anticipated low proliferative index of many salivary gland cancers, radiotherapy at a high dose is effective and may be employed in malignant salivary gland tumors. Postoperative radiation can contribute to cure and to improved local control, and is indicated for patients with residual disease following surgery, extensive perineural involvement, lymph node involvement, high-grade malignant disease, tumors with more than one local recurrence after surgery, inoperable tumors, malignant lymphoma, and for those who refuse surgery. Doses and fractionation similar to those used in the treatment of SCC are usually employed. Heavy-particle radiation sources (neutron beam and proton beam) have been shown to provide effective treatment for salivary gland tumors.[135,136]

Various single-agent chemotherapy protocols and combination protocols have been evaluated, but in general all with small studies, therefore limiting conclusions. Unlike with OSCC, chemotherapy does not seem to be effective for advanced or metastatic salivary gland disease. Perhaps the slow growth of salivary gland cancer could explain the overall poor results to date with chemotherapy protocols. In the future, advances in management may mirror those of breast cancer, where subtypes of salivary gland cancer may be assessed by evaluation of cell surface markers including HER2-neu, EGFR, and other markers, in order to guide chemotherapy and targeted therapies. Among the chemotherapeutics examined, limited benefit has been seen, while data on targeted agents is being evaluated alone or in combination with cytotoxic chemotherapy.[137]

The prognosis of salivary gland tumors is related to tumor type (histology and degree of differentiation) and stage of disease (tumor size, lymph node involvement, and extension of disease). Small tumors have a favorable prognosis and a high probability of cure with surgical management. Tumors with a poor prognosis include large tumors, adenocarcinoma, adenoid cystic carcinoma, high-grade mucoepidermoid carcinoma, poorly differentiated carcinoma, and SCC. Histologic findings that correlate with lymph node involvement include deep (>8 mm) and diffuse invasion of stromal tissue and invasion of lymphatics.[138,139]

ODONTOGENIC TUMORS

Odontogenic neoplasms form from epithelial and mesenchymal remnants of tooth germs. The WHO classifies tumors of odontogenic origin into malignant and benign odontogenic tumors. Of the malignancies, ameloblastic carcinoma, primary intraosseous carcinoma, sclerosing odontogenic carcinoma, clear cell odontogenic carcinoma, ghost cell odontogenic carcinoma, odontogenic carcinosarcoma, and odontogenic sarcomas are included.[22] These tumors are extremely rare and our knowledge of them is based on case reports and small case series, making standardized treatment recommendations difficult. Most of these tumors are aggressive and the primary treatment is radical excision.

MALIGNANT TUMORS OF THE JAW

Malignant lesions of the jaw may be of hematopoietic origin, such as lymphoma and multiple myeloma, or of bone origin, such as osteosarcoma, chondrosarcoma, and Ewing sarcoma. Metastases to the jaw should be considered during clinical evaluation of any cancer patient with a cancer history, particularly in breast, prostate, gastrointestinal, and renal carcinoma. This section focuses on osteosarcoma, which is the most common bone-originating jaw malignancy.

OSTEOSARCOMA

Osteosarcoma is a malignant tumor, characterized by the formation of bone or osteoid by tumor cells. Osteosarcomas of the jaws may develop in a broad range of ages, but are more common in the third and fourth decades.[140] Osteosarcoma occurs slightly more often in the mandible than in the maxilla. Most osteosarcomas of the jaws are centrally located in the bone. Juxtacortical or parosteal location, a location adjacent to the outer surface of the cortical bone, is unusual. Osteosarcomas may also develop in a patient affected by Paget's disease or in a patient who has been irradiated either for a benign bone lesion or for adjacent soft tissue disease. The latent time period may vary widely.

Clinical Presentation and Diagnosis

The most common presenting finding of osteosarcomas of the jaws is mass (85–95.5%). Pain accompanies the swelling in approximately half of cases, and trigeminal sensory disturbances occur in about a fifth of cases. Additional symptoms associated with intraosseous location are mobile teeth, toothache, and nasal obstruction.[141,142]

The radiographic appearance varies between radiopaque, radiolucent, and mixed. The border of the lesion is not well defined. The classic radiographic presentation is of a "sun-ray appearance," in which the radiograph may show an opaque lesion with bony trabeculae directed perpendicularly to the outer surface. This is observed in about 25% of cases. Over time, there is expansion and perforation of the cortical bone. The osteolytic type is far less characteristic and appears as an ill-defined radiolucency that causes expansion and destruction of the cortical bone. In the presence of teeth,

a widening of the periodontal ligament may be observed even before changes can be noticed elsewhere in the bone. Root resorption may create a spiked shape to the apical third of the root. Loss of follicular cortices of unerupted teeth is highly suggestive of malignancy. Widening of the mandibular canal is another ominous sign. Bone scintigraphy will show a positive uptake in tumor and indicate the extent of tumor, but is not diagnostic.

Histopathologic proliferation of atypical osteoblasts, irregular osteoid and bone formation, and anaplastic fibroblasts may be seen. Vascular clefts result in variants such as telangiectatic osteogenic sarcoma. Multinucleated giant cells may be scarce or abundant. Osteosarcomas of the jaws are, in general, better differentiated than similar tumors in the long bones. Even if the tumor largely consists of malignant-looking cartilage, the so-called chondroblastic type, it is still to be considered an osteosarcoma whenever osteoid and bone are present in the stroma. Low-grade osteosarcomas may be misdiagnosed as fibrous dysplasia or other benign fibro-osseous lesions. Osteosarcomas are usually graded according to histopathologic criteria from low-grade (grade I) to high-grade (grade III) malignancies.

Treatment and Prognosis

Treatment requires aggressive local surgery. Several authors report the use of (neo)adjuvant chemotherapy. Others report that the introduction of chemotherapy did not dramatically alter the prognosis of osteosarcoma of the jaw. Metastasis is usually via the bloodstream and often occurs within 1–2 years. Of the patients who die from osteosarcoma, most do so with uncontrolled local disease. The 5- and 10-year survival rates after treatment are approximately 60–70% and 50%, respectively. Large tumors, higher-grade secondary osteosarcomas, and recurrence are associated with decreased survival. Mandibular location and clear surgical margins are associated with improved survival.[143]

SARCOMAS OF THE SOFT TISSUES

Soft tissue sarcomas of the oral cavity are rare and account for approximately 1% of all oral malignancies. Subtypes include fibrosarcoma, malignant fibrous histiocytoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, angiosarcoma, and alveolar soft part sarcoma. Soft tissue sarcoma usually presents as a slow or rapid-growing swelling of the mucosa involving any part of the oral cavity. Treatment usually consists of surgery with adjuvant radiotherapy for those with high-grade tumors and/or positive margins following surgery. The efficacy of adjuvant chemotherapy is poorly defined.[144,145]

METASTASES TO THE HEAD AND NECK

Metastatic tumors to the oral region are uncommon and may occur in the oral soft tissues or in the jawbones. The most common primary sites from which oral metastases arise are the lung, kidney, liver, and prostate for men, and breast, female genital organs, kidney, and colo-rectum for women. Prostate and breast metastases are mainly concentrated in the jaws rather than the soft oral tissues.[68,72]

The clinical presentation of metastasis to the jawbones includes swelling, pain, and paresthesia.[68] Metastases to the oral soft tissues may manifest as a submucosal mass or gingival mass.[72] Radiographic presentation is mainly radiolucent with a poorly defined border, although radio-opacities or mixed radiographic lesions may be seen in some cases.[68,146] A diagnosis of oral metastasis is a poor prognostic indicator and the literature suggests an average seven-month survival time, with treatment being mainly supportive.

NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma (NPC) accounts for 0.7% of all cancers diagnosed in 2018 and is relatively uncommon worldwide. East and Southeast Asia account for 70% globally of all cases. The high rates of NPC in East and Southeast Asia are attributed to a combination of EBV, genetic morphology, and factors such as smoking, environmental toxins, consumption of preserved foods, and alcohol. EBV is a member of the herpesvirus family with a double-stranded, linear DNA viral genome. While an estimated 90% of the global population has been exposed to EBV, for most this was at an early age through saliva and they never experience symptoms or complications related to this infection. Some individuals, particularly with immunosuppression, experience latent infection in memory B cells and develop Hodgkin or Burkitt lymphomas. Malignant transformation of epithelial cells in the nasopharynx and oral cavity can lead to both nasopharyngeal and salivary gland carcinomas.[3]

Five-year survival is approximately 40% and 60%, for keratinizing and nonkeratinizing SCC, respectively. However, clinical stage at diagnosis is the most important prognostic factor for NPC survival. FNA can provide tissue diagnosis, and the sensitivity can be enhanced by DNA amplification (polymerase chain reaction) of the EBV genome, which is commonly associated with NPC but is rare in other head and neck cancers. Furthermore, rapid clearance of EBV DNA from plasma may be used as a marker for response to treatment.[147]

Treatment of early-stage disease without obvious neck metastasis is high-dose definitive radiotherapy to the nasopharynx (66–72 Gy) and often bilateral RT to the neck.

Obvious neck or distant metastasis is preferentially treated with a clinical trial or concurrent chemoradiotherapy, induction chemotherapy followed by chemoRT, or chemoRT followed by adjuvant radiotherapy. Chemotherapy for concurrent therapy includes cisplatin followed by cisplatin or carboplatin/5-FU, while induction chemotherapy begins with docetaxel/cisplatin/5-FU, cisplatin/5-FU, cisplatin/epirubicin/paclitaxel, or docetaxel/cisplatin, and agents typically include weekly cisplatin or carboplatin (Table 7-6).[90]

While standard of care is treatment with IMRT, oral complications are substantial and have great impact on the quality of life. Surgery may play a role in the treatment of recurrent or metastatic disease. Transoral robotic surgery is becoming more commonly used in early-stage NPC. Proton therapy can be considered when photon therapy is expected to damage critical structures, and has been demonstrated to decrease radiation dose to the oral cavity.[148] Some studies have reported an improvement in 5-year survival in patients treated with proton therapy versus photon therapy for paranasal sinus and nasal cavity malignant disease.[149]

NPC presents a number of concerns to dental providers, because patients may present with complaints that mimic temporomandibular disorders (TMDs). The common clinical presentation of NPC is otalgia and neck mass. Common TMD signs and symptoms include pain and limited jaw opening. Symptoms that aid in differentiation of TMD and NPC may occur late or concurrently and include dysphagia, nasal stuffiness, nose bleed, neck mass, or cranial involvement.[150] Cases of nonkeratinizing NPC for which EBV infection is a risk factor are endemic in Asia and, while uncommon, may be increasing in prevalence in the United States.[151]

Table 7-6 American Joint Committee on cancer staging for nasopharyngeal carcinoma 8th edition.

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No tumor identified, but EBV+ cervical node involvement
T1	Tumor confined to the nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T3	Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4	Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle
Regional Lymph Nodes (N)	
Nx	Regional lymph node cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), ≤6 cm, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), ≤6 cm, above the caudal border of the cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), >6 cm, and/or extension below the caudal border of cricoid cartilage
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Clinical Stage	
I	T1 N0 M0
II	T2 N0–1 M0, T0–1 N1 M0
III	T3 N0–2 M0, T0–2 N2 M0
IVA	T4 or N3 M0
IVB	Any T, any N, M1

EBV, Epstein–Barr virus.
Source: Reproduced with permission from Pfishter DG. *NCCN Guidelines: Head and Neck Cancers*. Plymouth, PA: National Comprehensive Cancer Network; 2019.

MUCOSAL MELANOMA

Mucosal melanomas (MMs) are very rare and only comprise 1.3% of all melanomas (see also Chapter 5, "Pigmented Lesions of the Oral Mucosa"). The most common sites in the head and neck are the conjunctiva, nasal cavity, paranasal sinuses, and oral cavity. MM is more common in those over the age of 65 and has a slightly higher incidence in women. Risk factors may include cigarette smoking and exposure to formaldehyde. MM is an aggressive disease with a poor prognosis and, unlike cutaneous melanoma, the biology and pathogenesis of MM are poorly understood. Presenting signs of MM depend on the anatomic site involved. In the nasal cavity and paranasal sinuses, signs such as nasal obstruction and discharge, epistaxis, and facial pain can be misinterpreted as signs of sinonasal inflammatory disease. In the oral cavity, lesions of MM are easier recognized and typically present as hyperpigmented/melanotic nodules or macules, but can also be amelanotic.

The most commonly involved sites in the oral cavity are the hard palate and gingiva. For both oral cavity and sinonasal MM, satellite lesions may accompany the primary lesion. Oral MM is categorized by the presence of pigmentation and growth type (nodular, macular, or mixed). Regional nodal metastasis is typically more likely at diagnosis in oral cavity MM than sinonasal MM and more common in lesions with a DOI >5 mm. Nodal metastasis may be more common in lesions with a nodular growth pattern. Treatment follows the treatment guidelines for cutaneous melanoma and usually involves surgical resection, with possible postoperative radiation therapy. Medical treatments in the form of targeted therapies and immunotherapies have changed the way in which cutaneous and MMs are treated. Targeted therapies for melanoma with a BRAF V600 mutation include BRAF inhibitors dabrafenib and vemurafenib and the MEK inhibitor trametinib. For melanomas with a KIT gene mutation, the KIT inhibitors imatinib, dasatinib, and nilotinib are recommended. For patients with metastatic or unresectable MM, immunotherapy is recommended with ipilimumab (anti-CTLA-4), nivolumab (anti-PD-1), and pembrolizumab (anti-PD-L1).[152]

PARANEOPLASTIC SYNDROMES AND ORAL CANCER

Oral cancer is reported in the literature in association with several syndromes or chronic diseases. These disorders are considered paraneoplastic because they accompany the malignant tumor, but are not directly related to the cancerous mass, its invasion, or its metastasis. The diagnosis of oral cancer may precede, develop simultaneously, or develop following the diagnosis of the paraneoplastic syndrome.

Within the group of endocrine paraneoplastic syndromes, oral cancer may be associated with inappropriate secretion of antidiuretic hormone (SIADH), humoral hypercalcemia, hypercalcemia with leukocytosis, and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Within the group of cutaneous paraneoplastic syndromes, oral cancer is associated with Bazex syndrome (acrokeratosis paraneoplastica), Sweet's syndrome (acute febrile neutrophilic dermatosis), and paraneoplastic pemphigus. Additional vascular, hematologic, rheumatoid, and ocular syndromes are associated with oral cancer.[153]

HEAD AND NECK MALIGNANT DISEASE IN HIV/AIDS

HIV infection that leads to immunosuppression increases the risk of the development of neoplastic disease. KS was the most common neoplastic disease of AIDS prior to antiretroviral therapies (ART). KS is a multicentric neoplastic proliferation of endothelial cells and was very common prior to ART, occurring in up to 55% of individuals with AIDS and often representing the first sign of progression to AIDS. KS is associated with the oncovirus human herpesvirus type 8 (HHV-8). KS can involve any oral site, but most frequently involves the attached mucosa of the palate and gingiva, or the dorsum of the tongue. Lesions begin as blue-purple or red-purple flat discolorations that can progress to tissue masses that may ulcerate (Figures 7-2 and 7-3). The lesions do not blanch with pressure. Initial lesions are asymptomatic, but can cause discomfort and interfere with speech, denture use, and eating if they progress. The differential diagnosis includes ecchymosis, vascular lesions, salivary gland tumors, and metastatic disease. Definitive diagnosis requires biopsy.

Intralesional chemotherapy for treatment of oral KS provides effective palliation.[154] Intralesional treatment with vinblastine and interferon has been reported. The lesions can be treated with the injection of vinblastine (0.2 mg/mL) under local anesthesia. The effect of treatment may continue for several weeks and may result in palliation for approximately four months. Repeat injection can be completed with similar efficacy. KS is radiosensitive, and radiation can be palliative for regional disease. Fractionated radiotherapy (for a total dose of 25–30 Gy over 1–2 weeks) may be provided for oral KS. If KS progresses at multiple sites, systemic chemotherapy is indicated. Additional approaches to management include drugs that reduce angiogenesis, antiviral agents for HHV-8 infection, and agents that block VEGF.

Certain lymphoma subtypes are more common in people with AIDS. Non-Hodgkin lymphoma (NHL) is considered an AIDS-defining entity, and this disease is currently the most common type of cancer in HIV-infected individuals in the United States and Europe. NHL, most commonly of B cell origin, may present with central nervous system involvement, but also may present with head, neck, or oral lesions. Hodgkin lymphoma is not considered an AIDS-defining malignancy; however, its incidence is increased in HIV-infected individuals. The lymphomas are aggressive and carry a poor prognosis. Treatment of lymphoma with chemotherapy for HIV patients on antiretroviral therapy may be challenging.

Oral and oropharyngeal SCC has been reported in patients with HIV disease. Despite the widespread use of ART, with HPV-related oral lesions being more prevalent, the prevalence of oral or oropharyngeal cancers in HIV patients is projected to increase.[155]

CONCLUSION

New understandings of head and neck cancers continue to emerge. These include information about the etiologic risk factors, current epidemiology, advances in treatment, recommendations for prevention, and importance of surveillance for possible cancer recurrence or new second cancers. The role of the dental professional extends from detection and diagnosis of head and neck cancers throughout the cancer continuum of treatment and survivorship, and requires close communication with the oncology team. With the emergence of new therapies and therefore new complications, an appropriate level of oral care requires a thorough understanding of these diseases and their treatments. Given advances in therapies and the subsequent increases in survivorship, the oral healthcare professional's involvement in the care of the cancer patient becomes crucial to helping these patients maintain an acceptable quality of life.

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8

Oral Complications of Nonsurgical Cancer Therapies

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OVERVIEW

Oral complications from cancer therapies are commonly of significant morbidity to the patient and may cause disruption of cancer treatment compromising the prognosis and increase health care costs. A wide range of oral complications of cancer therapies often appear concurrently which may complicate diagnoses and management; for example, intense oral and pharyngeal pain induced by a combination of oral mucositis, oropharyngeal candidiasis, salivary gland hypofunction, and xerostomia frequently lead to dysphagia in cancer patients compromising nutritional intake.[1] Thus, oral complications of cancer therapies may severely affect quality of life during cancer treatment or when manifest as late oral complications months or years following treatment.

Oral complications induced by cancer therapies result from a complex interplay among multiple factors and the recognition of the underlying mechanisms causing oral complications continues to develop. However, there are no effective agents or protocols to collectively prevent adverse effects from cancer therapies. Thus, the current approach to

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

minimize incidence and severity of oral complications of cancer therapies is the elimination of pre-existing dental, periodontal, and mucosal infections in coherence with regular oral assessment and implementation of basic oral care protocols and prompt diagnosis of emerging oral complications during and after cancer therapy with adequate alleviation and treatment.[2]

An interdisciplinary approach, including dental professionals, is required to work in close collaboration with the patient in order to regularly—and by validated outcome measures—evaluate, prevent, and treat oral complications of cancer therapies.

This chapter addresses oral complications of nonsurgical cancer therapies and evidence-based clinical practice guidelines for management.

Types of Cancer Therapies

Design of cancer treatment protocols is based on a number of key considerations, beginning with histopathologic confirmation of the type of malignancy. Additional components include staging (solid tumors), age and performance status of the patient, projected efficacy in relation to toxicity, and patient preferences.

Patients with hematologic malignancy

Patients with hematologic disease (Figure 8-1; Figure 8-2) may be treated by moderate or high-dose chemotherapy, with or without hematopoietic stem cell transplantation (HSCT). As with head and neck cancer patients, factors influencing incidence and severity of oral complications across patients with hematologic disease include extent of oral disease prior to cancer treatment, intensity of cancer therapy, genetically-governed susceptibility to oral mucosal injury, and patient compliance with health professional Recommendations regarding oral hygiene, diet, smoking cessation, and related variables.

HSCT-related oral toxicities are additionally influenced by the degree of genetic disparity between donor and patient. Acute and/or chronic graft-versus-host disease (GVHD) that results from immune-modulated injury to the patient's tissues can cause clinically significant salivary gland and/or oral mucosal disease.

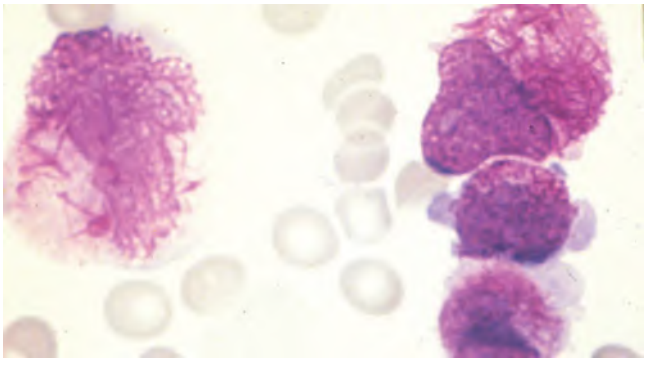

Figure 8-1 Peripheral blood smear from a patient with newly diagnosed acute myelogenous leukemia in blast crisis. The high-dose induction chemotherapy regimen that will be used to treat this patient is profoundly myelosuppressive, and typically causes severe ulcerative oral mucositis for at least two weeks duration. The interface of profound myelosuppression with disruption in integrity of the oral mucosal barrier can result in risk for life-threatening bacteremia and/or sepsis. *Source:* Quintessence 2019.[69]

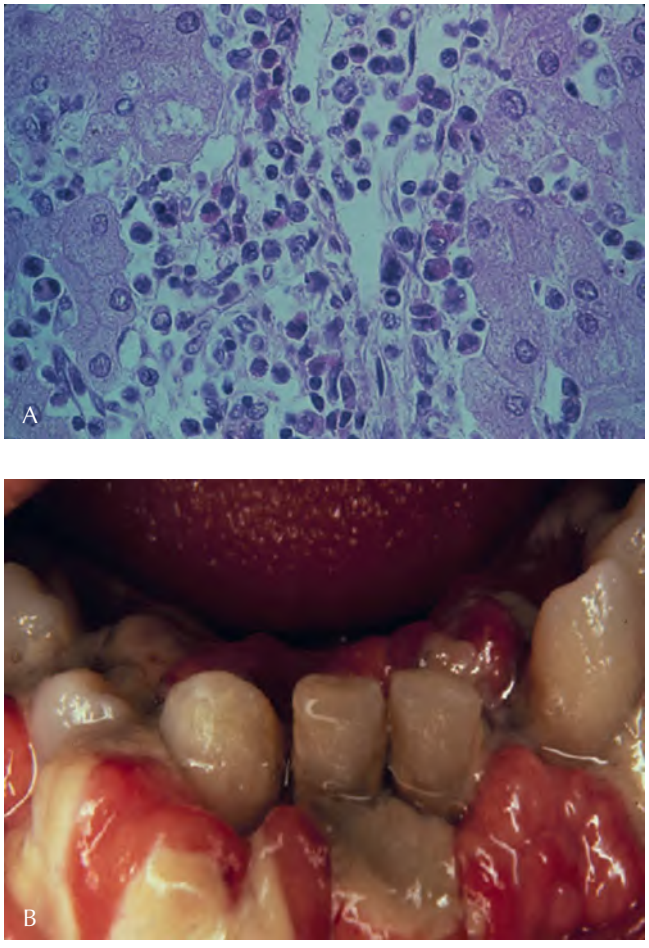

Figure 8-2 Acute leukemia can be considered "naturally metastatic" in that the neoplasm arises within the white blood cell progenitors produced in the bone marrow. Because of the inherent circulation of these cells the disease is widespread by time of diagnosis. (A) Histopathology based on hepatic biopsy, demonstrating widespread infiltrate of the blast leukemic cells. (B) Gingival leukemic infiltrate in newly diagnosed acute myelogenous leukemia patient. Note the evidence of extensive gingival engorgement caused by the infiltrating leukemic cells. The resulting ischemia can contribute to develop of tissue necrosis as well as opportunistic infection such as pseudomembranous candidiasis. *Source:* Quintessence 2019.[69]

Patients with Head and Neck Cancer

Depending upon these variables, cancer treatment for a patient with solid head and neck cancer (e.g., oral, oropharyngeal, or laryngeal tumor) can consist of:

- Surgical excision with resultant cure (early stage solid tumor).
- Head and neck radiation, administered in fractionated or hyperfractioned doses five times/week for 6–7 weeks for a total cumulative dose of approximately 60–70 Gy.
- Multimodality treatments that incorporate chemotherapy based on the following schema:

  Neoadjuvant chemotherapy:
  Administered prior to surgery, for purposes of debulking tumor.
  Adjuvant chemotherapy:
  Administered after surgery and prior to head and neck radiation.
  Concurrent/concomitant chemotherapy:
  Administered in combination with head and neck radiation, typically on a weekly basis throughout the duration of the 6–7 weeks of radiation.

Factors influencing incidence and severity of oral complications across patients with head and neck cancer include extent of oral disease prior to cancer treatment, dose and anatomic location of radiation therapy, genetically-governed susceptibility to oral mucosal injury, and patient compliance with health professional recommendations regarding oral hygiene, diet, smoking cessation, and related variables.

Patients Receiving Targeted Cancer Therapies

Use of targeted cancer therapies such as multitargeted tyrosine kinase inhibitors and mammalian target of rapamycin (mTOR) inhibitors has increased in recent years.[3,4] These biologics are directed to molecular pathways that are unique to tumor cells, versus normal cells. Despite their targeting, however, side effects such as oral mucosal and dermal lesions can occur.

Epidemiology of Oral Complications of Cancer Therapies

The types of oral complications vary in pattern, duration, and intensity for each individual patient and depending on the cancer therapy regimen and dose intensity: e.g. cancer chemotherapy, head and neck radiation therapy, targeted cancer therapies, and hematopoietic stem cell transplantation.[5–8] The Oral Care Study Group and the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) have performed systematic reviews of the most common oral complications of cancer therapies and provided prevalence of oral mucositis,[9–11] oral pain,[12] oral fungal infection,[13] oral viral infection,[14,15] salivary gland hypofunction and xerostomia,[16] dysgeusia,[17] trismus,[18] dental disease,[19,20] osteoradionecrosis,[21] and medication-related osteonecrosis of the jaw[22,23] in relation to various regimens of cancer therapy. The prevalence data presented in these systematic reviews highlight the multiple variables that translate into the degree to which a cancer patient experiences a given toxicity, including pre-existing oral status, type and intensity of cancer treatment, the patient's genetically governed response, and patient-reported outcomes.

ORAL CARE PROTOCOLS FOR PATIENTS RECEIVING CHEMOTHERAPY AND HEAD AND NECK RADIATION

Oral Care, Precancer Treatment

Elimination or stabilization of selected oral disease prior to initiation of chemotherapy or head and neck radiation can prevent or mitigate subsequent acute oral toxicities such as infection of dental, dental pulpal or, periodontal origin. Decision-making relative to this medically necessary oral care, precancer treatment is illustrated in Figure 8-3.

Implementation of Systematic Basic Oral Care Protocols for Oncology Patients

Oral care interventions are pertinent to all cancer patients in order to prevent and reduce the incidence and severity of oral complications and promote oral comfort during and following cancer therapies.

Development and implementation of oral care protocols should be interdisciplinary (nurse, physician, dentist, dental hygienist, dietician, pharmacist, and others as relevant) and include education of the patient, family, and health care professionals. The protocols should be focused on: Regularly scheduled oral assessment and decontamination to reduce the risk of infection, oral moisturization to reduce the risk of friction and trauma-induced oral mucosal injury, and pain management to promote oral comfort and avoid dose reduction and interruption of cancer treatment.

Evidence-based patient care fact sheets are available with a multidisciplinary approach on how to care for your mouth before, during and after radiation for head and neck cancer as well as during active chemotherapy (http://isoo.world/patient-education.html).[25] The fact sheets are multilingual and available in 21 languages.

Oral Decontamination

Toothbrushing two to three times a day with a soft nylon-bristled toothbrush (with regular replacement of the toothbrush) is recommended.[2,24,25] The bristles can be softened in

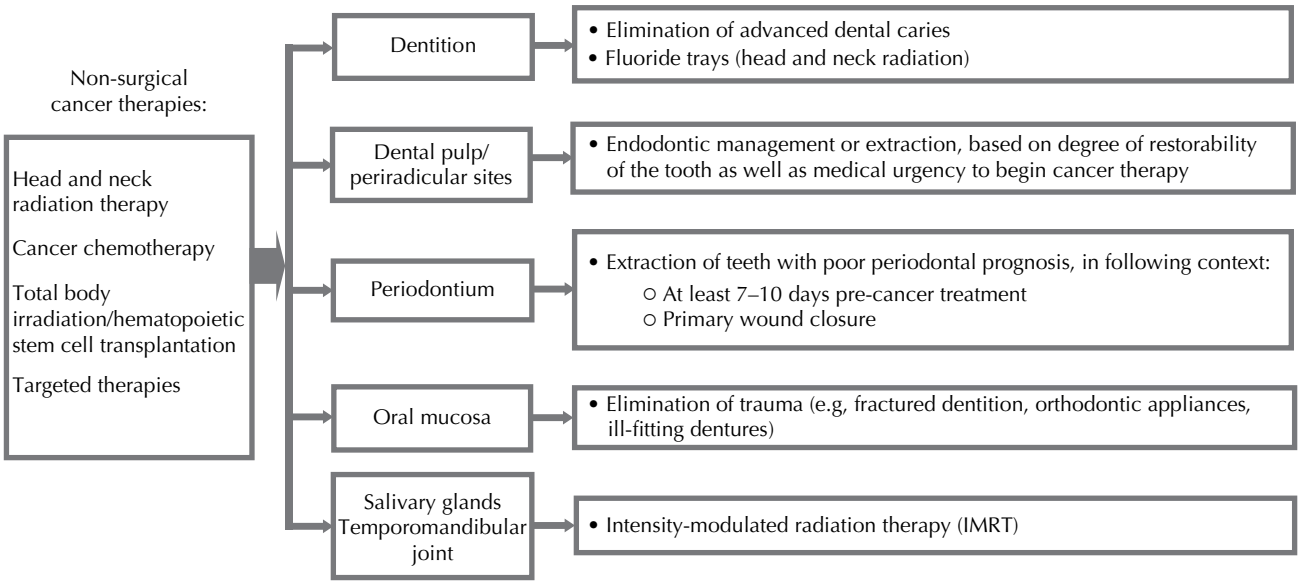

Figure 8-3 Oral care, precancer treatment.

warm water if oral hygiene procedures become discomforting, or can be modified to an ultrasoft toothbrush to ensure continued mechanical oral decontamination for as long as possible during cancer treatment. Toothbrushing should be supplemented by dental flossing once daily with instruction on atraumatic technique. Fluoridated toothpaste should be used, supplemented by high concentration prescription fluoride regimens if the patient's ability to perform oral care is compromised or if increased risk of dental caries due to salivary gland hypofunction (e.g., 5000 ppm fluoride toothpaste or 1% neutral sodium fluoride gel in a dental tray for 5 minutes before bedtime: the dental tray should overlap the gingival margins of the teeth and still avoid unnecessary contact with the gingiva). Toothpastes containing sodium dodecyl/laureth sulfate (surfactant) and mint flavor should be avoided if it causes soreness of the oral mucosa. Antiseptic mouthwashes such as 0.12% chlorhexidine gluconate may be administered as a supplement to toothbrushing depending on the manifestation of periodontal disease or if toothbrushing is no longer possible due to oral pain.[2,24,25] Professional mechanical bacterial plaque removal should be performed before the patient begins rinsing with chlorhexidine gluconate.[26]

Oral Hydration

Alleviation of xerostomia comprises gustatory, masticatory, or pharmacologic stimulation of residual salivary gland secretory capacity or regular and frequent sipping and topical application to the oral cavity of water, bland rinses, or saliva substitutes (e.g., mouthwash, spray, or gel).[25,27,28] Lubrication of lips should be incorporated to prevent crusting and ulceration of the prolabium.

The use of bland rinses, for example 0.9% saline rinse or sodium bicarbonate solution (1 teaspoon salt, 1 teaspoon baking soda in 1 liter of water) is recommended in cancer therapy populations for decontamination, moisturization, neutralization of pH, and for promoting oral comfort.[2,24,25] Saline and sodium bicarbonate rinses are considered harmless to the oral cavity, thus frequent rinsing without swallowing can be performed as needed.

Evidence-based clinical practice guidelines for management of salivary gland hypofunction and xerostomia are described in detail in Chapter 9 "Salivary Gland Diseases."

Integration of Tobacco Intervention in Oral Supportive Care in Cancer

Tobacco intervention is essential after the diagnosis of cancer to improve clinical outcomes and should be a multidisciplinary approach with screening carried out throughout the continuum of care with intervention services available at each point of care.[29,30]

ORAL TOXICITY MANIFEST IN PATIENTS BOTH DURING CHEMOTHERAPY AND HEAD AND NECK RADIATION

Cancer patients can be at high risk for oral complications secondary to their cancer treatment (Figure 8-4). Incidence and severity are governed by a number of cancer treatment variables, as described below.

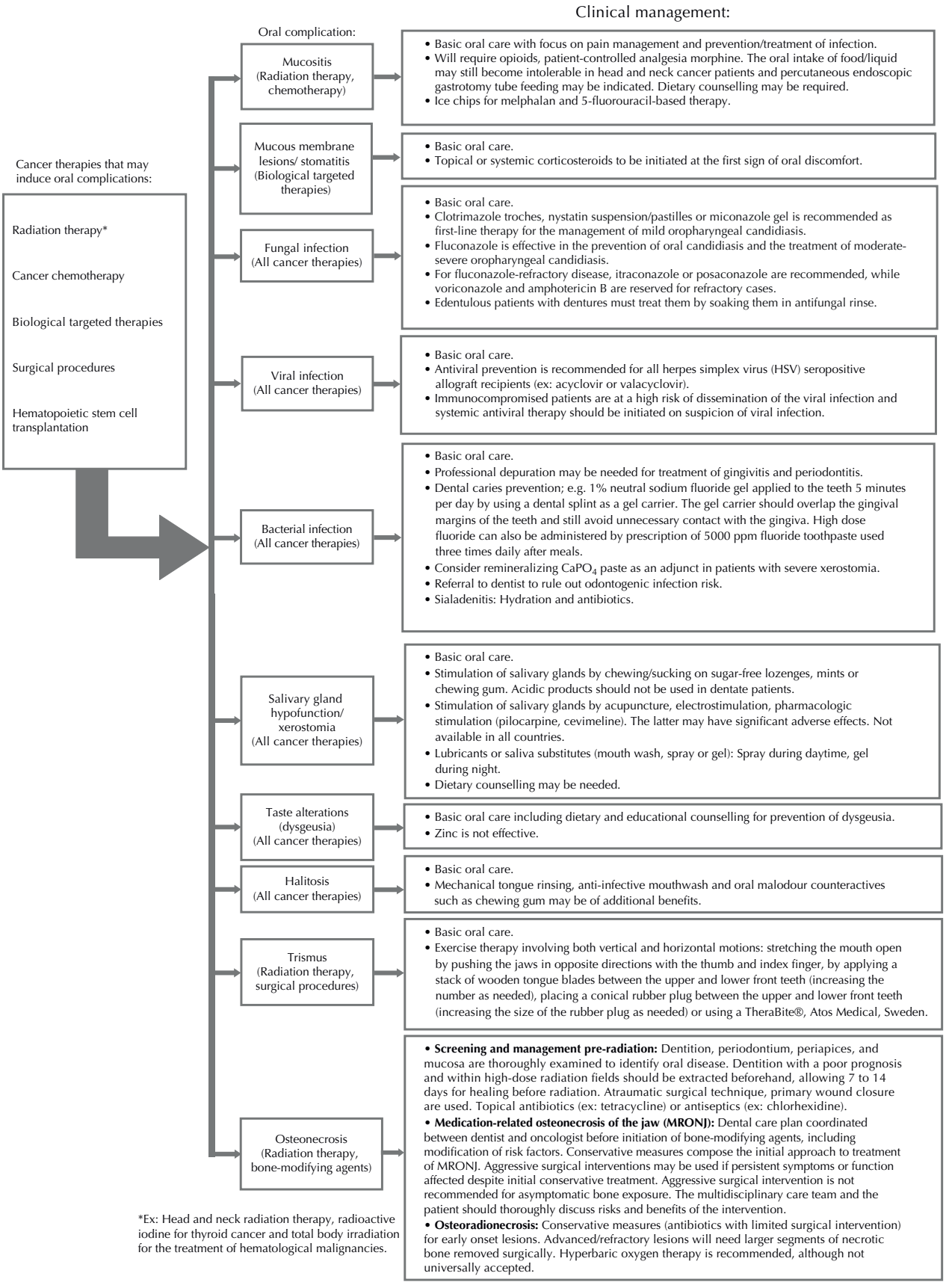

Figure 8-4 Clinical management of oral complications of nonsurgical cancer therapies.

Oral Mucositis

Oral mucositis can have significant clinical and economic consequence in oncology practice (Figure 8-5). The pain associated with the lesion can be sufficiently severe as to cause hospitalization in order to support nutritional intake and other daily functions. The pain can also cause dose reduction in future cycles of chemotherapy, thus compromising optimal delivery of the chemotherapy regimen.

Despite the prominence of oral pain in the clinical setting, however, there has been limited investigative research into the neuropathology component of the lesion. Mucosal injury in the neutropenic cancer patient can be source of systemic infection, with resultant morbidity and, in selected patients, mortality. Oral mucositis can thus cause clinically and economically adverse impact.

The current five phase pathobiologic model of oral mucositis is complex, and involves both epithelium as well as submucosa (Figure 8-6).[31–33] In addition, the potential role of the oral microbiome in relation to oral mucositis pathobiology has received increasing research attention as well. Incidence of moderate–severe oral mucositis in high-dose chemotherapy patients is approximately 40%.[34]

Evidence-based guidelines for management of oral mucositis are centered on supportive care.[9,11]

The evidence base for clinical practice guidelines for prevention and treatment of oral mucositis was reviewed in 2019 by the Mucositis Study Group, MASCC/ISOO. The results were incorporated into recommendations or suggestions at three levels: (i) *in favor* of interventions for oral mucositis; (ii) *against* interventions for oral mucositis; or (iii) no guideline possible due to insufficient or conflicting evidence.[10,11] Conclusions from these 2019 mucositis guidelines include:

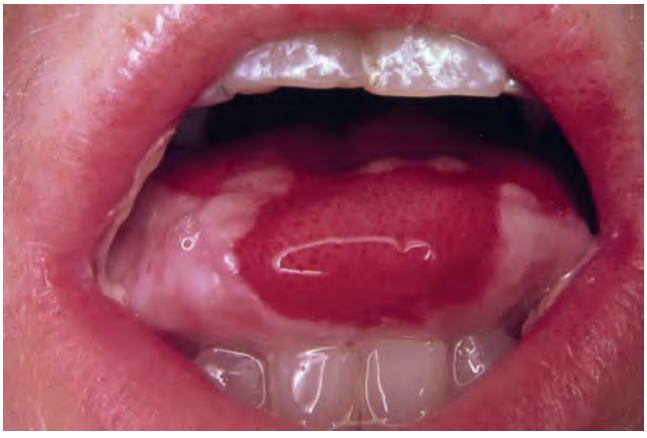

Figure 8-5 Oral mucositis in breast cancer patient receiving high-dose chemotherapy. The extensive pseudomembranous lesions can signficiantly impair normal oral function, and represent a portal of entry for severe systemic infection. *Source:* Quintessence 2019.[69]

1) Of the *growth factors and cytokines* studied for the management of oral mucositis, the evidence supports a recommendation *in favor* of intravenous keratinocyte growth factor (KGF)-1 for prevention of oral mucositis in patients with hematological cancer undergoing autologous HSCT with high-dose chemotherapy and total body irradiation and a suggestion *against* granulocyte-macrophage colony-stimulating factor (GM-CSF) in certain clinical settings.[35]
2) Numerous *natural products and herbal remedies* have been studied for the management of oral mucositis. Of the agents reviewed in the systematic review, a guideline *in favor* was made for honey (combined topical and systemic), while a guideline *against* was made for chewing gum.[36]
3) Of the agents studied for the management of oral mucositis-associated *pain*, the evidence supports a suggestion *in favor* of topical morphine 0.2% mouthwash in patients with head and neck cancer receiving radiation therapy and chemotherapy.[37] Additional guidance has been provided in a 2019 review by Epstein and Miaskowski, as cited in section Oral Pain.[38]
   The evidence supports recommendations for the use of *oral cryotherapy* for the prevention of oral mucositis for either (i) patients undergoing autologous hematopoietic stem cell transplantation with high-dose melphalan conditioning protocols or (ii) patients receiving bolus 5-fluorouracil chemotherapy.[39]
4) Regarding *basic oral care*, the evidence supports implementation of multiagent combination oral care protocols for prevention of oral mucositis (in chemotherapy, head and neck radiation therapy, and hematopoietic stem cell transplantation) defined as interventions carried out by the patients, lay caregivers, and/or nondental care professionals. The rationale for their implementation is to increase awareness of both patients and staff of the importance of good oral hygiene, which may indirectly lead to less frequent and less severe oral complications.
5) Typically, the protocols included in the systematic review involved a multifaceted approach to oral hygiene, including recommendations with regard to timing, frequency, and products such as combination of varying types of bland mouth rinses, toothbrushes, and flossing procedures.[2]
6) Chlorhexidine was suggested *not to be used* in basic oral care protocols to prevent oral mucositis in patients with head and neck cancer undergoing radiation therapy. However, it was emphasized by the systematic review panel that this recommendation is specific to the prevention of oral mucositis and this recommendation does not apply to other conditions where chlorhexidine is indicated; for example, oral infections.[2]

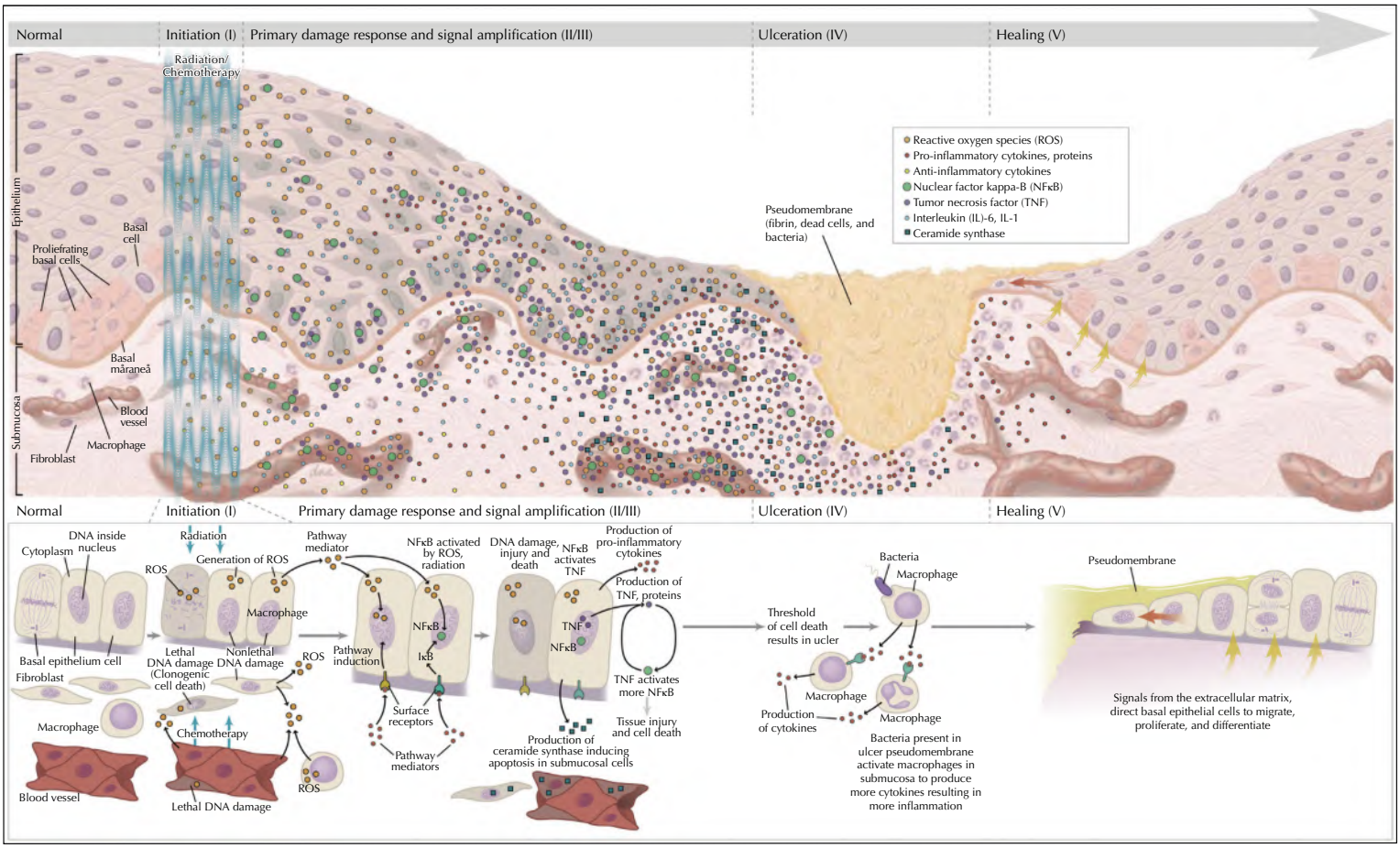

Figure 8-6 The conceptual framework for oral mucositis pathobiology consists of five stages, ranging from initial injury with hours of exposure to high-dose cancer therapy to eventual healing approximately 2–4 weeks after cessation of that treatment. Although the illustration depicts an orderly and sequential mechanistic process, the likely course of molecular and cellular events is more likely dysregulated and biologically confounded. *Source:* Sonis 2007.[31]

7) For other empiric basic oral care measures, only limited data were available. Thus, expert opinion supplements the basic oral care guidelines in support of the use of professional oral care for oral mucositis prevention; that is, dental evaluation and treatment as indicated prior to cancer therapy to reduce the patient's risk for local and systemic infections from odontogenic sources. It was also the panel's opinion that educating patients over the benefits of basic oral care strategies may improve the patient's self-management and adherence to the recommended oral care protocol during cancer treatment.
8) Despite the limited data available for oral bland rinses, the panel recommends saline and sodium bicarbonate mouth rinses that increase oral clearance which may be helpful for maintaining oral hygiene and improving patient comfort.[2]
9) Of the *anti-inflammatory agents* studied for oral mucositis, the evidence supports use of benzydamine mouthwash for prevention of oral mucositis in patients with head and neck cancer receiving radiation therapy and chemotherapy.[40]
10) Of the *vitamins*, *minerals*, *and nutritional supplements* studied for the management of oral mucositis, the evidence supports a recommendation *against* parenteral glutamine in patients receiving HSCT and a suggestion *in favor* of oral glutamine for management of oral mucositis in patients with head and neck cancer.[41]
11) The evidence supports the use of specific settings of *photobiomodulation* therapy for the prevention of oral mucositis in specific patient populations. Under these circumstances, photobiomodulation is recommended for the prevention of oral mucositis. The guidelines are subject to continuous update based on new published data.[42]
12) There is only one US Food & Drug Administration-approved biologic for prevention of oral mucositis (see the section Patients undergoing hematopoietic stem cell transplantation [HSCT]). Additional interventions, including pharmacologic and photobiomodulation, are also being studied.[42,43]

Oral Pain

Oral pain in cancer patients is likely due to both nociceptive and neuropathic pathways; treatment of both of these mechanistic processes is thus needed to achieve effective management.[38] The level of oral pain should be scored on a systematic basis, utilizing a validated pain ladder.

Pain management by patient-controlled analgesia with morphine in hematopoietic stem cell transplantation, topical 0.2% morphine mouthwash in head and neck radiation therapy, or 0.5% doxepin mouthwash (patient population not specified) have been recommended or suggested depending on the level of evidence as interventions to treat pain due to oral mucositis.[37] Management of pain from oral mucositis during head and neck radiation begins with nonsteroidal anti-inflammatory drugs (NSAIDs) since generally there is not an increased risk of hemorrhage and this can be combined with opioids as the severity of oral mucositis and pain increases.[44]

Depending on the severity of mucositis, topical anesthetic rinses can be used to allow for continuity of oral care and food intake with the precaution that the patient is carefully informed to avoid mechanical trauma and burns in the anesthetized mucosal areas.

Oral Hemorrhage

Compromised basic oral care increases the risk of oral infection (gingivitis, periodontitis, oral candidiasis) which increases the risk of oral hemorrhage. Hemorrhage may also be caused by cancer treatment-induced thrombocytopenia in patients receiving high-dose chemotherapy or undergoing hematopoietic stem cell transplantation.

Hemorrhage can be controlled with basic oral care and adequate periodontal and antifungal treatment. However, if prolonged hemorrhage occurs (> 2 min), periodontal treatment should be discontinued and the oncologist/hematologist consulted. Further management of oral hemorrhage includes the use of vasoconstrictors, clot-forming agents, and tissue protectants.[45]

PATIENTS RECEIVING HIGH-DOSE CHEMOTHERAPY

Chemotherapy can be used in a variety of primary or adjunctive oncology settings (Table 8-1). In addition to oral mucositis, oral infection can occur in association with chemotherapy-

Table 8-1 Single and multimodality cancer treatments for oral cancer.

Neoadjuvant: (debulk)	Sole use prior to surgery (e.g., 5 days 5-fluorouracil: mucositis)
Adjuvant: (curative)	Use after surgery/before radiation therapy (e.g., 5 days 5-fluorouracil: mucositis)
Concurrent/ Concomitant: (synergistic)	Combination with radiation therapy (e.g., head and neck radiation therapy + weekly cisplatin)

Source: Reprinted with permission from Peterson DE. Quintessence 2014.[68]

induced myelosuppression (Table 8-2). Unlike the head and neck radiation patient, however, long-term effects of high-dose chemotherapy on the oral tissues are rare.

Patients may develop pseudomembranous oral candidiasis during periods of bone marrow suppression (Table 8-3). Contributing factors may also include difficulties with oral hygiene during periods of oral mucositis as well as salivary gland hypofunction induced by medications used to support the care of the patient (e.g., antiemetics). Clinical diagnosis can often be established based on history and examination, although the assessment may be confounded by the concurrent presentation of chemotherapy-induced oral mucositis as noted above. Topical oral antifungal therapy with nystatin rinses or clotrimazole troches can be considered for management (Table 8-4). Resolution of the lesion typically occurs in the setting of bone marrow recovery and re-establishment of optimal oral care.

The periodontium may infrequently be a site of acute infectious flare during profound myelosuppression (Figure 8-7). These lesions are rarely encountered in oncology practice. When they do occur, however, the infection may not be readily detectable due to the impaired inflammatory response in the setting of profound neutropenia. Treatment usually consists of topical oral antimicrobial rinses and gentle mechanical plaque removal. Supervision of this intervention by a health professional with experience in dental management is highly recommended. Broad-spectrum antimicrobial therapy should be considered if the clinical presentation so indicates.

Table 8-2 High risk oral lesions in the myelosuppressed cancer patient.

Advanced and/or symptomatic dental caries
Periapical pathoses symptomatic within past 90 days
Severe periodontal disease for which prognosis of dentition is poor
Mucosal lesions secondary to trauma from prosthetic or orthodontic appliances

Source: Reprinted with permission from Peterson DE. Quintessence 2019.[69]

Table 8-3 Oral candidiasis.

Risk factors: • Myelosuppression • Mucosal injury • Salivary compromise • Antibiotics • Steroids • Increased length of hospital stay
Diagnosis: • History • Assessment of risk factors • Examination • Culture as needed
Treatment: • Nonmedicated oral rinse • Topical antifungal (systemic therapy if indicated) • Removal of dentures

Source: Reprinted with permission from Peterson DE. Quintessence 2019.[69]

Table 8-4 Topical therapies for oropharyngeal candidiasis (7–14 days).

Clotrimazole troche (10 mg)
Four to five times per day
Nystatin oral suspension (100,000 U/mL)
5 mL four times per day
Nystatin pastilles (200,000 U)
Four to five times per day
Fluconazole solution (e.g., 10 mg)
Swish and expectorate three times per day
Amphotericin B oral suspension (100 mg/mL)
1 mL, four times per day

Source: Reprinted with permission from Peterson DE. Quintessence 2019.[69]

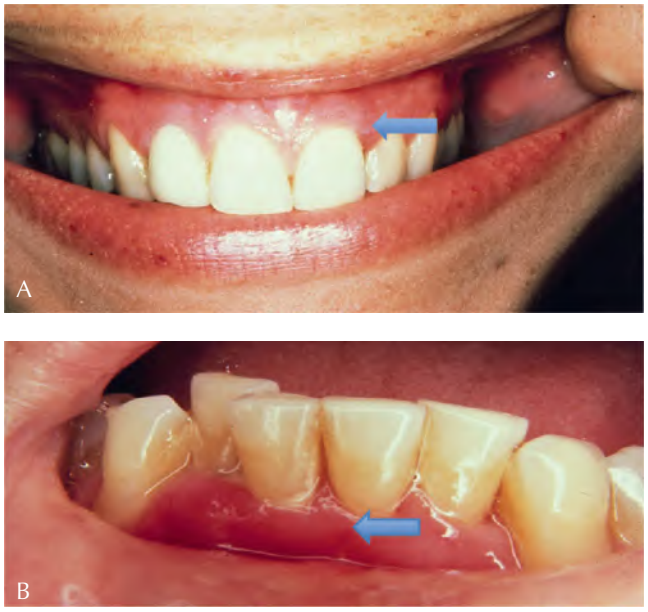

Figure 8-7 (A) Acute periodontal infection in a neutropenic cancer patient with < 500/mm^3. Classic inflammatory signs including erythema and purulence are not clinically prominent due to suppression of neutrophil number and function. (B) Acute periodontal infection in a chemotherapy cancer patient with < 1000 neutrophils/mm^3. Classic inflammatory signs are more evident due to a more robust neutrophil response. *Source:* Quintessence 2019.[69]

Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT)

Patients undergoing HSCT are at risk for development of a wide range of oral toxicities (Table 8-5).[24,46] Incidence and severity are directly influenced by a number of key variables. For example, the patient undergoing HSCT will typically receive a conditioning regimen containing chemotherapy at a high dose or reduced intensity level. As with chemotherapeutic regimens in the non-HSCT setting, risk for infection increases as the depth and duration of myelosuppression increases. An additional key factor is the degree of genetic homology between donor and recipient. Chapter 20, "Transplantation Medicine", provides further detail regarding these risk factors. Infections in patients undergoing HSCT can be of viral, bacterial, and/or fungal origin.

Oral Mucositis

Oral mucositis is a common toxicity in patients undergoing HSCT, with moderate–severe oral mucositis developing in patients undergoing high-dose conditioning regimens. Selected chemotherapeutic agents (e.g., melphalan) are also typically mucotoxic.

Table 8-5 Oral complications of hematopoietic stem cell transplantation.

Transplant phase	Oral complication
Phase I: Preconditioning	Oral infections: dental caries, endodontic infections, periodontal disease (gingivitis, periodontitis), mucosal infections (i.e., viral, fungal, bacterial)
	Gingival leukemic infiltrates
	Metastatic cancer
	Oral bleeding
	Oral ulceration: aphthous ulcers, erythema multiforme
	Temporomandibular dysfunction
Phase II: Conditioning, neutropenic phase	Oropharyngeal mucositis
	Oral infections: mucosal infections (i.e., viral, fungal, bacterial), periodontal infections
	Hemorrhage
	Salivary gland hypofunction/xerostomia
	Taste dysfunction
	Neurotoxicity: dental pain, muscle tremor (e.g., jaws, tongue)
	Temporomandibular dysfunction: jaw pain, headache, joint pain
Phase III: Engraftment, hematopoietic recovery	Oral infections: mucosal infections (i.e., viral, fungal, bacterial)
	Acute GVHD
	Salivary gland hypofunction/xerostomia
	Hemorrhage
	Neurotoxicity: dental pain, muscle tremor (e.g., jaws, tongue)
	Temporomandibular dysfunction: jaw pain, headache, joint pain
	Granulomas/papillomas
Phase IV: Immune reconstitution, late posttransplant	Oral infections: mucosal infections (i.e., viral, fungal, bacterial)
	Chronic GVHD
	Dental/skeletal growth and development alterations (pediatric patients)
	Salivary gland hypofunction/xerostomia
	Relapse-related oral lesions
	Second malignancies
Phase V: Long-term survival	Relapse or second malignancies
	Dental/skeletal growth and development alterations

GVHD = graft-versus-host disease.
Source: Reprinted from National Cancer Institute Physicion Data Query (NCI PDQ) website:Oral Complications of Chemotherapy and Head/Neck Radiation.[44]

The pathobiologic model and clinical trajectory appears to be similar to that of patients receiving high-dose chemotherapy without HSCT. An additional consideration, however, is the possibility of acute GVHD involving the oral mucosa. Acute GVHD can mimic oral mucositis clinically and can confound diagnosis and management of the concurrent toxicities.

In 2004, the US Food and Drug Administration approved the first-in-kind molecularly targeted drug for oral mucositis. This product, palifermin (KGF-1), was approved for the treatment of oral mucositis in patients with hematologic malignancies and who are receiving intensive chemotherapy and radiotherapy followed by a blood or bone marrow stem cell transplant.

See Oral Mucositis at the beginning of this section (Oral toxicity manifest in patients both during chemotherapy and head and neck radiation) for additional detail regarding assessment and treatment.

Oral Viral Infection

Oral viral infection caused by reactivation of herpes simplex virus (HSV) does not commonly occur in contemporary oncology practice, since prevention by thymidine kinase inhibitors such as acyclovir, valacyclovir, and their derivatives is highly effective. Pretransplant serologic testing for carrier status of HSV is important in identifying who patients may benefit from the viral prophylactic regimen. HSV titers greater than or equal to 1:16 are often used clinically as the indicator for initiation of the prophylactic regimen.

The infection (Figure 8-8), when it does occur, can co-develop in the setting of oral mucositis and/or acute GVHD.[47] This in turn not only confounds the diagnostic process but also intensifies the severity of the mucosal injury.

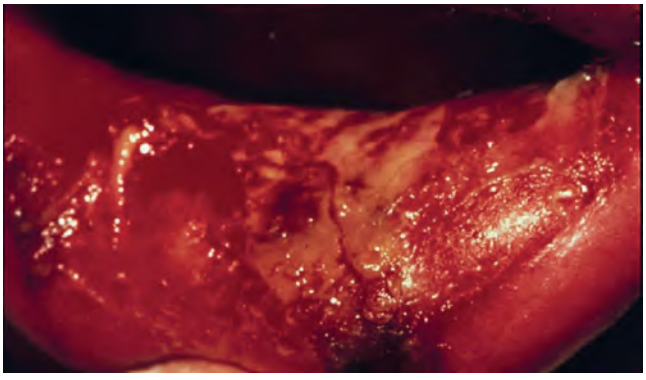

Figure 8-8 Reactivated herpex simplex virus in an immunocompromised hematopoietic stem cell transplant patient can be extensive and fatal. The compromised mucosal and circulating immune defenses result in a rapidly progressing, painful and sometimes fatal systemic viral infection. Fortunately, antiviral prophylaxis or treatment with thymidine kinase inhibitors such as acyclovir or its derivatives is highly efficacious. Drug-resistant herpes simplex is an infrequent occurrence. *Source:* Photo courtesy of M. M. Schubert: Quintessence 2019.[69]

As with all infections in this population, early diagnosis is essential in order to initiate prompt, directed treatment. Viral culturing remains the gold standard. Other types of testing, such as direct immunofluorescence, immunoassay, and shell vial testing, may be useful in context of producing more rapid results.

Oral Candidiasis

Pseudomembranous oral candidiasis, as with high-dose chemotherapy patients who did not undergo stem cell rescue, can occur in settings of compromised mucosal and salivary defenses (Figure 8-9). Other types of fungal infection can also occur including lesions caused by *Aspergillus*, *Mucormycosis*, and *Rhizopus* spp. Culturing and/or biopsy of these latter lesions are essential for diagnosis in that the lesions may mimic clinical appearance of nonyeast toxicities in patients receiving HSCT.

The reader is also referred to Chapter 20 "Transplantation Medicine" for more detailed discussion of these lesions as well as prevention and management of oral toxicity unique to the HSCT patient population.

TARGETED CANCER THERAPIES

Oral Ulcerations/Stomatitis Induced by Targeted Cancer Therapies

Targeted cancer therapies include monoclonal antibodies and small molecule drugs interfering with specific extra- and intracellular pathways required for tumor progression (Table 8-6). Such pathways include inhibition of growth factor receptors involved in cancer cell proliferation and angiogenesis, by intracellular delivery of small molecules toxic to cancer cells, by inducing apoptosis of cancer cells, or by triggering an immune response resulting in destruction specifically of cancer cells. They continue to be used to treat a broad range of cancers; for example, renal cell carcinoma, nonsmall cell lung cancer, breast cancer, colorectal cancer, squamous cell carcinoma of the head and neck, non-Hodgkin's lymphoma, and leukemia. Oral mucosal toxicity is a relatively frequent adverse effect of selected molecularly targeted cancer therapies, including multitargeted tyrosine kinase inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and PD-1 inhibitors.[3,4,7,48,49]

The clinical manifestation of mTOR inhibitor-induced oral toxicity resembles aphthous stomatitis and is distinct from conventional oral mucositis (Figure 8-10). Depending upon severity of pain, the lesion may result in the need for dose reductions of cancer treatment or delay of treatment. The lesions typically appear within a few days after

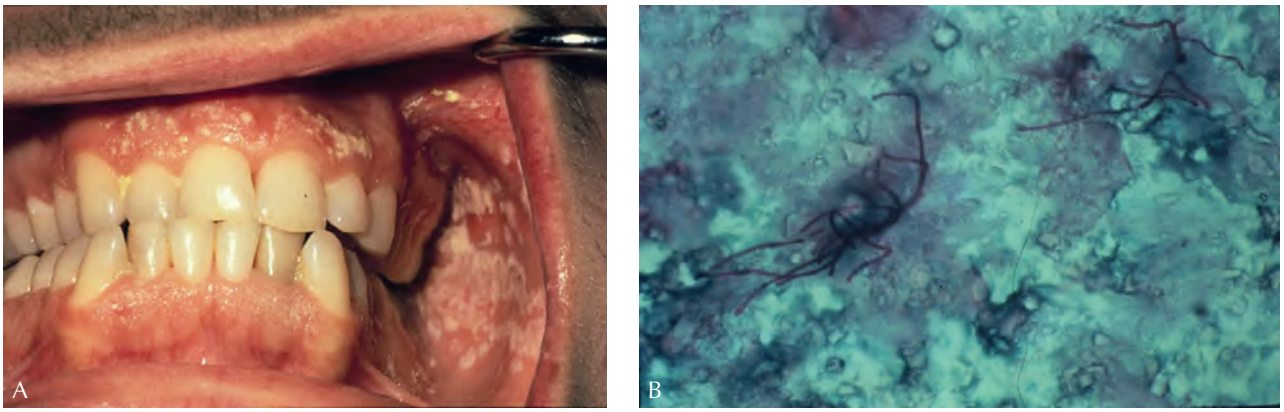

Figure 8-9 Pseudomembranous oral candidiasis can occur in oncology patients secondary to myelosuppression and/or compromised salivary defense mechanisms. (A) A Clinically documented pseudomembranous oral candidiasis in an allogeneic hematopoietic stem cell transplant patient with chronic graft-versus-host disease (GVHD) involving the major salivary glands. The resultant compromised salivary flow rate and composition (e.g., lactoferrin, salivary IgA, transferrin and mucins) can lead to this and opportunistic infections. (B) Cytologic smear demonstrating the dimorphic candidal organism and hyphae. Quintessence 2019.[69]

Table 8-6 Examples of targeted cancer therapies potentially causing oral ulceration/stomatitis.

Drug class	Active drug	Treatment indication
Mammalian target of rapamycin (mTOR) inhibitor	Temsirolimus	Kidney cancer
Epidermal growth factor receptor inhibitor (tyrosine kinase inhibitor)	Erlotinib	Pancreatic and nonsmall cell lung cancer
Multitargeted tyrosine kinase receptor inhibitor	Sunitinib	Kidney cancer, gastrointestinal stromal tumor
Vascular endothelial growth factor inhibitor	Bevacizumab	Colorectal, lung, breast, glioblastoma, kidney, and ovarian cancer
Protein kinase inhibitor	Sorafenib	Kidney, liver, and thyroid cancer

Source: Adapted from Elting et al.[70] and Martins et al. [71]

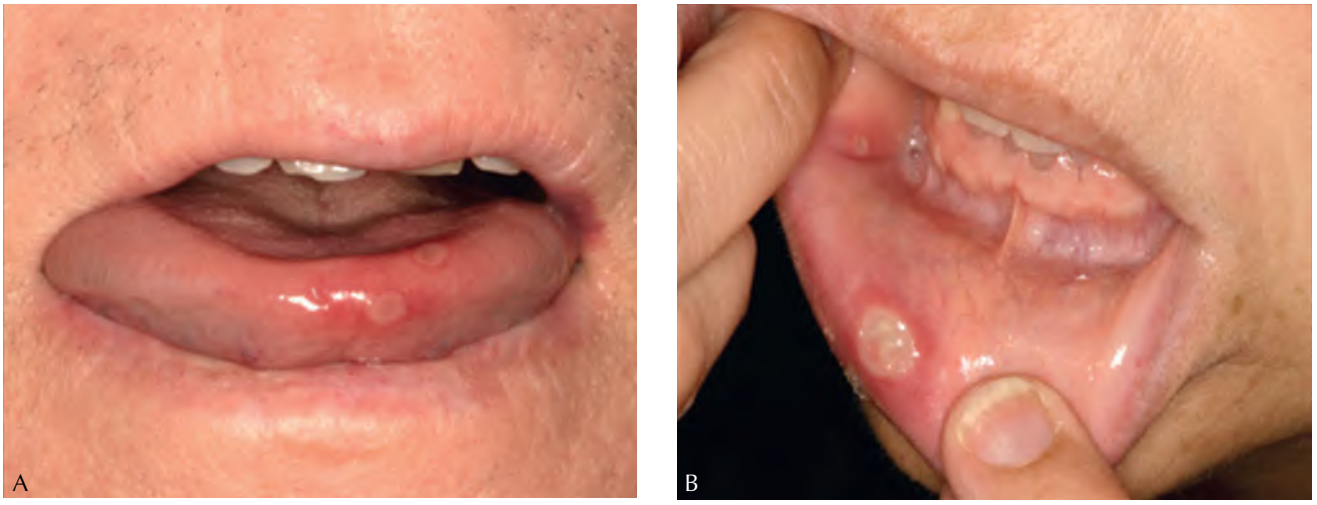

Figure 8-10 Selected mammalian target of rapamycin (mTOR) inihibitors used for treatment of cancer have caused oral mucosal lesions that clinically are uniquely distinct from oral mucositis caused by conventional cancer therapies such as chemotherapy and head and neck radiation. The oral lesions caused by targeted therapies resemble recurrent aphthous ulceration clinically and often respond to topical, intralesional or systemic corticosteroid management. This clinical phenotype is thus quite different from the traditional model of oral mucositis. Further research regarding pathobiology and optimal clinical management including prevention is needed. (A) Tongue, after patient received three 21-day cycles (63 days) of ridaforolimus. (B) Inner lips, in patient who developed mTOR inhibitor-associated stomatitis within 10 days of initiating treatment with everolimus (10 mg once daily) in combination with figitumumab. *Source:* Pilotte 2011.[72]

administration of the first cycle of the drug (a mean of 10 days has been reported (range of 4–25 days) and resolve in approximately 1 week.[4,50] It is a characteristic that the prevalence and severity are less pronounced during following cycles of targeted cancer therapy. The lesions are characterized by painful, distinct, ovoid, superficial, well-demarcated ulcerations with a central grey area surrounded by an erythematous halo and localized on the movable oral/oropharyngeal mucosa while not manifest on the keratinized mucosa of the hard palate, gingiva, or dorsum of the tongue. The pathogenesis is presumed but has not been definitively proven to be similar to recurrent aphthous stomatitis.[4,51]

Patients who develop oral mucosal ulcerations from molecularly targeted cancer therapies may be more prone to develop acneiform dermatitis and nonspecific cutaneous rashes.[4,7]

Among mucosal adverse effects, diarrhea was the most frequently reported in a meta-analysis of selected targeted cancer therapies (i.e., vascular endothelial growth factor inhibitor bevacizumab, epidermal growth factor (EGF) tyrosine kinase inhibitors gefitinib and erlotinib, the dual tyrosine kinase inhibitor lapatinib (interferes with HER2/neu and EGF receptors), multitargeted receptor tyrosine kinase inhibitor sorafenib and sunitinib, and trastuzumab which interferes with HER2/neu receptors).[52]

The clinical management strategy of mTOR inhibitor-associated stomatitis is empirically based on drugs that have been used for the prevention and treatment of aphthous stomatitis and includes topical, intralesional, or systemic corticosteroid therapy depending on severity of the oral lesions.[4]

PATIENTS UNDERGOING HEAD AND NECK RADIATION

Acute Oral Complications

Oral Mucositis

Oral mucositis induced by radiation therapy is the consequence of a complex cascade of biological events involving the epithelium and the submucosa.[6] The extent of oral mucosal damage is strongly related to the radiation dose, volume of irradiated mucosa, and fractionation regimen and is characterized by mucosal atrophy and erythema followed by ulceration and subsequently healing after completing cancer therapy. Oral mucositis is primarily affecting the buccal mucosa, lateral margins and ventral surface of the tongue, soft palate, floor of the mouth, and lips. The ulcerations are commonly colonized with bacteria contributing to the mucositis development. The first clinical signs of oral mucositis in radiation therapy are erythema, epithelial sloughing, and oral discomfort presenting by the end of the first week (days 7 to 14) of a conventional 2 Gy/day, five times a week radiation regimen. Ulceration will typically become clinical evident during the second week of radiation and increase in severity in the subsequent weeks of radiation therapy. The lesions will then usually resolve during the 4 weeks following cessation of the cancer treatment. Oral mucositis results in severe pain and the patient often requires systemic narcotics for pain relief. Oral mucositis also negatively affects nutrition, oral hygiene, and quality of life. In general, the oral lesions will heal within 2 to 4 weeks after radiation; however, some patients will develop late radiation effects of the oral mucosa characterized by epithelial atrophy, telangiectasia, loss of deeper capillary vessels, and fibrosis of the submucosa leaving the oral mucosa permanently prone to infection, in particular oral candidiasis and mechanical trauma (Figure 8-11).

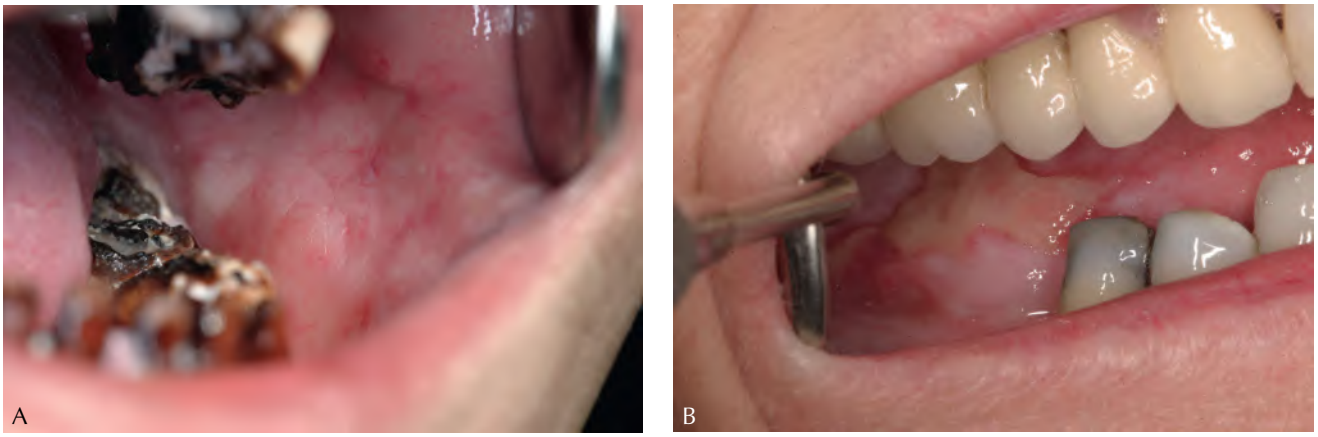

Figure 8-11 Late oral mucosal radiation sequelae. (A) Dryness, telangiectasia, and fibrosis of the left buccal mucosa with pronounced soreness. Conventional radiation therapy 1 year previously for oral cancer. The unstimulated whole saliva flow rate is 0.04 mL/min and the stimulated whole saliva flow rate is 0.16 mL/min. The patient also has rampant caries due to hyposalivation and impaired oral hygiene (complicated by oral pain and trismus). (B) Chronic ulceration of the right margin of the tongue as late radiation sequelae. Intensity-modulated radiation therapy 2 years previously for tonsil cancer on the right side. The patient's mandibular denture had to be adjusted to reduce mechanical friction in the area.

Management of oral mucositis includes oral pain control, basic oral care, prevention and treatment of infection, and nutritional support, see details of basic oral care in the previous section in this chapter Implementation of Systematic Basic Oral Care Protocols for Oncology Patients.[2] See section High-dose Chemotherapy Patients: Oral Mucositis for additional detail regarding management.

Acute and Late Oral Complications

Salivary Gland Hypofunction and Xerostomia

Radiation therapy may induce salivary gland hypofunction (decreased saliva secretion) and xerostomia (a subjective feeling of oral dryness); that is, radiation therapy in head and neck cancer involving the salivary glands within the radiation field, total body irradiation in hematopoietic stem cell transplantation, and radioactive iodine in thyroid cancer.[28] Irradiation of salivary glands in head and neck cancer patients results in a substantial decline in saliva secretion within the first week of radiation therapy with a continuous reduction that may reach scarcely measurable saliva secretion by the sixth week of treatment. A further decline may be noted up to 3 months after completion of radiation therapy (Figure 8-12). However, salivary glands may hold a potential to gradually recover within 1 to 2 years if gland-sparing radiation regimens have been applied, such as intensity-modulated radiation therapy, and if it has been achievable to keep the radiation dose to the gland tissue below thresholds of ~26 Gy to the parotid gland and ~39 Gy to the submandibular gland.[28]

Xerostomia is the most common late adverse effect of radiation therapy in head and neck cancer patients with an immense negative impact on quality of life affecting general comfort and oral functions of speech, taste, and chewing/swallowing, which may further result in inadequate food intake and difficulties with social interaction. Thus, to increase coping mechanisms, it is of great importance to the patient to be informed of the expected acute and late salivary gland physiologic changes and the timeline of late radiation sequelae, in particular to prepare the patient for the further deterioration of salivary gland function initially after the end of cancer therapy.

Management of salivary gland hypofunction and xerostomia is symptomatic by stimulation of a residual salivary gland secretory capacity or by use of water, bland rinses, or saliva substitutes, see the section on "Oral Hydration".[25,27,28] For evidence-based clinical practice guidelines for management of salivary gland hypofunction and xerostomia, see Chapter 9, "Salivary Gland Diseases". Furthermore, salivary gland hypofunction implies a high risk of dental caries, attrition, abrasion, and erosion (Figure 8-13), oral candidiasis (Figure 8-14), and increased mucosal sensitivity and risk for mucosa/mucosal trauma (Figure 8-11).

Oropharyngeal Candidiasis

Oral and oropharyngeal candidiasis are common in patients undergoing head and neck radiation with a prevalence of oral candidiasis of 37% during treatment.[13] The most common cause of oral candidiasis is *Candida albicans* with clinical presentations as: (1) erythematous candidiasis manifest as red inflamed areas of the mucosa; (2) pseudomembranous candidiasis (thrush) manifest as removable white curd-like pseudomembranes; (3) chronic hyperplastic candidiasis manifest as hyperkeratotic white patches, which cannot be removed; and (4) angular cheilitis manifest as erythema, fissuring, and ulceration of the labial commissures (Figure 8-14). Oral candidiasis is often associated with a burning mucosal sensation

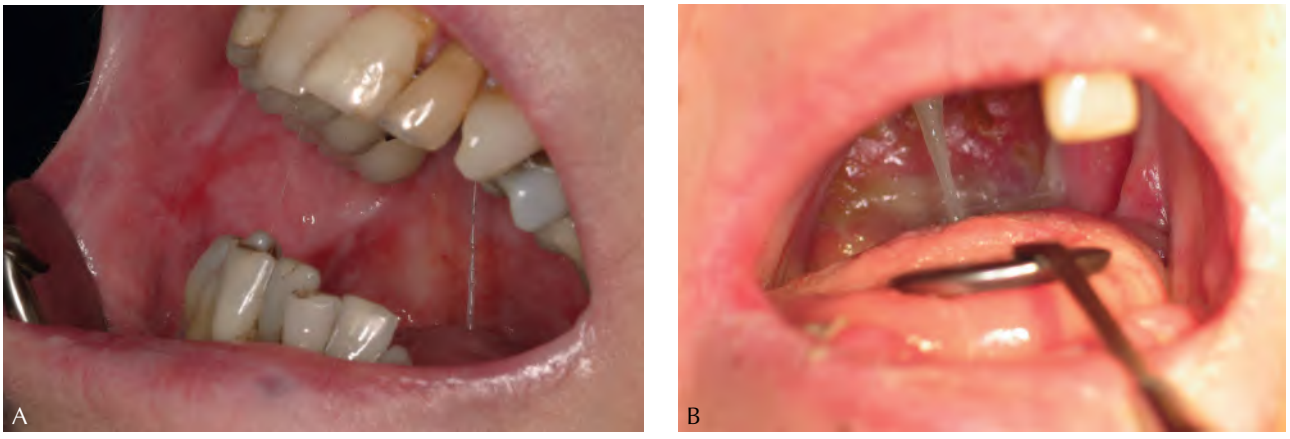

Figure 8-12 Hyposalivation and viscous saliva following radiation therapy. (A) Unilaterally irradiated for tonsil cancer 2 years previously, unstimulated whole saliva flow rate 0.01 mL/min, stimulated whole saliva flow rate 0.23 mL/min, the saliva is thick and sticky which is a hallmark of salivary gland dysfunction during and after radiation therapy. (B) Intensity-modulated radiation therapy for cancer of the left maxillary sinus, unstimulated whole saliva flow rate 0 mL/min, stimulated whole saliva flow rate 0.20 mL/min. The saliva is extremely thick and sticky and crusts of dried saliva constituents are seen at the back of the oropharynx causing immense discomfort to the patient.

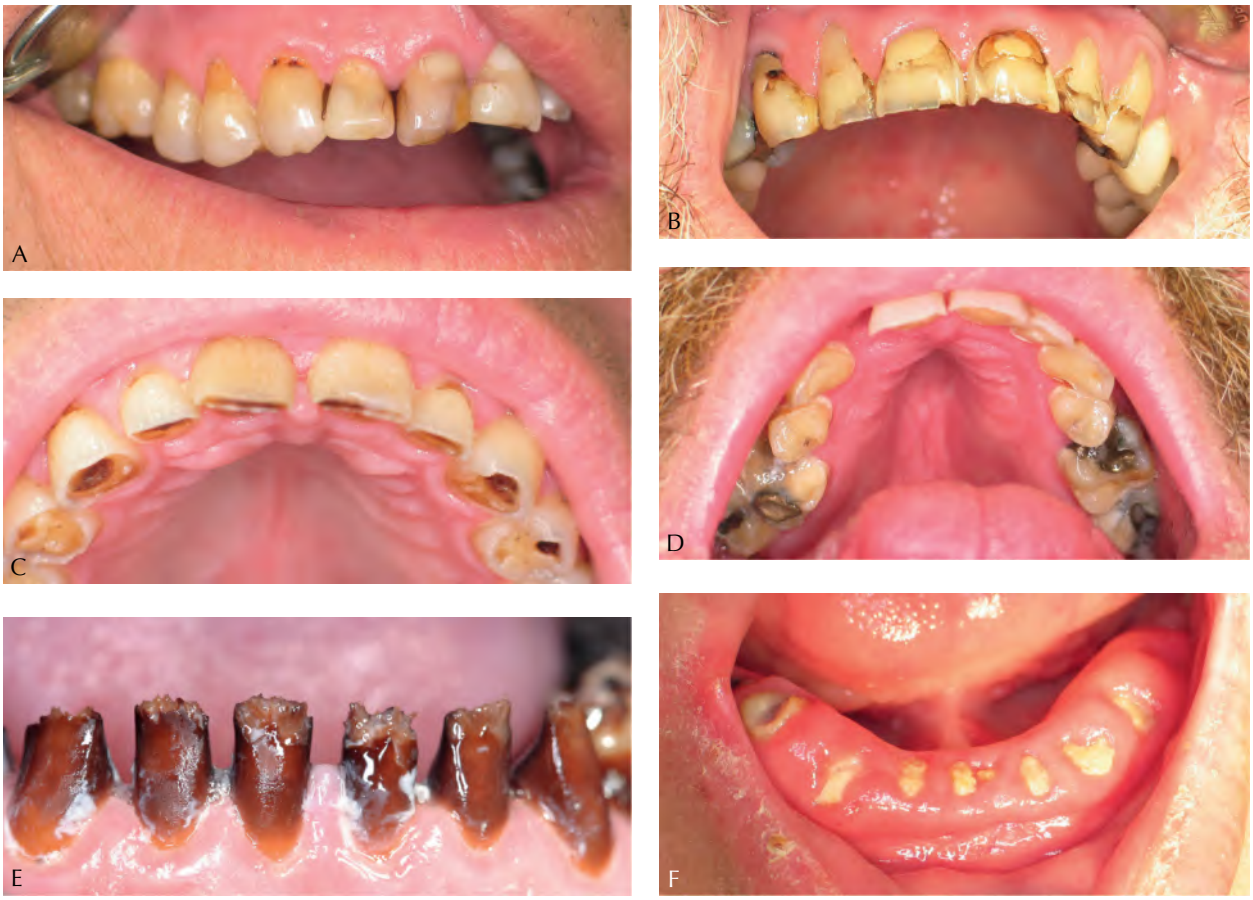

Figure 8-13 Characteristic clinical manifestations of dental caries, attrition, abrasion, and erosion in patients with radiation-induced hyposalivation. (A and B) Dental caries along the cervical area of the incisors and canines. This type of lesion often spreads circumferentially in the cervical area of the tooth and may result in amputation of the tooth crown if profound carious lesions develop. (C and D) Generalized demineralization (less translucent and whitish color of the teeth) with rapid and pronounced attrition/abrasion/erosion of the incisal, occlusal, and palatinal surfaces of the teeth. (E) Complete loss of enamel and extensive demineralization of the dentine with heavy brown discoloration of the teeth. Notice the caries localization to the lower anterior teeth which are normally least prone to dental caries. (F) Complete carious destruction of the tooth crowns. The roots have been treated endodontically and left in the jaw to avoid surgical intervention and prevent osteoradionecrosis. Also note the dry lips.

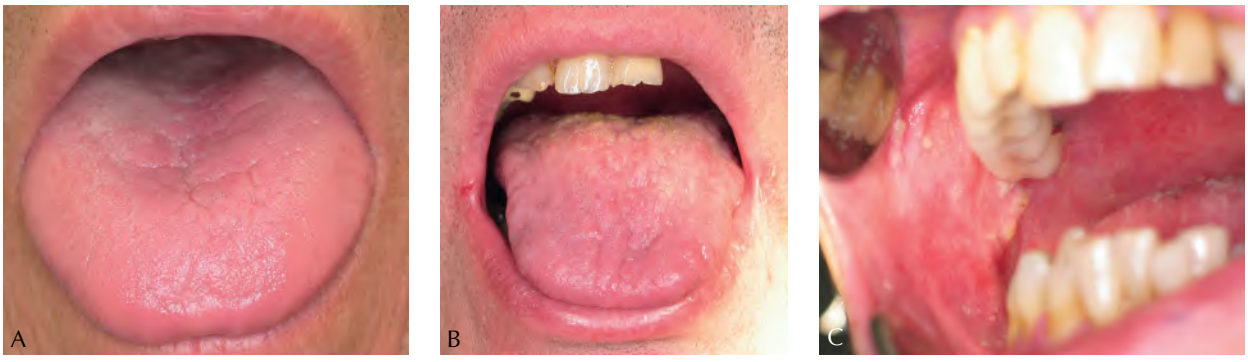

Figure 8-14 Oral candidiasis following radiation therapy. For all the patients shown periodic acid-Schiff (PAS) stained smear tests were positive for Candida blastospores and hyphae. Furthermore, all the patients have radiation-induced hyposalivation and xerostomia. (A) Erythematous oral candidiasis. The dorsum of the tongue is depapillated, fissured, and with slight central erythema. The patient describes a stinging sensation from the tongue. (B) Erythematous oral candidiasis and angular cheilitis caused by *Candida albicans*. The dorsum of the tongue is depapillated, fissured, and erythematous and the corners of the mouth are erythematous, fissured, and ulcerated. The patient describes a burning sensation from the tongue. (C) Recurrent pseudomembraneous oropharyngeal candidiasis 2 years after radiation therapy for tonsil cancer. The oral mucosa is erythematous and covered with white plaques that can be scraped off. The patient suffered from dysphagia which resolved when prophylactic antifungal treatment was established.

and taste changes (e.g., metallic taste). During radiation therapy, manifestations of erythematous and pseudeomembranous candidiasis are each common. They should be considered within the differential diagnosis of oral mucositis or as a comorbidity contributing to the symptom profile of oral mucosal injury.[37,53]

In general, topical agents are considered preferable to systemic agents due to lower risk of side effects and drug interactions; however, compliance can be compromised with administration of topical agents several times a day during active cancer treatment compared to once a day administration of systemic agents. Also, studies present an inconsistent picture of the efficacy of topical agents in patients receiving cancer therapy.[13] Additional considerations of antifungal treatment decision-making in the radiation head and neck cancer population are salivary gland dysfunction and oral mucositis/chronic mucosal radiation sequelae, since administration of antifungal treatment as troches/pastilles requires saliva to dissolve and can be traumatic to a vulnerable oral mucosa. Systemic agents may be limited by their side effects and drug interactions while the emergence of resistant species is also an important concern, in particular for antifungal prophylaxis.[13,54] For further details on oral candidiasis and management guidelines, see Chapter 4 "Red and White Lesions of the Oral Mucosa."

Oral Bacterial Infections

Patients irradiated for head and neck cancer are prone to oral mucosal infection/gingivitis due to salivary gland hypofunction, trismus, oral mucositis/chronic mucosal radiation sequelae, oral pain, and compromised oral hygiene. Additionally, dental caries is a disease of infectious character and head and neck cancer patients are at high risk of rampant caries.[20] Bacterial infections involving the bone, such as periodontal infection and periapical infection, increase the risk of osteoradionecrosis (see section Osteoradionecrosis).[55]

Thus, prevention of oral bacterial infection is directed towards reducing the microflora, and dental caries should be managed by supplemental administration of high-dose fluoride; see the section Oral Decontamination. In patients irradiated for head and neck cancer and suffering from salivary gland hypofunction, the major salivary glands may become acutely infected (bacterial sialadenitis) due to retrograde bacterial colonization through the gland ducts.[56]

Oral and Perioral Viral Infections

The risk of oral and perioral reactivation or *de novo* viral infections is low in patients undergoing radiation therapy for head and neck cancer. Herpes simplex virus infection is the most common viral infection followed by other Herpes viridae; for example, varicella zoster virus, Epstein-Barr virus, and cytomegalovirus.[14,15] There is a significant increase in prevalence if treated with combined chemotherapy and radiation therapy.[14,15]

For further details on viral infections and management guidelines, see Chapter 3 "Ulcerative, Vesicular and Bullous Lesions" and Chapter 21 "Infectious Diseases."

Dysgeusia (Taste Alterations)

Dysgeusia often occur with head and neck radiation therapy and chemotherapy and can appear as hypogeusia (decreased taste sensation), dysgeusia (distorted taste sensation; e.g., bitter, metallic, sour, salty, or unpleasant) or hypergeusia (increased taste sensation).[17] Dysgeusia may onset within the first week of head and neck radiation due to a direct toxic effect on taste cells further aggravated by salivary gland hypofunction, oral infections, compromised oral hygiene, drug intake, zinc deficiency, gastrointestinal reflux, or as sequelae from cancer surgery and may not resolve until months after cancer treatment.[57,58] Some patients may experience permanent dysgeusia.[59]

Halitosis

Halitosis (oral malodor) may be due to compromised oral hygiene during cancer therapy. Further aggravating oral factors can be accumulation of food debris, oral mucositis, oral candidiasis, periodontal infection, salivary gland hypofunction, or tumor growth/tissue necrosis. Systemic causes of halitosis can be gastrointestinal disease, hepatic disease, renal disease, or upper airway/lung infections. Halitosis can be reduced by comprehensive basic oral care procedures with an emphasis on mechanical tongue rinsing, supplemented by antiseptic mouthwashes and oral malodor interventions.[60]

Late Oral Complications

Trismus

Trismus (restricted mouth opening) is frequent in patients irradiated for head and neck cancer and may severely impact food intake, speech, and compromise oral hygiene. Radiation therapy can induce fibrosis of the temporomandibular joint and oral soft tissues depending on the inclusion in the radiation field and this can be further aggravated by tumor growth into the temporomandibular joint/masticatory muscles and surgical procedures. Radiation-induced trismus can onset from the end of radiation therapy or any time (e.g., years) following cancer therapy. The appearance and severity is rather unpredictable and thus it is recommended that an attempt is made to prevent trismus with daily exercise therapy, although the evidence base for this is inconclusive.[18,61,62]

Osteoradionecrosis

Osteoradionecrosis (ORN) is defined as bone death secondary to radiotherapy and is characterized by a nonhealing area of exposed bone.[63] Patients who have received high-dose radiation therapy to the head and neck are at lifelong risk for the lesion, the risk being directly related to the radiation

dose to the bone, with an overall risk of approximately 15% (Figure 8-15). ORN most frequently involves the mandible compared with the maxilla. Clinical manifestations include pain, sensory disturbances, infection, and fistulae.

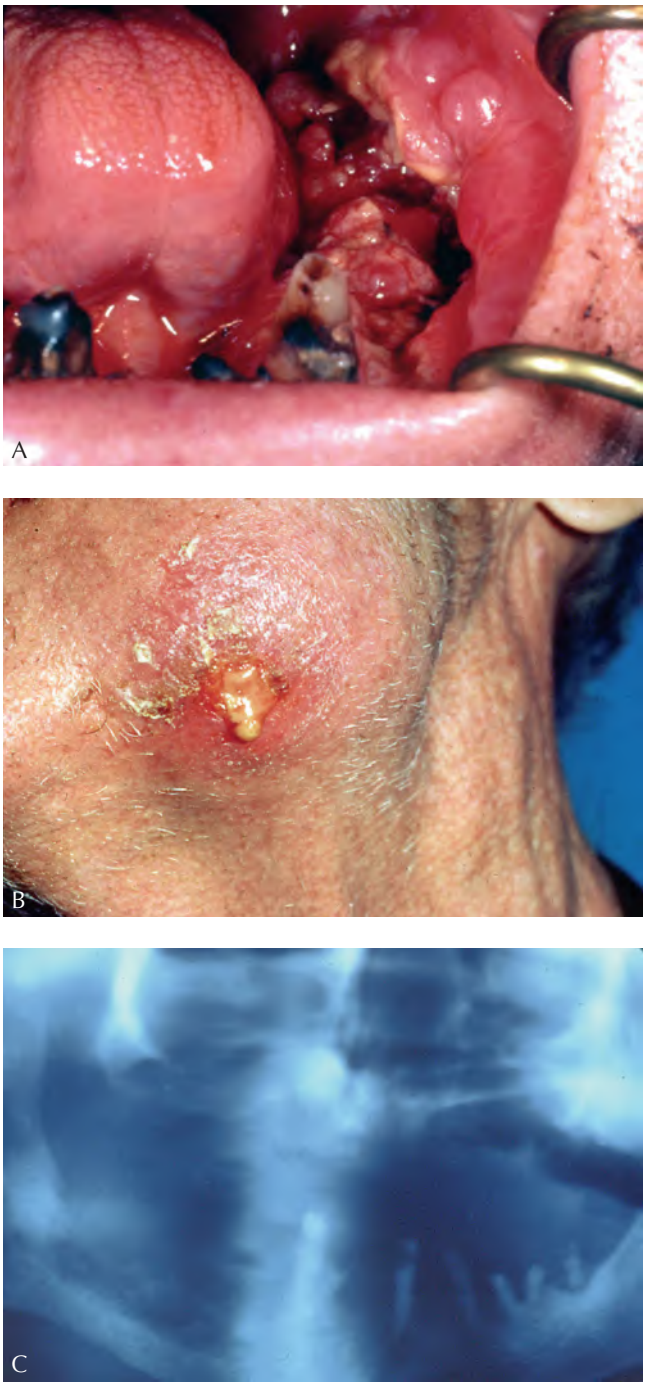

Figure 8-15 Osteoradionecrosis of the left mandible. (A) Root tips were present several months after completion of high-dose external beam radiation to the left mandible. (B) Facial skin lesion exhibiting purulent drainage. (C) Panoramic radiograph demonstrating findings consistent with extensive left mandibular bone destruction. *Source:* Photos courtesy of L. Assael.

Management of ORN is based on prevention that begins with comprehensive oral and dental care before radiation therapy and close follow-up postradiation. If smaller lesions form, management is conservative with limited surgical intervention and antibiotics, while advanced or treatment refractory lesions will need large segments of necrotic bone removed. The cure rate associated with minimally extensive ORN by conservative therapy is approximately 50%, while the cure rate of surgical approaches when conservative therapy has failed is approximately 40%.[63]

Hyperbaric oxygen therapy has been historically recommended to prevent or treat ORN, but clinical efficacy is inconclusive. Hyperbaric oxygen therapy is thus not currently routinely used at many centers.[64]

THE ONCOLOGY PATIENT RECEIVING BONE-MODIFYING AGENTS

Patients with skeletal metastatic disease (e.g., multiple myeloma) may benefit from use of a bone-modifying agent (Figure 8-16; Figure 8-17).[23,65] There are three different classes of these agents, all designed to reduce of skeletal bone fracture:

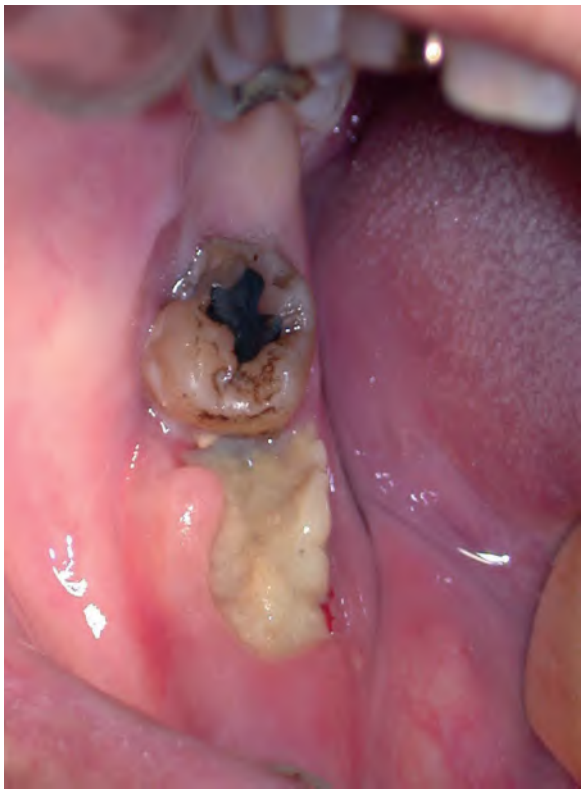

Figure 8-16 Medication-related osteonecrosis of the jaw (MRONJ). *Source:* Courtesy of Dr. Eduardo Fregnani.

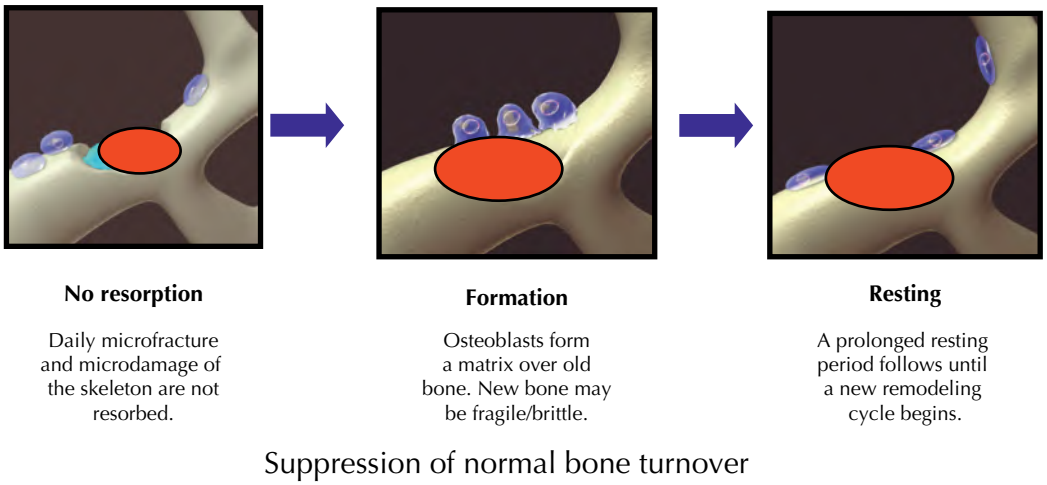

Figure 8-17 Inhibition of bone remodeling by bisphosphonates. *Source:* Photo courtesy of C. Migliorati.

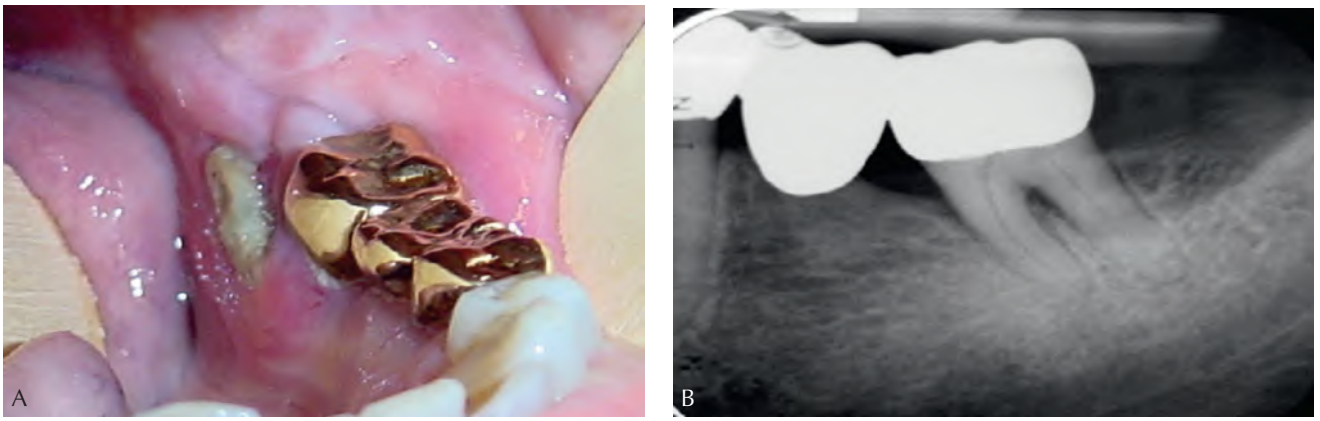

Figure 8-18 Osteonecrosis of the jaw in cancer patient receiving a bone-modifying agent. (A) Exposed bone on lingual aspect of posterior left mandible. (B) Periapical radiograph demonstrating evidence of diffuse osseous destruction. *Source:* Photos courtesy of C. Migliorati.

- bisphosphonates
- denosumab
- antiangiogenics.

Medication-related osteonecrosis of the jaw (MRONJ) can develop in a small subset of these patients (Figure 8-18; Table 8-7). Despite differences in mechanism of action across these three classes, risk for development of MRONJ is comparable (approx. 1–2%) in the oncology population. Documentation of the MRONJ lesion in a patient is established when all three of the following criteria are met:[23]

- current or previous treatment with a bone-modifying agent or angiogenic inhibitor;
- exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region and that has persisted for longer than eight weeks; and
- no history of radiation therapy to the jaws or metastatic disease to the jaws.

It is important to note, however, that clinically exposed oral bone may not be evident in the early stage of MRONJ.

Although actual incidence in the clinical setting is low, resolution of the lesion can be protracted and associated with considerable oral morbidity in some patients. Patients about to be placed on a long-term protocol of one of these agents should undergo oral evaluation and dental treatment of lesions that may in the future contribute to risk for development of MRONJ.[66] Examples of such pre-existing oral lesions include advanced dental caries, moderate–severe periodontal disease, and periradicular lesions. These lesions should ideally be eliminated prior to initiation of the bone-modifying regimen.

Treatment for MRONJ depends upon staging of the lesion (Table 8-8).[23,65,67] Current literature suggests that conservative, nonaggressive therapy may be most beneficial in management of early stage MRONJ. As with any dental intervention, it is essential that thorough discussion and informed consent documentation be performed with the patient prior to initiating MRONJ management (Table 8-9).

Table 8-7 Key differences between bisphosphonates and denosumab as utilized in oncology practice.

Medications	Action	Medical Use
Bisphosphonates Alendronate Risedronate Pamidronate Zoledronic Acid	Osteoclast inhibitor via mevalonate pathway	Osteoporosis Bone metastasis Multiple myeloma Antitumor
Denosumab	Receptor activator of nuclear factor kappa-beta ligand (RANK-RANKL) pathway inhibitor	Osteoporosis Bone metastasis
Antiangiogenics Bevacizumab Sunitinib Sorafenib	Vascular Endothelial Growth Factor (VEGF) inhibitors	Advanced tumors

Source: C. Migliorati.

Table 8-8 American association of oral and maxillofacial surgeons staging criteria for osteonecrosis of the jaw.

Category	Criteria
At risk	Clinically normal, asymptomatic patients who have received antiresorptive therapy
Stage 0	No clinical evidence of exposed bone, but presence of non-specific symptoms or clinical and/or radiographic abnormalities
Stage 1	Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone associated with pain and/or signs of infection in the region of bone exposure with or without purulent drainage
Stage 3	Exposed and necrotic bone in patients with pain, infection, and at least one of the following: • exposure and necrosis extending beyond the local alveolar tissues; • radiographic evidence of osteolysis extending to the inferior mandibular • border or the maxillary sinus floor; • pathologic fracture; • oro-antral, oro-nasal or oro-cutaneous communication

Source: Ruggiero et al.[67].

Table 8-9 Treatment of medication-related osteonecrosis of the jaw (MRONJ).

• Patients with MRONJ should be managed by professionals with experience in managing such lesions.
• Use of systemic antibiotics is recommended for patients with active infection and or clinical paresthesia.
• Home oral hygiene maintenance is essential; utilize oral rinses with chlorhexidine as needed.
• Conservative protocol, with periodic clinical evaluation of the progress of disease in MRONJ stages 1 and 2
• Pain management as needed
• Surgical intervention in advanced cases (stage 3, American Association of Oral and Maxillofacial Surgeons Staging Criteria) and in non-responding lesions

Source: C. Migliorati.

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9

Salivary Gland Diseases

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INTRODUCTION

The most common presenting complaints of a patient with salivary gland disease are oral dryness (xerostomia) or a glandular swelling or mass. This chapter discusses how to evaluate a patient with these and other signs and symptoms suggestive of salivary gland disease, including clinical examination techniques and imaging. Diseases, disorders, and some neoplasms affecting the salivary glands are introduced as well as management of xerostomia, hyposalivation, and sialorrhea.

Optimal function of the salivary glands results in the production of adequate amounts of saliva: a complex and unique biologic fluid with myriad functions. The importance of saliva in maintaining oral, dental, and general health cannot be understated. It provides lubrication to the oral and oropharyngeal mucosae, protects dental and mucosal surfaces, facilitates speech, mastication, and swallowing, and is involved in taste and digestion, among other functions. Hyposalivation, or even the perception of a lack of saliva, can have a significant impact on quality of life. Quantified salivary hypofunction or a significant change in the composition of saliva can increase the risk of oral diseases such as dental caries, dental erosion, and fungal infections.

SALIVARY GLAND ANATOMY AND PHYSIOLOGY

Saliva is produced by three paired major salivary glands (the parotid, submandibular, and sublingual glands), and numerous minor salivary glands (Figure 9-1). The parotid glands, the largest of the major salivary glands, are located on the lateral aspects of the face overlying the posterior surface of the

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

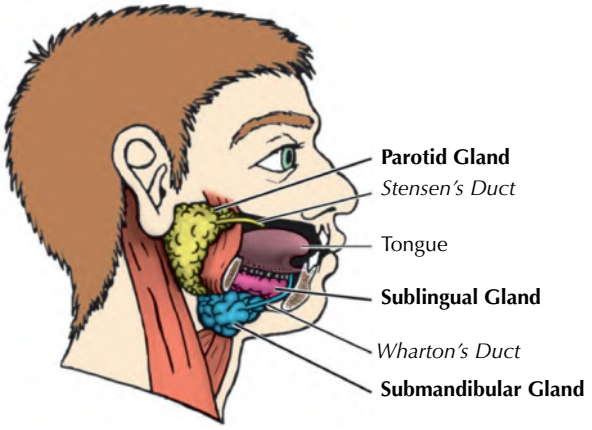

Figure 9-1 Diagrammatic representation of the major salivary glands and associated ducts.

mandible, anteroinferiorly to the auricle. The parotid gland is often described as being divided into superficial and deep lobes by the intraparotid facial nerve and its branches. Encapsulation of lymphoid tissue during embryogenesis results in the presence of intraglandular lymphoid tissue; a feature not seen in the other major salivary glands and one that results in a predilection for development of parotid gland lymphomas, most notably in patients with Sjögren's syndrome.

The submandibular glands are a pair of organs shaped like flattened hooks that reside in the submandibular triangle. Although they are often described as being a pair of glands, the two parts are contiguous forming a "U" shape enveloping the posterior border of the mylohyoid muscle.

Each of the paired sublingual glands is composed of a major sublingual gland and approximately 8 to 30 minor sublingual glands. The glands lie on opposite sides of the lingual frenulum, superior to the mylohyoid muscle. Bimanual palpation, using one hand intraorally on the floor of the mouth and the other hand extraorally below the mandible, is necessary to evaluate these glands adequately.

There are an estimated 450 to 1000 minor salivary glands distributed primarily in the oral cavity and oropharynx, but they may be found anywhere along the aerodigestive tract as well as in the sinonasal cavity and middle ear. The minor salivary glands are named for the sites they occupy (e.g., labial, buccal, lingual, palatal, retromolar) and contribute approximately 8% to 10% of the total volume of saliva.[1]

There are also three sets of minor salivary glands of the oral tongue: the glands of Weber, found along the lateral borders of the tongue; the glands of von Ebner, surrounding the circumvallate papillae; and the glands of Blandin and Nuhn (also known as the anterior lingual glands), found in the musculature of the anterior ventral tongue. Distinctive mucoceles may arise in the glands of Blandin and Nuhn, highlighting their unique anatomic location.

Salivary glands can be classified based on the dominant saliva-producing acinar cell type: serous, mucous, or a mix of serous and mucous cells. Serous cells produce a watery, enzyme-rich saliva, while mucous cells secrete a more viscous fluid with plentiful salivary glycoproteins known as mucins. Salivary mucins expressed from the submandibular and minor salivary glands act as lubricants and help to form a selectively permeable barrier of mucosal membranes. Their presence helps maintain tissue hydration and an overall sense of comfort.

The parotid gland is composed primarily of serous cells; the submandibular gland is a mix of mucous and serous types, and the sublingual and minor salivary glands are of the mucous type. The glands of Weber are mucus-secreting, the glands of von Ebner are purely serous, and the glands of Blandin and Nuhn are of mixed type.

Parotid gland saliva is secreted through Stensen's ducts which emerge from the glands, traverse the buccal fat pad superficial to the masseter muscles, and pierce the buccinator muscles to open at papillae in the vicinity of the maxillary first or second molars (Figure 9-2). Stensen's duct is, on average, between 4 and 6 cm in length and has a diameter between 2.0 and 2.5 mm with the narrowest portions typically appearing at the papilla and where it pierces the buccinator.[2] The masseteric bend, where the duct curves around the anterior border of the masseter, may present a navigational challenge; for example, during an endoscopic procedure.

Saliva from each submandibular gland is secreted through a submandibular (Wharton's) duct. Each Wharton's duct is approximately 5 cm in length and between 1 and 3 mm in diameter. Along its course, two bends are encountered; a typically obtuse angle is formed as the duct curves around the mylohyoid muscle, resulting in a propensity for stone formation and obstructive kinks.[3] A second bend occurs adjacent to the duct punctum just before the duct opens into the oral cavity at the sublingual caruncles on either side of the lingual frenulum (Figure 9-3). As Wharton's duct

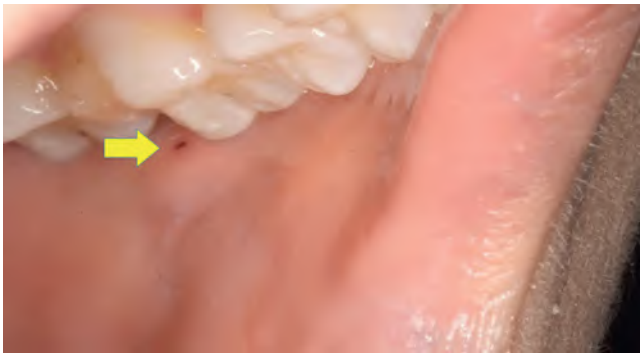

Figure 9-2 Arrow indicating opening of Stensen's duct on the left buccal mucosa.

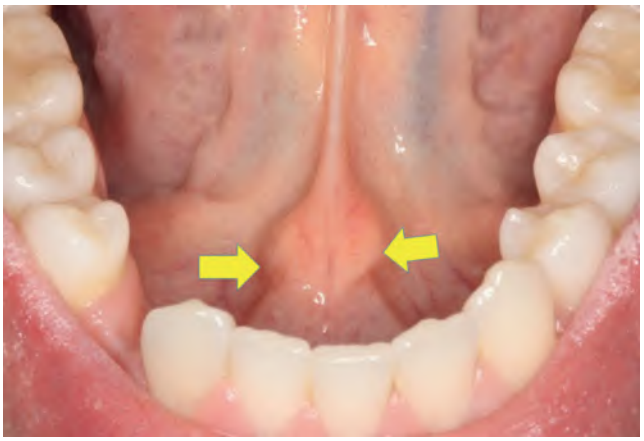

Figure 9-3 Arrows indicating openings of Wharton's ducts on the floor of mouth.

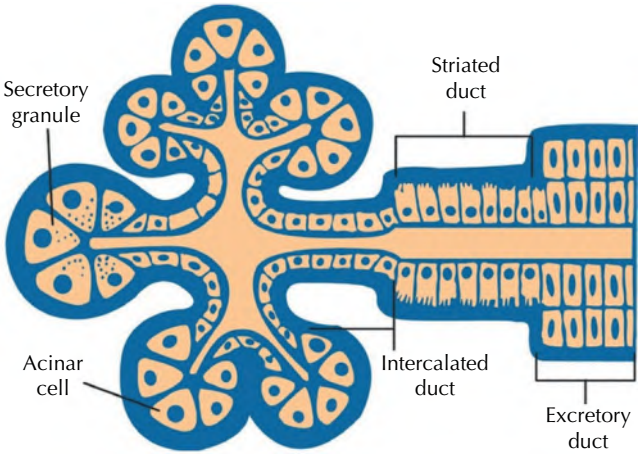

Figure 9-4 Diagrammatic representation of salivary gland acini and ducts.

traverses the glandular parenchyma, it demonstrates an abrupt transition in diameter, in contrast to that of the parotid gland which shows a more gradual decrease.

Saliva from the anterior, major portion of each sublingual gland drains through the sublingual (Bartholin's) duct into the submandibular (Wharton's) duct, while saliva from the smaller, posterior portion of the sublingual glands drains directly onto the floor of the mouth via multiple smaller ducts of Rivinus. The minor salivary glands secrete their mucinous product onto the mucosa through short ducts. A minor salivary gland may share an excretory duct with an adjacent minor salivary gland or may have a duct of its own.

Histologically, the major salivary glands are composed of acinar (secretory cells) and ductal cells arranged like a cluster of grapes on a stem. The clustered acinar cells (the "grapes") make up the secretory end pieces, while the ductal cells (the "stems") form an extensively branching system that modifies and transports the saliva from the acini into the oral cavity. There are three types of ductal cells: intercalated, striated, and interlobular (Figure 9-4).

Production of saliva involves water transport from the serum into the terminal portion of the acinar cell followed by selective reabsorption of sodium and chloride and the secretion of potassium and bicarbonate to produce a hypotonic solution. Upon stimulation of salivary flow, sodium, chloride, and bicarbonate concentrations increase while potassium decreases via ion exchange in the ductal system. Salivary proteins are contributed mostly from the acinar cells.[4]

Whole saliva (WS; the mixed fluid contents of the oral cavity) is composed of more than 99% water and less than 1% proteins and salts. It is hypotonic relative to blood plasma and contains secretions from the major and minor salivary glands along with variable amounts of gingival crevicular fluid, microorganisms, food debris, exfoliated mucosal cells, and mucous. Salivary proteins are numerous and serve a variety of functions including digestion (e.g., α-amylase, lipase, proteinases, DNase and RNase), and protection (e.g., immunoglobulins, lysozyme, lactoferrin, lactoperoxidase, and mucins).

Normal daily production of WS ranges from 0.5 to 1.5 L. The composition of WS follows a circadian rhythm: at night and in the resting state, the submandibular and sublingual glands are the main contributors with some saliva being produced by the minor salivary glands.[5] At stimulation, the parotid and submandibular glands are responsible for the majority of saliva production with minor gland secretions accounting for less than 10% of the volume. Stimulation of salivation typically occurs between 10% and 20% of the day, influenced by olfactory, gustatory, and mechanical stimuli.

The secretion of salivary fluid and salivary proteins is controlled by both the sympathetic and parasympathetic subsystems of the autonomic nervous system. Stimulus for fluid secretion is transmitted via muscarinic-cholinergic receptors, which release acetylcholine, inducing the secretion of saliva by acinar cells. The stimulus for salivary protein secretion is transmitted via sympathetic β-adrenergic receptors that release noradrenaline.[6]

Electrolyte concentrations and volume of saliva may be influenced by a number of factors including circadian rhythm, various stimuli, and number of functional secretory units. Factors that may increase salivary flow include taste and olfactory stimuli, mechanical stimulation (chewing), pain, hormonal changes, aggression, and sympathomimetic and parasympathomimetic drugs. Menopause-related hormonal changes, stress, antiadrenergic and anticholinergic drugs will decrease salivary flow rate.[7] A loss of acini, seen in a number of clinical conditions, particularly in Sjögren's syndrome, also results in decreased saliva production.

Whether salivary flow diminishes with normal aging has been the subject of much debate. Many studies suggest age-related changes in either volume or salivary constituents, while others have found no related changes. Postmortem histologic studies show that with aging, parenchymal tissue of the salivary glands undergo replacement with fat, connective tissue, and oncocytes. Acinar atrophy, ductal dilatation, and inflammatory infiltration have also been observed with aging in normal subjects.[8]

In reports that assert that in healthy, unmedicated adults, salivary production remains stable with age despite the loss of acinar cells, it is hypothesized that a secretory reserve capacity exists and that disease, surgery, radiotherapy, and chemotherapy, for example, tax this reserve resulting in compromised function.[9,10] A gradual, age-related loss of this reserve capacity may explain the greater magnitude of effect from conditions adversely affecting saliva production in older individuals compared to their younger counterparts.

DIAGNOSIS OF THE PATIENT WITH SALIVARY GLAND DISEASE

The most common complaint associated with salivary gland disease is xerostomia, denoting subjective mouth dryness. Hyposalivation refers to a quantified reduction in salivary flow rate which may or may not be accompanied by xerostomia. Similarly, xerostomia may or may not be associated with hyposalivation and can be the result of a change in salivary composition. The term "salivary gland dysfunction" is commonly used to indicate decreased salivary flow (hyposalivation) or other quantifiable alteration in salivary performance. Hypersalivation (sialorrhea or ptyalism) refers to an increase in production of saliva and/or a decrease in oral clearance of saliva.

Since the causes of xerostomia and salivary gland dysfunction are numerous, a systematic approach to establish a diagnosis is necessary. Salivary gland dysfunction may be the result of a systemic disorder and therefore early recognition and accurate diagnosis may be of great benefit to an individual's general health and well-being.

Where salivary gland dysfunction is suspected, a thorough examination to identify the cause of the condition is warranted. Patients should be queried regarding the severity and duration of their complaint, inciting events, whether the condition is progressive or intermittent, known relieving and exacerbating factors, possible circadian associations, and effect on quality of life. Patients should also be asked about dryness affecting other areas, especially the eyes, nose, and other mucosal surfaces.

An initial evaluation should also include a detailed inquiry into associated symptoms, medical and dental history, medications, and dietary habits. A head/neck/oral examination and an assessment of salivary function involving quantification of unstimulated and stimulated salivary flow should be performed (see section: Sialometry). Additional techniques that may be indicated are analysis of salivary constituents, imaging, biopsy, and clinical laboratory assessment, some of which are described below in greater detail.

Some causes of salivary gland hypofunction include xerogenic medications (including many antidepressants, anticholinergics, antispasmodics, antihistamines, antihypertensives, sedatives, diuretics, and bronchodilators) and other xerogenic agents (e.g., caffeine, alcohol, cigarette smoking), head and neck radiation (i.e., external and internal beam radiation therapy), systemic disease (e.g., diabetes mellitus), salivary gland masses, psychological conditions (e.g., depression, anxiety), malnutrition (e.g., bulimia, dehydration), and autoimmune disease (e.g., Sjögren's syndrome).[11] A list of some differential diagnoses for salivary gland dysfunction is outlined in Table 9-1.

Table 9-1 Partial list of differential diagnoses for salivary gland dysfunction.

Autoimmune
Chronic graft-versus-host disease
Sjögren's syndrome
Developmental
Salivary gland aplasia and hypoplasia
Iatrogenic
Botulinum toxin injection
External beam radiation
Internal radiation (e.g., Radioactive iodine [^{131}I])
Postsurgical (e.g., adenectomy, ductal ligation)
IgG4-related disease (i.e., Küttner tumor; Mikulicz's disease)
Infectious
Bacterial: *Staphylococcus aureus,* MRSA, *Haemophilus influenzae*
Viral: CMV, HIV, hepatitis C, paramyxovirus
Inflammatory
Granulomatous: Tuberculosis, sarcoidosis
Medication-associated
Neoplastic
Benign and malignant salivary gland tumors
Non-neoplastic
Sialolithiasis
Systemic
Anorexia nervosa, chronic alcoholism, diabetes mellitus,

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; CMV, cytomegalovirus; HIV, human immunodeficiency virus

Symptoms of Salivary Gland Dysfunction

Symptoms of salivary gland hypofunction are related to decreased fluid in the oral cavity affecting mucosal hydration and oral functions. Patients may complain of dryness of all the oral mucosal surfaces, including the lips and throat, and difficulty chewing, swallowing, and speaking due to dryness. Other associated complaints may include oral pain, an oral burning sensation, chronic sore throat, and pain on swallowing (odynophagia). The mucosa may be sensitive to spicy or coarse foods limiting the patient's enjoyment of meals, which may compromise nutrition.[12]

Patients experiencing chronic salivary gland dysfunction may carry water with them at all times and drink frequently in an attempt to relieve oral dryness. However, as wettability of the oral mucosa and enamel by water is poor, relief of xerostomia is usually very temporary.[13] Patients may describe drinking copious amounts of water throughout the day which may effectively wash away saliva as well as disrupt sleep due to nocturia.

A complaint of oral dryness (xerostomia) does not always correlate with a quantified decrease in salivary function, although related specific symptoms may.[14] For example, complaints of oral dryness while eating, the need to sip liquids in order to swallow food, or difficulties in swallowing dry foods (i.e., activities that rely on stimulated salivary function), have all been highly correlated with measurable decreases in secretory capacity. In contrast, complaints of oral dryness at night or upon awakening have not been consistently found to be associated with reduced salivary function. Furthermore, xerostomia, particularly in the elderly, may be due to an impaired or altered perception of oral moisture or change in the composition of saliva rather than due to true hyposalivation.

Medical History

A thorough review of the patient's medical history may reveal medical conditions, both past and present, medications, or procedures associated with salivary gland dysfunction leading to a direct diagnosis (e.g., a patient who received radiotherapy for a head and neck malignancy or an individual taking a tricyclic antidepressant). Medications can have a number of adverse effects on salivary gland function (see section: Medication-Induced Salivary Dysfunction). The most well-known of these are hyposalivation and xerostomia but medications may also produce objective or subjective sialorrhea. More than 400 drugs with xerogenic potential have been identified including antidepressants, anticholinergics, antispasmodics, antihistamines, antihypertensives, sedatives, and bronchodilators, and attempts have been made to compile a comprehensive list of medications with documented effects on salivary gland function.[15]

A thorough review of all the patient's medications (including over-the-counter medications, supplements, and herbal preparations) must be performed. Often, upon further inquiry, a temporal association of symptom onset with a culpable agent may be made. Some side effects, however, including xerostomia and hyposalivation, may not appear until years after initiation of treatment, upon increase in dose, or other change in medication regimen. Furthermore, it is possible that certain drugs taken individually do not exert a xerogenic effect, but xerostomia arises as a result of a drug–drug interaction.[16] When history alone does not offer an obvious diagnosis, further exploration of the symptomatic complaint should be undertaken. For example, a report of eye, throat, nasal, skin, or vaginal dryness, in addition to xerostomia and fatigue, may be an indication of the presence of a systemic condition, such as Sjögren's syndrome.

Clinical Examination

Signs of salivary gland hypofunction may affect several areas of the oral cavity and mouth. The lips are often dry with cracking, peeling, and atrophy; the buccal mucosa may be pale and corrugated; and the dorsal tongue may appear smooth, erythematous, and depapillated, or fissured.

In the absence of the buffering capacity usually afforded by saliva, there is often an increase in dental caries and erosive lesions. These lesions often affect root surfaces and cusp tips of teeth: areas usually resistant to decay. The decay may be progressive, even where good oral hygiene is maintained, and recurrent decay is common. An increased accumulation of food debris and plaque may occur in interproximal areas due to a lack of cleansing salivary flow. Patients with hyposalivation, therefore, may have increased plaque indices and bleeding on probing scores.[17]

Two additional indicators of oral dryness are the "lipstick" and "tongue blade" signs. The former denotes the presence of lipstick or shed epithelial cells on the labial surfaces of the anterior maxillary teeth. A positive "tongue blade" sign results when a tongue blade, pressed gently and then lifted away from the buccal mucosa, adheres to the tissue. Both signs suggest that the mucosa is not sufficiently moisturized by saliva.

Oral candidiasis is often associated with salivary gland hypofunction and may be due to the effect of hyposalivation on the oral microbiome. The erythematous form of candidiasis (red patches of mucosa) is more prevalent in the presence of hyposalivation than the more familiar white, curd-like pseudomembranous (thrush) form (Figure 9-5). Angular cheilitis (persistent cracking or fissuring of the oral commissures) may also be present. Clinical examination should include noting the presence of the stigmata of an oral colonization and may include taking a smear or buccal swab for diagnosis.

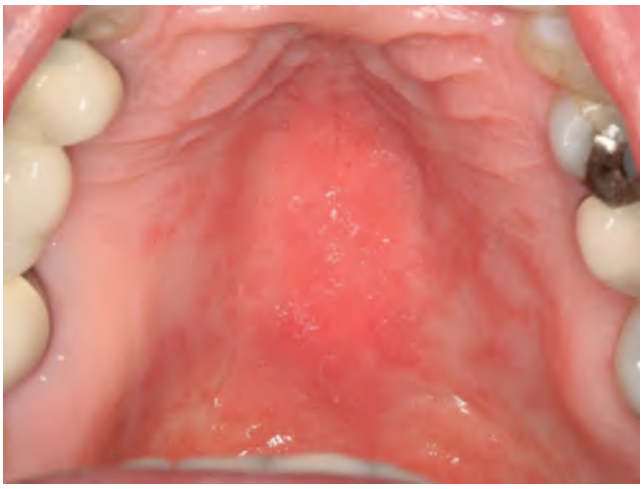

Figure 9-5 Erythematous candidiasis of the hard palate in a patient with salivary gland hypofunction.

Salivary gland dysfunction can present as enlargement of the salivary glands due to inflammatory, infectious, neoplastic, or other conditions. Inspection and palpation of the normal salivary gland should be painless and without detection of masses. The consistency of the glands should be slightly rubbery but not hard. Enlarged glands that are painful on palpation are indicative of infection, acute inflammation, or tumor. Neoplasms of the salivary glands, either benign or malignant, usually present as painless masses but may present with dull pain suggestive of an inflammatory-based process.

The major salivary glands should also be massaged to express saliva from the main excretory ducts. Normally, saliva can be easily expressed from each major gland orifice by gently compressing the glands and drawing pressure toward the orifice. The expressed saliva should be colorless, transparent, and of sufficient volume. In health, saliva should be seen to pool on the floor of the mouth during examination. Viscous or scant secretions suggest chronically reduced function. Saliva that appears frothy, ropy, or stringy also indicates hyposalivation. A cloudy exudate may be a sign of infection, although some patients with very low salivary function will have hazy, flocculated secretions that are sterile. In these cases, mucoid accretions and clumped epithelial cells result in a cloudy appearance. The exudate should be cultured if it does not appear clinically normal, particularly in the case of an enlarged gland.

Sialometry

Sialometry refers to the measurement of salivary flow. Sialometric techniques and specialized devices can be used to ascertain the production rate of whole saliva, saliva from individual major salivary glands, and in the stimulated and unstimulated state. Although no single sialometric technique is perfect, these methods allow for objective assessment of salivary flow where salivary gland dysfunction is suspected.

Since the resting, unstimulated state of the salivary glands is predominant, it has a greater influence on perceived oral comfort and health of the tissues. Normal subjects typically report mouth dryness when unstimulated whole salivary flow is reduced by approximately 50% or more.[18] Examination of stimulated salivary flow allows for assessment of the relative functional capacity of the salivary glands and can determine whether sialogogues are likely to be of benefit. It is therefore important to assess both unstimulated and stimulated salivary flow when investigating a complaint of xerostomia.

To prepare for sialometry, the patient is instructed to refrain from eating, drinking, smoking, chewing gum, and oral hygiene practices or any other oral stimulation for at least 90 minutes prior to the assay. Excessive movement and talking is discouraged during the testing period. At least 10 minutes before the test begins, the patient should rinse the mouth gently with water to remove debris.

The main methods of whole saliva collection are the passive and active drainage methods, suction, and absorption methods. In the passive drainage method, saliva is allowed to passively flow from the oral cavity into a pre-weighed graduated container (Figure 9-6). This method is reproducible and reliable, but is vulnerable to inaccuracy if there is significant evaporation of saliva. The active drainage method requires the patient to allow saliva to accumulate in the mouth and expectorate into a pre-weighed tube, usually every 60 seconds for 5–15 minutes. This method is also reproducible and reliable but is susceptible to inaccuracy due to saliva evaporation and stimulation of salivary flow by the act of spitting.

In sialometric methods employing suction, saliva pooling at the floor of the mouth is suctioned into a pre-weighed graduated container. The advantage of this technique is that it does not rely on patient collaboration. The vacuuming of saliva during the assay, however, may act as a stimulus for salivary flow.

Absorption sialometric methods involve placing a pre-weighed absorbent swab or roll into the patient's mouth for a set period of time after which it is re-weighed. This technique is potentially portable to outpatient clinics and does not require specialized equipment. It is not considered as reliable as the aforementioned methods, however. The absorbent material may act as a stimulus for salivary flow and this method cannot be used to determine the constituents of saliva as the concentration of some salivary components may be altered due to the interaction of saliva with the absorbent material.[19]

Figure 9-6 Patient demonstrating the active drainage method of whole saliva collection by spitting into a pre-weighed graduated container.

With respect to assessing stimulated salivary flow, the type of stimulus will influence how the glands are affected. Mechanical stimulation (chewing) results in a marked response of the parotid glands while a gustatory stimulus activates all three pairs of major salivary glands.[19] Mechanical stimulation may be elicited by instructing the patient to chew a piece of paraffin wax, silicone, or unflavored gum base at a controlled rate (usually 60 times per minute, paced using a metronome). Gustatory stimulation may be provoked by application of a 2% citric acid solution to the lateral borders of the tongue at timed intervals. This stimulation technique, often used in a research setting, should not be used where analysis of whole saliva is required but can be used when assessing parotid gland saliva via the use of Lashley cups, for example (see below).

Using specific apparatuses, it is possible to collect saliva from the right or left parotid or submandibular/sublingual glands. Isolation of saliva from either the submandibular or sublingual glands is not possible as they share a common duct. Quantitative and qualitative analyses may reveal changes such as selective hyposecretion or changes in electrolyte and protein (enzyme) levels, such as observed in Sjögren's syndrome. Collection of saliva from the parotid glands can be achieved using Carlson–Crittenden collectors

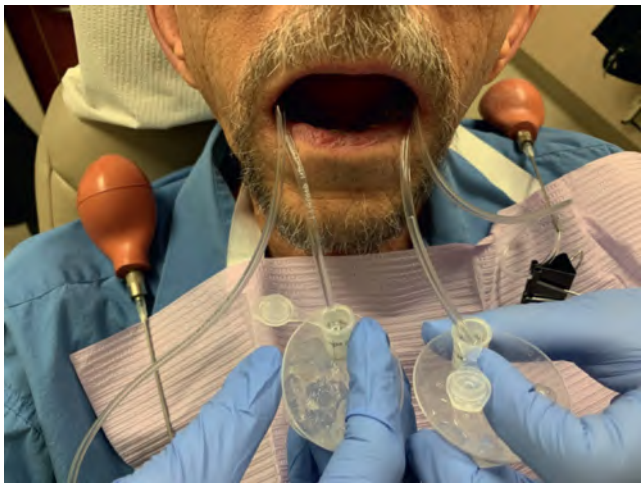

Figure 9-7 Patient with Carlson–Crittenden collectors in place undergoing collection of parotid gland saliva.

or Lashley cups placed over Stensen's duct orifices and held in place with gentle suction (Figure 9-7). Collection of saliva from the submandibular/sublingual glands may be accomplished using a Wolff collector or Schneyer apparatus placed over the opening of Wharton's duct or by using an alginate-held collector called a segregator.[20]

Flow rates are determined gravimetrically in milliliters per minute, assuming that the specific gravity of saliva is 1 (i.e., 1 mL of saliva is equivalent to 1 g). Samples to be retained for compositional analysis should be collected on ice and frozen until tested. Flow rates may be affected by many factors such as patient position, hormonal status, hydration status, diurnal and seasonal variation, and time since stimulation. Regardless of the technique chosen, it is important to use a well-defined, standardized, and clearly documented procedure which allows for meaningful comparisons between individuals and for repeat measurement in an individual over time.

It is difficult to define absolute "normal" values for salivary output due to great interindividual variability and, consequently, a large range of normal values exists. About 0.3–0.4 mL/min for unstimulated flow and 1.5–2.0 mL/min for stimulated flow are considered normal. Unstimulated whole saliva flow rates of < 0.1 mL/min and stimulated whole saliva flow rates of < 0.7 mL/min are abnormally low and indicative of marked salivary gland hypofunction.[21] Higher levels of output do not guarantee that function is normal, however, as they may represent marked hypofunction for some individuals. Therefore, these stated values represent a lower limit of normal and should serve only as a guide for the clinician.

Sialochemistry

Normal saliva is a colorless, transparent fluid with a pH between 6 and 7. It is composed of approximately 99% water

with inorganic ions of, amongst others, sodium, chloride, calcium, potassium, bicarbonate (HCO_3^-), phosphate (i.e., dihydrogen phosphate, $H_2PO_4^-$), fluorine (i.e., fluoride, F^-), iodine (i.e., iodide, I^-), magnesium, and thiocyanate (SCN^-). Bicarbonate ions buffer saliva, while calcium and phosphate ions neutralize acids detrimental to tooth structure and contribute to remineralization of the tooth surface.

The organic components of saliva include urea, ammonia, uric acid, glucose, cholesterol, fatty acids, lipids, amino acids, steroid hormones, and proteins. Many of the constituent proteins such as mucins, amylases, agglutinins, lactoferrin, and secretory IgA play a role in protection of the oral tissues.[22] The proline-rich proteins (PRPs), another group of protective proteins, are amongst the most prevalent group of proteins in saliva accounting for 70% of all salivary proteins in humans.[23] PRPs are antimicrobial and contribute to lubrication of oral surfaces, formation of the salivary pellicle, and tooth mineralization.[24]

When investigating a complaint of xerostomia, it is important to recognize that changes in salivary composition may be as important as a reduction in salivary output. That is, demonstration of apparently adequate salivary flow alone is not a guarantee of normal salivary gland function. While changes in saliva chemistries have been associated with a variety of salivary gland disorders as well as the sequela of radiation therapy, most alterations are changes in electrolytes related to reduced gland function as a result of damaged parenchyma, reduced salivary secretion, or a combination of both, rather than a specific disorder. Therefore, most salivary constituent changes are nonspecific diagnostically and have minimal utility in determining the cause of the salivary gland dysfunction.

An example of how systemic disease may affect sialochemistry is in patients with renal failure. These patients often develop high levels of salivary urea because of reduced renal clearance. Salivary urea is converted into ammonia and CO_2 by plaque bacteria resulting in an increase in plaque pH which can cause supersaturation and precipitation of the calcium phosphate species hydroxyapatite, dicalcium phosphate dihydrate (brushite), β-tricalcium phosphate (whitlockite), and octacalcium phosphate. Consequently, these patients have a tendency to develop greater amounts of calculus. Similarly, in patients who are exclusively tube fed, with no oral consumption of fermentable carbohydrates, plaque pH tends to remain high, favoring supersaturation of the aforementioned calcium phosphates leading to a greater propensity for calculus formation.[25]

Salivary Diagnostics

Saliva is an important medium in disease detection and can provide information about both local and systemic health. The use of saliva in diagnostics has many advantages over blood, for example, including relative ease of collection with no requirements for special equipment or training, noninvasiveness, and cost-effectiveness for screening large populations.[22]

Salivary diagnostics can allow for monitoring of hormone levels and other endocrine functions through the use of dynamics tests (e.g., dexamethasone suppression tests), determining the concentration and metabolism of hormones used as drugs (e.g., hormone replacement therapy), and in determining the free fraction of many hormones. Saliva can be used to help in diagnosis and monitoring of a number of systemic conditions, including Sjögren's syndrome, for screening for drugs of abuse such as alcohol, cocaine, and MDMA (3,4-methylenedioxy-methamphetamine), and for the presence of viral infection (e.g., HIV, hepatitis C, and human papilloma virus).

Established tests for the detection of antibodies to HIV-1 and HIV-2 in saliva, such as the Food and Drug Administration [FDA]-approved OraQuick ADVANCE Rapid HIV-1/2 Antibody Test (OraSure Technologies, Bethlehem, PA), provide for rapid, convenient, and relatively inexpensive screening. Other saliva-based assays can detect and quantify specific periodontal pathogens and high-risk human papilloma viruses (e.g., MyPerioPath® and OraRisk HPV®, OralDNA Labs, Eden Prairie, MN).

Saliva can serve as a source of biomaterial for DNA extraction and screening for the presence of biomarkers (objectively measurable markers indicating presence of a disease, condition, or susceptibility) which may be used in diagnosis, staging, prognosis, and to indicate response to treatment. Using saliva for detection of disease biomarkers presents many advantages. Apart from being readily available and easy to collect, some disease-discriminating biomarkers are present only in saliva or are found at a greater concentration in saliva compared to other biofluids.[26]

At present, various salivary biomarkers have been proposed and few have shown promise. MMP-8 (matrix metalloproteinase-8), for example, has been proposed as a salivary biomarker for diagnosis and prediction for progression of periodontal disease. Given the complex nature of disease, however, it is unlikely that any single biomarker will be both sufficiently sensitive and specific. In future, biomarkers will likely be used in combination with other data as in the "precision medicine" model where genetic, genomic, environmental, and clinical information is used to identify the most effective patient care. Prior to this, however, large-scale multicenter research is needed to establish normative biomarker values.

Saliva-based assays for early detection and diagnosis of cancer and Sjögren's syndrome are in development. Research

into the presence of tumor markers in saliva for oral cancers and precancers and variation in the salivary microbiome associated with other cancers shows promise.[27] A "liquid biopsy" refers to the use of a biofluid (such as saliva, serum, or urine) to detect circulating tumor cells and fragments of tumor DNA shed from tumor cells into the circulatory system. Circulating tumor DNA (ctDNA) can be distinguished from normal cell-free DNA by the presence of mutations, thereby potentially allowing for early, noninvasive detection. Since the mutations and amplifications caused by ctDNA are closely related to the occurrence and development of tumors, it is hoped that they may also be used to monitor therapeutic effect.[28]

Salivaomics

Salivaomics refers to the study of diagnostic components such as the salivary genome, proteome, transcriptome, metabolome, and microbiome. The salivary genome, composed of approximately 70% host and 30% oral microbiota DNA, allows access to the host genome via saliva collection.[29] This feature has been exploited by companies (e.g., 23andMe®, AncestryDNA®) who provide direct-to-consumer genetic testing kits that can determine the presence of genomic variants (e.g., single nucleotide polymorphisms), gene mutations (e.g., in *BRCA1* and *BRCA2*), and provide information regarding ancestry.[26]

The salivary proteome, composed of the entire set of proteins produced or modified by an organism, allows comparison of proteins produced in health versus disease. The human salivary proteome has been characterized for several diseases including oral squamous cell carcinoma, chronic graft-versus-host disease, and Sjögren's syndrome.[30]

The salivary microbiome refers to the nonpathogenic, commensal bacteria present in healthy salivary glands as distinct from the oral microbiome of the oral cavity. The Salivaomics Knowledge Base (SKB) is a data repository management system and web resource dedicated to salivaomic studies.[31] It is likely that information gleaned from the SKB will be used to develop saliva-based diagnostic point-of-care technologies for the detection of salivary biomarkers for human diseases.

Salivary Gland Imaging

Imaging in patients with suspected salivary gland disease can help confirm the salivary gland(s) as the origin of pathosis and can distinguish inflammatory from neoplastic processes. Some imaging modalities may also provide information on gland function, anatomic alterations, and space-occupying lesions. The following describes the application of plain film radiography, ultrasonography (US), computed tomography (CT), including cone beam computed tomography (CBCT), magnetic resonance imaging (MRI), positron emission tomography (PET) fused with CT or MRI (i.e., PET/CT, PET/MRI), sialography, salivary gland scintigraphy, and sialendoscopy as they relate to the diagnosis of salivary gland disorders. A summary of indications, advantages and disadvantages of each modality is presented in Table 9-2.

Advances in imaging have resulted in a shift from reliance on plain films and sialograms to nearly sole use of US, CT, MRI, and sialendoscopy. When selecting the best imaging modality or modalities, consideration should be made for relative accuracy, reliability, cost, radiation exposure, and patient desires, among other factors.

Plain Film Radiography

Plain film radiography may be the initial imaging modality employed in investigating a chief complaint involving the major salivary glands due to its availability; however, its clinical value may be limited. Use of conventional radiography has diminished with time in favor of cross-sectional imaging.

Signs and symptoms suggestive of salivary gland obstruction (e.g., painful, acute swelling of a gland, clinical detection of a sialolith) (Figure 9-8) warrant plain film radiography to help confirm or refute the presence of calcified blockages. Plain film may also depict bony destruction associated with malignant neoplasms and can provide a background for interpretation of a sialogram.

While plain film radiography is particularly useful for visualization of radiopaque sialoliths, phleboliths, hemangiomas with calcifications, and calcified lymph nodes may mimic sialoliths while smaller or poorly calcified sialoliths may not be visible.[32] If a stone is not evident on plain film but clinical evaluation and history are suggestive of salivary gland obstruction, additional imaging, such as CBCT, may be necessary.

Since the salivary glands are located relatively superficially, radiographic images may be obtained using standard dental radiographic techniques. Panoramic or lateral oblique projections can be used to image the parotid glands; however, overlap of anatomic structures, particularly in panoramic views, may obscure the appearance of a stone. A standard occlusal film placed intraorally adjacent to the parotid duct can help visualize a stone close to the gland orifice but may not capture the entire gland. The submandibular gland can be imaged in anterior posterior (AP) and ipsilateral oblique projections with the chin extended, mouth open, and the tongue pressed down to the floor of the mouth.[32] Sialoliths obstructing the submandibular gland

Table 9-2 Salivary gland imaging modalities: indications, advantages, and disadvantages.

Imaging Modality	Indications	Advantages	Disadvantages
Plain film	Sialolithiasis	Readily available; Inexpensive	Prone to anatomic overlap; Radiolucent sialoliths not visualized
Ultrasonography	Mass detection; Biopsy guidance; Helpful in assessment of Sjögren's syndrome	Noninvasive; Cost-effective	No visualization of deep parotid; No quantification of function; Observer variability
Computed Tomography	Inflammatory conditions; Calcified structures; Bony erosion	Differentiates osseous structures from soft tissue	No quantification; Requires contrast injection; Radiation exposure
Cone Beam Computed Tomography	Sialolithiasis	Can be combined with sialography; Reduced image degradation from metallic artefacts	Some radiation exposure
Magnetic Resonance Imaging	Neoplastic processes	Superior soft tissue resolution; No radiation exposure	Contraindicated with ferromagnetic materials and some pacemakers; High cost
Positron Emission Tomography fused with CT (PET/CT)	Staging and re-staging of malignant salivary gland tumors	Combines functional data with anatomic imaging	Radiation exposure; Cannot reliably distinguish malignant from benign tumors
Positron Emission Tomography fused with MRI (PET/MRI)	Salivary gland tumors	High sensitivity for detecting perineural spread; Reduced radiation exposure compared to PET/CT	Not widely available
Sialography	Sialolithiasis; Abnormalities of ductal system	Visualizes ductal anatomy/blockages; Superior spatial resolution	Invasive; No quantification; Contraindicated in active infection
Salivary Gland Scintigraphy	Assessment of salivary gland function after surgery, radiation therapy and in Sjögren's syndrome	Relatively easy to perform	Lengthy procedure; High cost; Radiation exposure; No morphologic data; Invasive
Sialendoscopy	Sialolithiasis; Ductal strictures and stenosis; Treatment of mucus plugs in Sjögren's syndrome	May allow for simultaneous visualization and treatment	Invasive; Cannot be used in acute sialadenitis

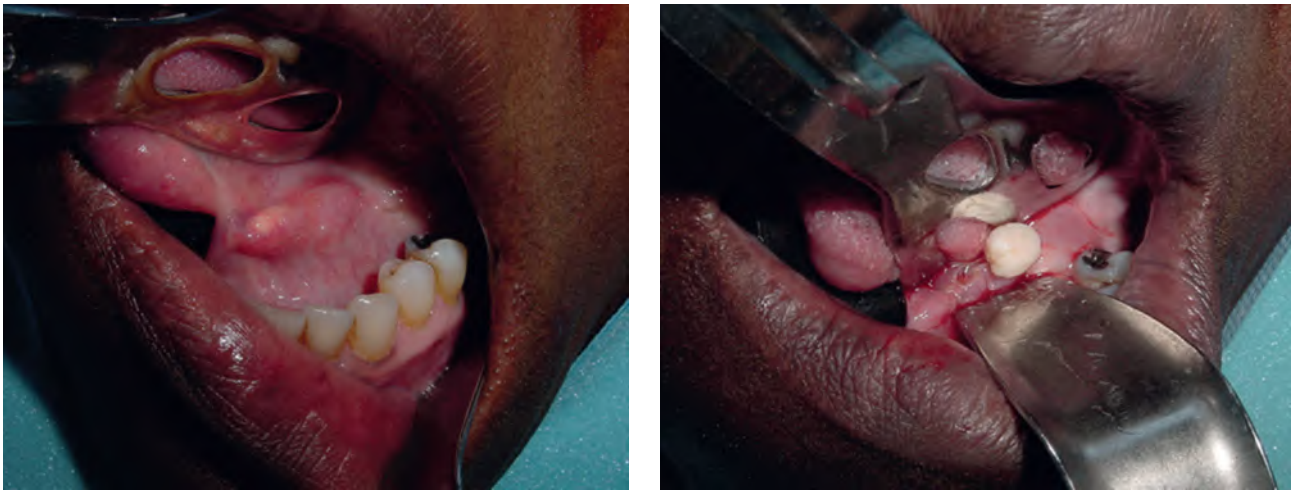

Figure 9-8 Left: Sialolith within the left submandibular gland duct. Right: Surgical exploration of a sialolith within the left submandibular duct. *Source:* Courtesy of Dr. Michael D. Turner, New York University.

may also be visualized in panoramic, occlusal, or lateral oblique views.

Ultrasonography

Using sound waves, ultrasound (US) generates a two-dimensional picture based upon the relative echogenicity of tissue; that is, the tissue's capacity to reflect or transmit ultrasound waves. US is often used during an initial evaluation, particularly where there is suspicion of sialolithiasis, acute sialadenitis or parotitis, and salivary gland abscesses. It is relatively inexpensive, widely available, safe and patient-friendly, even for children and pregnant women, and can delineate superficial salivary gland lesions as precisely as CT and MRI. High-frequency US also provides excellent resolution and characterization of tissue without exposure to radiation.[33]

US can also help distinguish focal from diffuse disease, assess adjacent vascular structures, distinguish solid from cystic lesions, guide fine-needle aspiration biopsy (FNAB), and evaluate lymph nodes for nodal staging.[34] It can also correctly differentiate malignant from benign lesions in 90% of cases and distinguish glandular from extraglandular masses with an accuracy of 98%.[35] Initial use of US, therefore, may guide the clinician in determining whether further imaging is required.

Due to their peripheral locations, the superficial portion of the parotid gland and the submandibular glands are easily visualized by US (Figure 9-9); the overlying mandibular ramus impedes evaluation of the deep portion of the parotid. Although US cannot directly visualize the facial nerve, it can suggest its position by accurate identification of intraglandular vessels within the parotid. Superficial lesions of the parotid and the submandibular glands may be amenable to core biopsy or fine-needle aspiration cytology (FNAC) under US guidance. US can also be used to guide procedures such as ductal stricture dilation and injection of botulinum toxin into a salivary gland as treatment for sialorrhea.

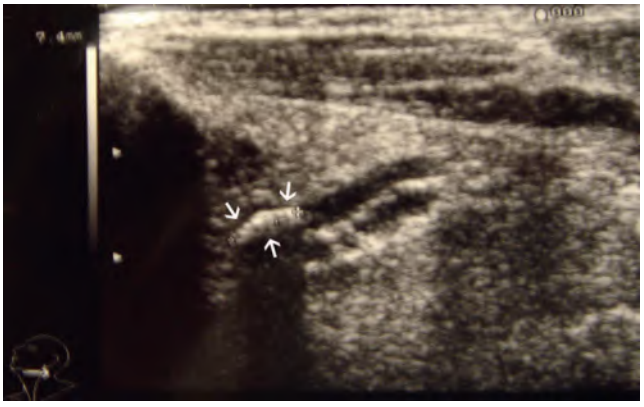

Figure 9-9 Ultrasound image with arrows indicating a sialolith within the left submandibular gland.

Salivary gland US can be a very helpful adjunct in the diagnosis and monitoring of Sjögren's syndrome. When compared to other diagnostic modalities, including scintigraphy, sialography, and salivary gland biopsy, salivary gland US consistently demonstrates high specificity and diagnostic accuracy. It provides a means to evaluate all the major salivary glands in one procedure, can highlight intraglandular calcifications and abnormal lymph nodes, and has been shown to be effective in identifying changes indicative of lymphoma development.[36] Further clinical testing, however, is needed with large cohorts to determine its overall diagnostic value in Sjögren's syndrome.

In order to be visible during US, the salivary ductal system must be filled. Filling may have occurred secondary to an obstructive pathology, or may be induced by oral administration of ascorbic acid. Retrograde administration of a contrast agent, similar to the procedure described for sialography (see below), can further aid in the visualization of the ductal system.

Sialoliths of less than 2 mm or those that are semicalcified may not be detected by US. Since it lacks the sensitivity required to fully visualize the internal ductal architecture, mucus plugs will also not be detected. In addition, US may not always allow for discrimination of phleboliths, arterial calcifications, and calcified lymph nodes from salivary gland calculi.

Ultrasound elastography, an imaging technique which evaluates the relative elasticity or stiffness of tissues, has been proposed to help differentiate between benign and malignant salivary gland tumors since malignant tumors are usually harder than benign ones. Current research suggests that real-time elastography could be used as an adjunct to conventional US for evaluation of salivary gland masses. Ultrasound elastography has already proven to be able to distinguish salivary glands affected by Sjögren's syndrome from normal glands.[37]

Conventional Computed Tomography

Conventional computed tomography (CT) is often the preferred initial imaging modality for evaluation of suspected calcifications and inflammatory conditions of the salivary glands owing to its high sensitivity and spatial resolution.[38] It is especially useful in the evaluation of malignant processes since it is able to depict mandibular cortical bone erosion and destruction, and cutaneous changes. Since CT can help define cystic walls and highlight the characteristic enhancing wall seen in abscesses, it is possible to distinguish fluid-filled masses (i.e., cysts) from abscesses. Landmark structures such as the retromandibular vein, carotid artery, and deep lymph nodes can also be identified on CT.

Imaging the major salivary glands can be optimally achieved using a standard neck CT protocol, which includes the skull base, nasopharynx, and oral cavity extending to include potentially enlarged lymph nodes in the neck, using continuous fine cuts through the gland(s) of interest. Both pre- and postcontrast studies must be performed in order to detect calcifications (precontrast) and enhancement patterns (postcontrast), and to allow distinction from normal anatomy. The initial precontrast scans are also reviewed for the presence of sialoliths (Figure 9-10), masses, glandular enlargement or asymmetry, nodal involvement, and loss of tissue planes.

Since glandular damage from chronic disease often alters the density of the salivary glands making identification of masses more difficult, contrast-enhanced images are often indicated as they will accentuate pathology. With contrast, tumors, abscesses, and inflamed lymph nodes may show abnormal enhancement when compared to normal structures. Enhanced CT can therefore help in staging malignant disease of the salivary glands by assessing lymphadenopathy of the pharynx and neck. Coronal and sagittal reconstructions are particularly useful in the evaluation of perineural spread, which, when present, implies a poor prognosis.[39]

CT maintains several advantages over MRI: it is less costly, more readily available, and it can be used in patients for whom MRI is contraindicated (e.g., individuals with certain implanted medical devices). CT may also be an alternative for patients who are unable to lie still long enough for an MRI (e.g., pediatric or geriatric patients or patients with mental or physical disabilities), and for whom MRI is otherwise contraindicated.

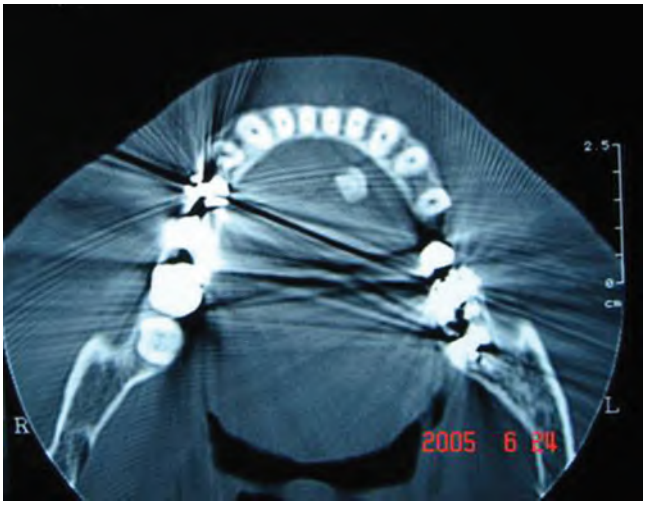

Figure 9-10 Axial CT image showing a sialolith of the left submandibular duct. *Source:* Courtesy of Dr. Michael D. Turner, New York University.

Dental restorations, maxillofacial fixation hardware, or other metallic hardware residing in the area imaged may produce streak artifact which may necessitate additional CT scans acquired with a different head position or gantry tilt angle and application of metal artifact reduction techniques. Additional disadvantages of CT include radiation exposure and the administration of iodine-containing contrast media for enhancement. Significantly impaired renal function and prior allergic reaction to a contrast agent may be contraindications for contrast-enhanced CT.

Cone Beam CT (CBCT)

Using a cone-shaped x-ray beam and two-dimensional detectors, a CBCT scanner collects volume data by means of a single rotation around the patient taking 9–40 seconds. It provides reduced superimposition and distortion of anatomic structures and higher sensitivity over two-dimensional radiography.

When compared with conventional CT, CBCT provides higher spatial resolution of osseous structures at a lower radiation dose, requires a shorter scan time, demonstrates reduced image degradation from metallic artifacts, and is less costly and more likely to be available in outpatient clinics and dental offices.[33,40] After plain film radiography, CBCT may be employed in patients with signs and symptoms consistent with sialolithiasis (see section: Sialolithiasis).[41]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) employs strong, dynamic magnetic fields and radio waves to produce diagnostic images. It has proven value in assessment of major salivary gland diseases, especially neoplastic processes (Figure 9-11). It is the imaging modality of choice for preoperative evaluation of salivary gland tumors, especially where there is a strong suspicion for malignancy, because of its ability to differentiate soft tissues and availability of multiplanar imaging.[42] When comparing US, CT, MRI, PET/CT, and real-time elastography, MRI has demonstrated the greatest potential to discriminate malignant from benign neoplasms (see section: Imaging in the differentiation of benign and malignant salivary gland tumors).

MRI provides a higher degree of accuracy in assessing malignant perineural invasion, intracranial spread, deep tissue extension, and marrow infiltration/edema over CT.[34,43] It is also optimal for detection of extracapsular spread in regional lymph nodes.[44] For these reasons, MRI is indicated to assess complete tumor extent, local invasion, and perineural spread in deep tissues for staging and treatment planning purposes. MRI can also highlight postoperative recurrences.[34]

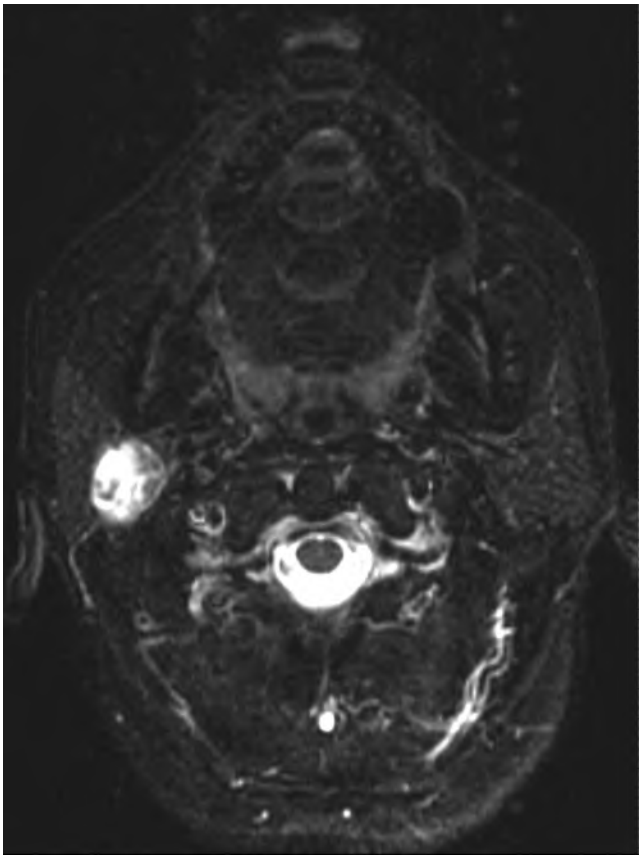

Figure 9-11 Axial MRI demonstrating a pleomorphic adenoma of the right parotid gland.

MRI may also be useful in the discrimination of disorders that mimic parotid gland swelling such as hypertrophy of the muscles of mastication and for detection of parotid gland changes associated with undiagnosed Sjögren's syndrome.[33,45] Such changes on MRI that can be associated with Sjögren's syndrome are an inhomogeneous internal pattern in both T1- and T2-weighted images giving a "salt-and-pepper" or "honeycomb-like" appearance.[46] A head and neck MRI can also help detect central nervous system and cranial nerve involvement in Sjögren's syndrome and can highlight changes associated with the development of malignant B-cell lymphomas, in particular mucosa associated lymphoid tissue (MALT) lymphomas; a true advantage as lymphomas arise in approximately 5–10% of Sjögren's syndrome patients.

The superior soft tissue contrast that MRI affords allows excellent discrimination of the salivary gland parenchyma and ductal structures. The utility of MRI is further enhanced by combining it with sialography allowing for a much finer evaluation of ductal alterations and filling defects (see section: MR Sialography). With respect to causes of ductal obstruction, however, MRI does not allow for differentiation between calcified sialoliths, fibrin, and mucus plugs and it may overestimate the size of calcified sialoliths from 10% to 30%.[47]

Additional advantages of MRI are that it does not expose patients to radiation, intravenous contrast media is not routinely required, and it is less susceptible to artifact from dental restorations than CT. MRI is contraindicated in patients with some cardiac pacemakers, automatic cardioverter defibrillators, or ferromagnetic metallic implants. Patients who cannot maintain a still position for the required scan time or those with claustrophobia may have difficulty tolerating the MRI procedure. Open bore or wide bore scanners are becoming more available to address these issues; however, the image quality is inferior to that of closed bore scanners.

PET/CT and PET/MRI

PET/CT is a whole-body imaging technique which combines the functional imaging provided by positron emission tomography (PET) with anatomic data from the CT scan. PET typically employs the radioactive tracer 2-deoxy-2-(^{18}F) fluoro-D-glucose (FDG); a glucose analogue taken up by cells with high glucose demand such as in the brain and kidneys, and cancer cells. A low level of physiologic uptake also occurs in normal tissues such as in the parotid and submandibular glands and tonsils. Uptake is increased at sites of active inflammation and infection and in benign, non-neoplastic processes, such as sarcoidosis and radiation-induced sialadenitis.[38]

PET/CT has an established role in staging head and neck cancer, searching for an unknown primary, assessing response to treatment, and differentiating relapse or recurrence from treatment effects.[48] It is considered a useful complementary technique to conventional imaging for staging malignant salivary gland tumors and for follow-up and restaging of treated tumors. In discriminating benign from malignant salivary gland processes, however, the PET/CT suffers from unacceptably high rates of false-positive and false-negative results.[38]

PET/CT has also demonstrated utility in assessing patients with primary Sjögren's syndrome. It can depict systemic manifestations such as lymphadenopathy and pulmonary and salivary gland involvement in these patients. In the parotid glands, a maximum standardized uptake value (SUVmax), a measure of FDG uptake, of ≥4.7 and/or the presence of focal lung lesions has been associated with the diagnosis of lymphoma in primary Sjögren's syndrome patients.[49]

The use of fused PET/MRI has recently been explored. Studies using retrospective fusion of MRI and PET datasets demonstrated that the fused PET/MRI images offered higher sensitivity and specificity with respect to the presence of

head and neck malignancy than with the unfused MRI and PET images. When compared with PET/CT, PET/MRI offers two additional advantages: the relative high sensitivity of MRI for detecting perineural spread, a route of metastasis favored by many salivary gland tumors, and reduced radiation dose.[50]

Sialography

Sialography achieves radiographic visualization of parotid and submandibular gland ducts, ductules, and parenchyma following retrograde instillation of soluble contrast material into Stensen's or Wharton's ducts, respectively. Since cannulation of multiple smaller ducts can be technically challenging, it is not typically used to image the sublingual glands. The most common sialographic findings include calcified sialoliths, noncalcified obstructive lesions (e.g., fibrin or mucus plugs), granulomatous collections on ductal walls, stenoses, strictures, and ductal kinks.

Because of its superior spatial resolution over CT, MRI, and scintigraphy, sialography allows for examination of the microanatomy of salivary duct systems.[51] It is used for evaluating intrinsic and acquired abnormalities (e.g., ductal stricture, obstruction, dilatation, and ruptures), and for identifying and localizing sialoliths, because it provides the clearest images of branching ducts and acinar end pieces.

In a patient who presents with a history of rapid-onset, painful swelling of a single gland (typically brought on by eating), sialography may be of value to detect the presence of calculi, ductal stricture, or obstruction due to mucus plugging. Sialoliths usually appear as voids (Figure 9-12) while focal collections of contrast medium within the gland usually indicate sialectasis (abnormal salivary ductal dilation) such as seen in sialadenitis and Sjögren's syndrome.

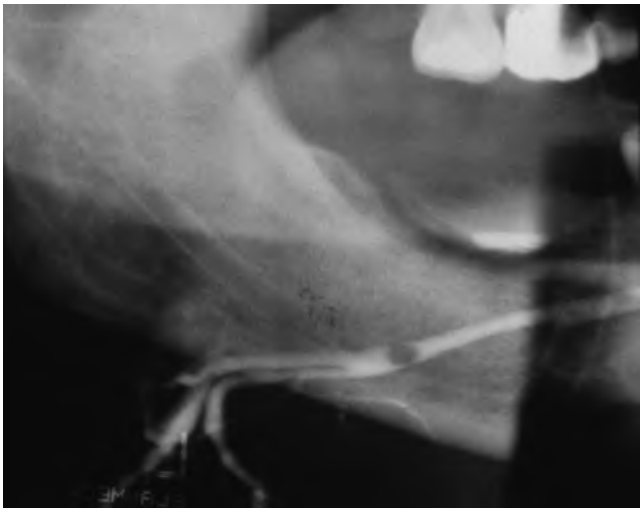

Figure 9-12 Sialogram showing an uncalcified sialolith in Wharton's duct visualized where the submandibular duct overlies the inferior alveolar canal. *Source:* Courtesy of Dr. Elisa Mozaffari, University of Pennsylvania.

Sialography may also be a valuable tool in presurgical planning for removal of salivary gland masses or to estimate ductal diameter prior to sialendoscopy. One of the chief advantages of sialography is that salivary stones can be localized to the salivary gland duct or gland parenchyma, which may influence the choice of treatment.[52] The ability to manipulate patient head position during examination may also provide enhanced visualization.

There are three main types of sialography: conventional sialography (with or without digital subtraction), CT sialography (including CBCT sialography), and MR sialography. In conventional sialography, the papilla of Stensen's or Wharton's duct is identified and, if required to facilitate access, the ductal orifice is dilated using incremental sizes of lacrimal probes. Once maximum ductal dilation is achieved, a sialographic catheter is introduced. Prior to infusion of a water- or fat-soluble sialographic contrast agent, an image is obtained to aid in distinguishing structures enhanced by the contrast agent or as a precontrast image for digital subtraction sialography (see below). Ductal filling is achieved by application of gentle, constant pressure on the syringe plunger until complete opacification of the ductal system is observed.

During sialography of a normal salivary gland, contrast medium will be seen initially in the peripheral portions of the duct extending towards the gland, filling and infiltrating into the intraglandular ductal branches (ductal phase). The image will resemble tree branches, initially leafless, gradually bursting into bloom, which represents introduction of the contrast material into the salivary gland parenchyma (parenchymal phase).[52] Radiographic views employed in conventional sialography include panoramic, lateral oblique, AP, and "puffed-cheek" AP views.

Following the sialographic procedure, the patient is instructed to massage the gland and/or to suck on lemon drops to promote the flow of saliva and contrast material out of the gland. Postprocedure imaging is performed to ensure that all contrast material elutes or is fully resorbed. Incomplete clearing can be due to obstruction of salivary outflow, extraductal or extravasated contrast medium, collection of contrast material in abscess cavities, or impaired secretory function.

Digital subtraction radiography refers to an image analysis technique which allows for detection of small radiographic changes between successive radiographs by "subtracting" distracting static anatomic structures. In digital subtraction sialography (DSS), precontrast images are subtracted from postcontrast images to provide high-resolution imaging of the extraglandular and intraglandular salivary ductal system, permitting detection of even small

sialoliths.[53] A distinct advantage DSS has over conventional sialography is that the former allows images to be captured during the initial filling of the main duct thereby preventing obscuration of mucus plugs by contrast medium.[54] Functional information can also be obtained after sialogogue administration.

Clinical indications for DSS are an acute swelling or palpable mass in the submandibular or parotid regions or gradual or chronic enlargement of a salivary gland where sialolithiasis or sialadenitis is suspected.[55] The principle weaknesses of DSS are that it is invasive (since it requires ductal cannulation), it requires the use of contrast and ionizing radiation, and that it has a high incidence of technical failure.[33]

Potential complications of sialography include ductal rupture, activation of clinically dormant infection, and adverse reaction to contrast agents.[32] Sialography is contraindicated in the presence of active infection (acute sialadenitis) and in a patient with a history of allergy to contrast agents. Performing sialography during an active infection may cause further glandular irritation and potential ductal rupture. Injection of contrast material may also force bacteria throughout the ductal structures, thereby spreading infection.

CT Sialography

CT sialography employs sialographic contrast to delineate the salivary ducts and enable the evaluation of the salivary gland parenchyma in fine detail. It is performed in the same manner as conventional sialography except that the patient is positioned in a CT scanner in a neutral supine position. Although CT sialography has a number of potential advantages over conventional sialography, it is not routinely performed for the following reasons: conventional CT without sialography typically provides adequate visualization of the main duct while the inability to dynamically visualize filling of the ducts in real time may lead to overfilling and subsequent rupture.

CBCT Sialography

Combining CBCT with sialography represents a relatively new approach that is showing promise as a supplementary noninvasive diagnostic method for visualizing the intraglandular ductal system. Using 3D and multiplanar reconstruction (i.e., converting data acquired in a one plane into another plane or planes), accurate mapping of salivary ducts can be achieved.[56]

CBCT sialography may be especially useful where US or sialendoscopy have failed to demonstrate pathology in patients with suspected salivary gland disease. It may serve as an advanced imaging modality since, following injection of contrast agent, visualization up to the sixth division of the ductal system is possible. While CBCT sialography is not a substitute for sialendoscopy (see section: Sialendoscopy), its selective use may eliminate the need for sialendoscopy if the causative pathology is identified in the intraglandular duct system or in the area around the hilum as these areas are not accessible to sialendoscopy.[57]

CBCT sialography provides several advantages over conventional sialography with respect to imaging the intraglandular ductal system including three-dimensional reconstruction, greater image manipulation, and generation of various cross-sectional slices. These advantages are particularly valuable in cases of complex anatomy.[39] By selecting appropriate parameters, the effective radiation dose from CBCT sialography can be equivalent to that of conventional sialography and it is less costly and more widely available than CT or MRI.

MR Sialography

Magnetic resonance sialography represents a fairly sensitive and reliable method for evaluating the salivary glands and may be used as the diagnostic method of choice in patients with suspected sialolithiasis where unenhanced CT has failed to demonstrate pathology. It provides several advantages over other imaging modalities: it can be employed in the diagnosis of parenchymal and ductal lesions with simultaneous visualization of all major salivary glands, it does not employ radiation, and, since it does not always require ductal cannulation and injection of contrast medium, it can be noninvasive and used in cases of acute sialadenitis.[58]

MR sialography is considered as accurate as conventional sialography in detecting obstructions, stenosis, and strictures of the main salivary gland ducts.[51] Advances in 3-D volumetric techniques and the ability to reformat images allow for the generation of virtual endoscopic views.[59] Disadvantages of MR sialography include a more limited availability and higher cost. It is also considered to have a lower sensitivity with respect to ductal pathologies, since its resolution does not extend beyond secondary divisions.[51]

Salivary Gland Scintigraphy

Scintigraphy using technetium (Tc) 99m pertechnetate is a dynamic and minimally invasive diagnostic assay employed to assess salivary gland function.[60] Technetium 99m pertechnetate is a pure gamma ray-emitting radiopharmaceutical, which, following intravenous injection, is taken up and transported by the salivary glands and secreted into the oral cavity generating quantitative information on the glands' function (Figure 9-13).[61] Salivary gland scintigraphy (SGS) can provide information on both the parenchyma and function of the parotid and submandibular glands after a single intravenous

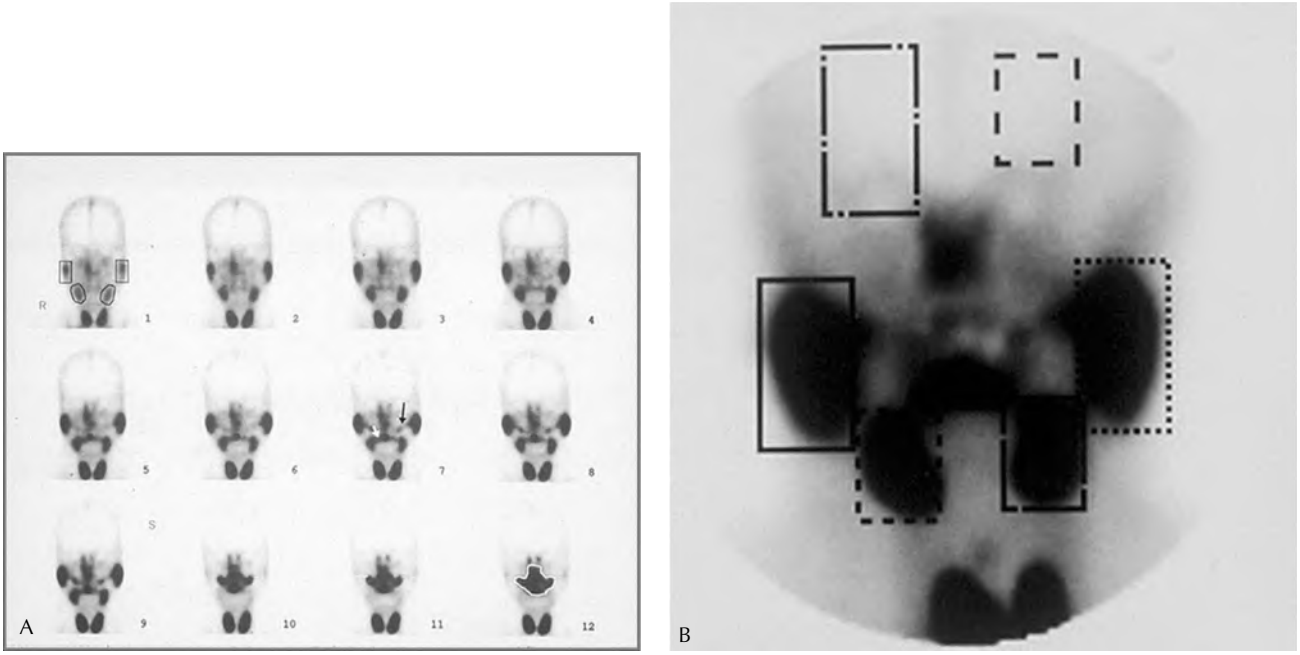

Figure 9-13 (A, left) Technetium 99m pertechnetate radionuclide image (scintigram) of the parotid and submandibular glands. This sequential salivary scintigram is an anterior Water's projection of an individual with normal salivary gland function. The four glands are outlined in frame 1 as regions of interest for further analyses. In frame 7, the dark arrow denotes Stensen's duct and the white arrow indicates Wharton's duct. A secretagogue, usually citric acid, is placed in the oral cavity between frames 9 and 10, inducing a rapid emptying of the glands. In frame 12, 10 minutes following the secretagogue, tracer is absent in the salivary glands and concentrated in the outlined oral cavity. (Courtesy of Dr. Frederick Vivino, University of Pennsylvania.) (B, right) A single frame of a salivary scintigram demonstrating significant uptake in both parotid and submandibular glands (four lower windows) with excretion into the oral cavity. The two upper windows represent background activity from blood flow, which is subtracted from the four regions of interest to determine specific salivary activity. *Source:* Courtesy of Dr. Frederick Vivino, University of Pennsylvania.

injection: a clear advantage over other imaging techniques.[62] Both uptake, which indicates the presence of functional epithelial tissue, and secretory phases can be recognized. SGS is indicated for the evaluation of patients when sialography is contraindicated or cannot be performed (i.e., in cases of acute sialadenitis or iodine allergy), or when the major duct cannot be cannulated successfully.

SGS can also estimate the severity of salivary gland involvement and functional change—even that which is not accurately reflected by morphologic damage.[63] As such, it has been used to assess salivary gland function following surgery, radiation, and radioiodine therapy. It has also been used to aid in the diagnosis of ductal obstruction, sialolithiasis, gland aplasia, and Sjögren's syndrome.[32] SGS has been proposed as a valid alternative to other forms of functional evaluation of the salivary glands in patients with Sjögren's syndrome. An abnormal SGS result is accepted as part of the 2002 American–European consensus group classification criteria for Sjögren's syndrome, but is not included in the 2012 ACR or 2016 ACR/EULAR criteria.[64–66]

A normal scintigraphic time–activity curve may be separated into three phases: flow, concentration, and washout. The flow phase is about 15–20 seconds and represents the time immediately following radionuclide injection when the isotope is equilibrating in the blood and accumulating in the salivary gland at a submaximal rate. The concentration (uptake) phase represents the accumulation of Tc 99m pertechnetate in the gland via active transport. With normal salivary gland function, the radionuclide will be secreted and tracer activity should be apparent in the oral cavity after 10–15 minutes. Approximately 15 minutes after administration, tracer concentration begins to increase in the oral cavity and decrease in the salivary glands. A normal image will demonstrate symmetric uptake of Tc 99m by both the parotid and submandibular glands.

In the excretory or washout phase, the patient is given a lemon drop, or citric acid is applied to the tongue, to stimulate secretion. Normal clearing of Tc 99m should be prompt, uniform, and symmetric. Activity remaining in the salivary glands after stimulation is suggestive of obstruction, certain tumors, or inflammation. With some exceptions, neoplasms arising within the salivary glands do not concentrate Tc 99m and will appear as voids or areas of decreased activity on the scintigram. The notable exceptions are Warthin's tumor and oncocytomas which will retain Tc 99m because they do not communicate with the ductal system and hence will appear as areas of increased activity on static images.[67]

Several rating scales have been used for the evaluation of salivary scintigrams; however, no standard method exists. Current approaches to functional assessment include visual interpretation, time–activity curve analysis, and numeric indices. Semiquantitative methods are also used in which Tc 99m uptake and secretion are calculated by computer analysis of user-defined regions of interest.

Although salivary gland scintigraphy is considered the gold standard for assessing salivary function and it is relatively easy to perform and reproducible, its use has fallen out of favor to noninvasive methods that do not subject the patient to radiation, such as US and MR imaging, including MR sialography.[68]

Sialendoscopy

Sialendoscopy has emerged as a valuable diagnostic and therapeutic technique for many salivary gland disorders affecting the submandibular and parotid glands. Using a small camera, it allows visualization of intraductal anatomy and strictures or other pathoses within the ducts. Insertion of surgical instruments or lasers through the endoscope may permit simultaneous fragmentation and removal of calcified material, biopsy, or stricture dilation. Typically, US, conventional sialography, contrast-enhanced CT, or MR sialography is employed prior to the sialendoscopic procedure to assess the ductal system. In many cases, the use of sialendoscopy may obviate the need for additional procedures or adenectomy.[47]

Sialendoscopy has also been used to flush out mucus plugs and irrigate the ductal system with saline or corticosteroids to enhance salivary flow and diminish xerostomia in patients with Sjögren's syndrome.[69] Following the sialendoscopic procedure, a stent may be placed to allow for healing of the duct and maintenance of salivary flow.

One limitation of sialendoscopy is that it can only be used for extraglandular duct pathologies or those close to the hilum.[57] The deepest portions of the gland (i.e., the proximal ductules) may not always be accessible, especially where stenosis is present. Very small stones, the presence of multiple smaller stones within different ductal branches, very large (> 9 mm) or immobile stones may also present a challenge.[41] Sialendoscopy is contraindicated in the presence of acute sialadenitis due to the increased risk of duct perforation.[70]

Imaging in the Differentiation of Benign and Malignant Salivary Gland Tumors

The ideal imaging modality would allow definitive discrimination between benign and malignant salivary gland tumors. In comparing US, CT, MRI, PET/CT, and real-time elastography (RTE), there is no statistically significant difference and no consensus on the use of one single modality or combination of modalities for this task. Of these, however, MRI shows the greatest potential.[43]

Histopathologic analysis remains the gold standard in evaluating the malignant potential of a neoplasm and imaging characteristics alone may never allow for definitive distinction between benign and malignant processes. One reason for this is because on imaging, lesions can demonstrate overlapping features; for example, a low-grade malignancy may appear well-defined with smooth borders.

Salivary Gland Biopsy

Definitive diagnosis of salivary gland pathology often requires histologic examination. The labial minor salivary glands are the most commonly biopsied, especially where Sjögren's syndrome is suspected, since they are the most accessible. Biopsy of the minor glands can also be used to diagnose amyloidosis, sarcoidosis, and chronic graft-versus-host disease (cGVHD), among other pathoses.

Minor Salivary Gland Biopsy

The minor salivary gland biopsy (MSGB) is a minimally invasive procedure that can be performed with limited morbidity using appropriate techniques.[71] An incision is made on the inner aspect of the lower lip, to one side of the midline, through normal-appearing mucosa, avoiding areas of trauma or inflammation that could influence the appearance of the underlying tissue. Six to ten minor gland lobules from just below the mucosal surface are removed and submitted for histopathologic examination. Clinicians should ensure an adequate specimen is obtained when Sjögren's syndrome is suspected, as generation of a focus score (see below) requires at least 8 mm^2 of evaluable salivary gland tissue.

The MSGB performed as part of a work-up for Sjögren's syndrome is considered the most accurate sole criterion for diagnosis of the salivary component of this disorder.[72] Histologically, the presence of focal lymphocytic sialadenitis is supportive of the diagnosis. The pathologic grading system results in a Focus Score (FS) which relates to the number of aggregates of ≥ 50 lymphocytes per 4 mm^2 of salivary gland tissue. A FS ≥ 1 is considered positive for Sjögren's syndrome.

Recent use of corticosteroids, smoking, and radiation exposure to the area of biopsy may adversely affect results. Complications associated with MSGB include long-term lower lip numbness (reported at 0–10%) and mucocele formation.[71]

Major Salivary Gland Biopsy

The parotid gland biopsy has been shown to be superior to the MSGB with respect to diagnosis of several conditions including sarcoidosis and lymphomas.[73] Where salivary

gland lymphoma is suspected, histopathologic analysis is often combined with techniques such as flow cytometry, and fluorescence *in situ* hybridization for definitive diagnosis and characterization. Here, the parotid gland as a biopsy site offers important advantages over the MSGB. The larger gland size offers multiple sites and opportunities for sampling and, since mucosa-associated lymphoid tissue (MALT) and non-Hodgkin lymphomas (NHL) are rarely observed in labial salivary glands, there is the opportunity to make a diagnosis even prior to clinical manifestation.[74] In addition, histopathologic results from the parotid gland can be directly compared with imaging or assays involving the same gland (e.g., scintigraphy, US, sialometry).[71]

With respect to Sjögren's syndrome, while the sensitivity and specificity of the parotid and minor salivary gland biopsies are comparable, the former may offer unique value in assessing disease activity, progression, and response to treatment. Risks that have been associated with biopsy of the parotid gland include sialocele and salivary fistula formation, injury to the facial nerve, and visible external incision, but these have not occurred where an appropriate technique has been applied. There are no reports of permanent morbidity associated with the parotid gland biopsy in contrast to the relatively higher hazard of permanent damage to the sensory nerves of the lower lip with the MSGB.[71]

Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) is a simple technique that aids in the diagnosis of lesions using a fine-gauge needle to obtain a biopsy specimen for histopathologic analysis. Its use may prevent a significant number of patients from undergoing an open surgical procedure. The diagnostic sensitivity and specificity of FNAB for salivary gland lesions has been reported as above 80% and 95%, respectively. Limitations include difficulty in obtaining an adequate specimen, inability to determine tumor grade (i.e., discerning between high and low grade), reduced accuracy for non-neoplastic processes, and lack of information with respect to tissue architecture, capsular invasion, and lymphovascular involvement.[75]

Core Needle Biopsy

A core needle biopsy (CNB), in which a large bore needle is used to remove cylinders of tissue, may be used in the preoperative evaluation of salivary gland lesions. CNB has the advantages of having a lower rate of complications (bruising being the most commonly reported problem), and reduced risk of tumor seeding over FNAB.[75] CNB also provides increased material over the FNAB, allows preservation of histologic architecture, and can allow for assessment of extracapsular tumor invasion. Immunohistochemical stains are also more likely to be reliable with core biopsy specimens. Disadvantages of CNB include the requirement for local anesthesia and possibly increased pain and morbidity.

Ultrasound-Guided Core Needle Aspiration

US-guided core needle aspiration is indicated for distinct salivary gland masses of the major salivary glands and can also be used to investigate cervical lymphadenopathy.[76] Employing US significantly improves the safety, accuracy, and diagnostic rate over non-US guided biopsies.[77] A cytopathologist familiar with salivary gland cytology should inspect the aspirated specimen and offer a diagnosis or differential diagnoses based upon the cellular characteristics observed. Even if a definitive diagnosis is not rendered, it may be possible to determine whether a lesion is benign or malignant, which is helpful as awareness of the biologic aggressiveness of the tumor prior to definitive surgery aids in treatment planning.

Frozen Section Analysis

Frozen section analysis is a procedure in which specimens are rapidly processed and analyzed during a surgical procedure. It can help confirm or refine a presurgical diagnosis, including establishing whether a neoplasm is benign or malignant, and is used to evaluate margins for tumor involvement, and determine if there is neural or lymph node involvement. Frozen section analysis in parotid gland surgery has important implications. For example, discovery of involvement of the facial nerve by a malignancy will require sacrifice of one or more of its branches; lymph node involvement may necessitate neck dissection or radiation therapy. Frozen section analysis is estimated to have a 90% sensitivity and 99% specificity for salivary gland lesions.[78]

Serologic Evaluation

In addition to a review of medical history and clinical examination, serologic analyses can be helpful in the evaluation of a patient with dry mouth especially where an autoimmune process such as Sjögren's syndrome is suspected. Indeed, detection of serum autoantibodies has a central role in the diagnosis and classification of Sjögren's syndrome. The most extensively studied of these autoantibodies are the antinuclear antibodies (namely subtypes anti-SSA/Ro and anti-SSB/La), and rheumatoid factor (RF): 59–85% of patients with primary Sjögren's syndrome will display antinuclear antibodies and, of these, 50–70% will show anti-Ro/SSA and anti-La/SSB antibodies.[79] Although the anti-SSA/Ro

autoantibody is considered the most specific marker for Sjögren's syndrome, it may be found in a small percentage of patients with systemic lupus erythematous or other autoimmune connective tissue disorders and even in some normal individuals.

Serologic evaluation can also help to distinguish between Sjögren's syndrome and IgG4-related disease (IgG4-RD) since they may present similarly (i.e., salivary gland enlargement, sicca symptoms, arthralgias). In both, patients may have circulating antinuclear antibodies; however, anti-SSA/Ro and anti-SSB/La reactivity is not frequently found in patients with IgG4-RD. Similarly, in suspected cases of Sjögren's syndrome/sicca syndrome triggered by the cancer immunotherapy drugs known as immune checkpoint inhibitors, the serologic profile can be helpful as anti-SSA/Ro and anti-SSB/La antibody screening is usually, but not always, negative. However, as this phenomenon has a distinct phenotype with respect to histopathology and other features, additional assays including a minor salivary gland biopsy may be required to distinguish it from idiopathic Sjögren's syndrome (see section: Sjögren's Syndrome/Sicca Syndrome Triggered by Cancer Immunotherapies).[80]

SPECIFIC DISEASES AND DISORDERS OF THE SALIVARY GLANDS

Developmental Abnormalities

Salivary Gland Aplasia and Hypoplasia

Patients with salivary gland aplasia (incomplete development or absence) experience hyposalivation, xerostomia, and increased dental caries; in fact, rampant dental caries in children without other significant risk factors has led to the diagnosis of congenitally missing salivary glands. Although rare, salivary gland aplasia may occur with other developmental defects, especially malformations of the first and second branchial arches seen as various craniofacial anomalies. Enamel hypoplasia, congenital absence of teeth, and extensive occlusal wear are other oral manifestations associated with salivary gland aplasia.[81] There is often a hereditary pattern but some patients have no relevant familial history.

Parotid gland aplasia has been reported alone and in conjunction with congenital conditions, including hemifacial microsomia, mandibulofacial dysostosis (Treacher Collins syndrome), cleft palate, lacrimo-auriculodento-digital syndrome, and anophthalmia.[82] It has also been observed in patients with ectodermal dysplasia. Hypoplasia of the parotid gland has been associated with Melkersson–Rosenthal syndrome.

The Stafne Bone Defect

The Stafne bone defect (SBD; also known as the Stafne bone cyst) is an asymptomatic depression of the lingual surface of the mandible often associated with ectopic salivary gland tissue. It is, however, not a true cyst as there is no epithelial lining. The most common location of the SBD is inferior to the mandibular canal between the angle of the mandible and the mandibular first molar. There is also an anterior variant of the SBD occurring in the premolar, canine, or incisor regions of the mandible.[83]

SBDs are often diagnosed on plain film where they typically appear as a round, unilocular, well-circumscribed radiolucency. The characteristic location and radiographic appearance make the SBD easily recognizable. They can appear radiographically akin to a residual cyst and therefore may require further investigation including advanced imaging. Surgical intervention is reserved for atypical situations in which the diagnosis is unclear or a neoplasm or other pathology is suspected. Where indicated, fine-needle aspiration biopsy can be an accurate, cost-effective diagnostic tool for these lesions.[84]

The definitive etiology of the SBD has not been established. One theory suggests they result from pressure exerted by adjacent glandular tissue. The finding of salivary gland tissue upon surgical exploration of these defects is evidence to support this theory; however, other case reports have described finding muscle, lymphatic, or vascular tissues within the cavity.[83]

Ectopic Salivary Gland Tissue

Ectopic salivary gland tissue may occur as accessory tissue, associated with branchial cleft anomalies, or as heterotopic tissue (described below). Ectopic salivary glands have been reported in a variety of locations, including the middle and external ear, neck, mandible, pituitary gland, thyroglossal duct, thyroid and parathyroid gland capsules, lymph nodes, and cerebellopontine angle.[85]

The parotid gland is the most common major salivary gland associated with accessory tissue.[86] An accessory parotid gland is present in about 21% of the population and is considered a normal anatomic variant.[85] The most frequent location of the accessory gland is superior and anterior to the normal location of Stensen's duct. Ectopic salivary gland tissue associated with branchial cleft anomalies, such as the rare Huschke foramen (also known as foramen tympanicum), have been reported as presenting with fistula formation between the parotid gland and the external auditory meatus.[87] True heterotopic salivary gland tissue consists of mature salivary gland tissue found in a nonphysiological site usually in coexistence with original tissue in its usual anatomical location. The tissue has an independent ductal system and will clinically present as a saliva-draining skin fistula or an asymptomatic nodule.[88]

The histological features of the ectopic tissue are usually identical to those of the original major gland, but the ectopic tissue is more susceptible to neoplasms. Heterotopic salivary gland tissue is typically treated with excision for definitive diagnosis and serves to prevent neoplastic transformation.[89]

Diverticula

A diverticulum is a pouch or sac protruding from the wall of a duct. Diverticula in the ducts of the major salivary glands can be visualized by sialography. They often lead to local pooling of saliva and recurrent sialadenitis. Patients with diverticula are encouraged to regularly milk the involved salivary gland to promote salivary flow through the duct.[90]

Sialolithiasis (Salivary Stones)

Etiology and Pathogenesis

Sialoliths (salivary calculi or salivary stones) are calcified organic masses that form within the secretory system of the salivary glands. Although the exact mechanism of sialolith formation has not been established, it has been proposed that microcalculi are frequently formed in salivary ducts during periods of secretory inactivity. Migration of food debris and bacteria from the oral cavity into the main ducts and along into the smaller intraglandular ducts at the site of the impacted microcalculi eventually result in a focal obstructive atrophy. Since the nidus is protected from flushing, the antimicrobial effects of saliva, and the systemic immunity, bacteria may proliferate resulting in local inflammation and further atrophy. The inflammatory process may then spread to involve adjacent lobules resulting in swelling and fibrosis of the large intraglandular ducts. The resulting partial obstruction leads to ductal dilatation and stagnation of calcium-rich secretory material resulting in further lamellar calcification.[91]

The etiologic factors favoring sialolith formation may be classified into two groups: factors favoring decreased saliva production or stasis (i.e., dehydration, use of anticholinergics or diuretics, irregularities in the duct system, local inflammation), and changes in saliva composition (i.e., calcium saturation, deficit of crystallization inhibitors such as phytate). Bacterial infection also promotes sialolith formation due to an associated increase in salivary pH favoring calcium phosphate supersaturation.[92]

Sialoliths may be composed of a variety of organic and inorganic substances including calcium carbonates and phosphates, cellular debris, glycoproteins, and mucopolysaccharides.[93] They contain cores that vary from purely organic to heavily calcified material, surrounded by less-calcified or purely organic lamellae.[91] Hydroxyapatite is the most common mineral found in sialoliths, but other minerals such as β-tricalcium phosphate (whitlockite), dicalcium phosphate dihydrate (brushite), and octacalcium phosphate, are variably present depending on the mineral microenvironment.[94] Trace amounts of magnesium, potassium chloride, and ammonium salts are often also present.

Epidemiology

The true prevalence of sialolithiasis is difficult to definitively establish since many cases are asymptomatic or involve sialomicroliths which can only be detected microscopically. Sialolithiasis is more common in males and can occur in a wide age range of patients including children. The average age of patients with sialolithiasis in the submandibular gland is 40.5 years, it is 47.8 years for the parotid gland, and 50 years for the minor salivary glands. Since the underlying cause is frequently unidentified and uncorrected, the recurrence rate is estimated at around 20%.[95]

Sialoliths occur most commonly in the submandibular glands (80–90%), followed by the parotid (5–15%) and sublingual (2–5%) glands, and only very rarely occur in the minor salivary glands. Spontaneous secretion in the minor and sublingual salivary glands may provide continuous salivary flow, thereby preventing stasis.[90]

The higher rate of sialolith formation in the submandibular glands is due to: (1) the torturous course of Wharton's duct; (2) the higher calcium and phosphate levels of the secretions contained within; (3) the dependent position of the submandibular glands which leaves them prone to stasis; and (4) the increased mucoid nature of the secretion. In addition, since the submandibular and parotid glands' secretion is dependent on nervous stimulation, in its absence, secretory inactivity increases the risk of stone development.

When sialoliths form within the submandibular glands, they usually occur within the ductal system, predominantly in the proximal section of Wharton's duct or hilar area. These stones are more likely to produce symptoms indicative of inflammation, such as pain, than when stones form in the glandular parenchyma.[52] Sialoliths within the duct are also more likely to be calcified due to the increased alkalinity of submandibular saliva, increased calcium and phosphate concentrations, and increased mucin content.[47] Calcified sialoliths especially are most commonly found at the mylohyoid turn of the duct, due to the relative stasis at this approximately 90-degree turn, and at the orifice to Wharton's duct.

Up to 80% of parotid gland sialoliths and 20% of submandibular gland sialoliths are poorly calcified, and as such, may not be detected on plain film. Noncalcified obstructions may be due to fibrin or mucus plugs, especially in Stensen's duct and the secondary ducts of the parotid.[47]

Risk factors for sialolithiasis include hypovolemia, infection, inflammation, diabetes mellitus, Sjögren's syndrome, the use of diuretics and anticholinergic medications, trauma, gout, smoking, and a history of nephrolithiasis. There are

also reported associations between sialolith formation and chronic periodontal disease and between sialolith formation and higher salivary concentrations of calcium, magnesium, and phosphorus.[94,96] Some studies indicate that the saliva of patients with calcified sialoliths contains more calcium and less phytate (a potent inhibitor of hydroxyapatite crystallization found in wheat bran and seeds), than in that of a healthy group and in patients with purely organic sialoliths.[92]

With the exception of gout, in which the associated calculi consist mainly of uric acid, there is no proven link between sialolithiasis and development of stones in other areas of the body. There are, however, shared risk factors between sialolithiasis and urolithiasis (stones of the kidney, ureter, and urinary bladder), namely hypovolemia and diabetes mellitus, and there may be a familial predisposition.[97] Patients with hyperparathyroidism demonstrate an increased incidence of sialolithiasis and those with hyperparathyroidism and sialolithiasis show a greater incidence of nephrolithiasis than those without sialolithiasis, indicating that hypercalcemia may be a common contributing factor.[91]

Clinical Manifestations

Patients with sialoliths most commonly present with a history of acute, colicky, periprandial pain and intermittent swelling of the affected gland(s). The severity of symptoms is dependent on the extent of duct obstruction and whether secondary infection is present. Since the submandibular and parotid glands are encapsulated with limited space for expansion, their enlargement will likely result in pain. Typically, salivary gland swelling will be evident upon eating since the stone completely or partially blocks the flow of saliva resulting in salivary pooling within the ductal system. Where there is partial obstruction, swelling will subside when salivary stimulation ceases and output decreases.[98]

Sialolithiasis without infectious sialadenitis is predominately unilateral without drainage or overlying erythema, and presents without systemic manifestations such as fever. Often, there is a history of sudden onset swelling and pain. The involved gland is often enlarged and tender to palpation, and the soft tissue adjacent to the duct may be edematous and inflamed. Using bimanual palpation along the course of the involved duct directed from the affected gland towards its orifice, it may be possible to palpate or even express a stone.[99]

Chronic salivary stasis may lead to infection, fibrosis, and gland atrophy. If there is concurrent infection, there may be expressible suppurative or nonsuppurative drainage, and erythema or warmth of the overlying dermis. Fistulae, a sinus tract, or ulceration may also develop in the tissue overlying the stone. Other complications from sialoliths include acute sialadenitis, ductal stricture, and ductal dilatation.[100]

Imaging

Imaging modalities which can help visualize sialoliths include plain film radiography, ultrasonography, computed tomography including cone beam computed tomography, sialography, and sialendoscopy.

Plain Film

Plain film radiography can be a helpful initial imaging modality to visualize sialoliths. It is inexpensive, readily available, and has minimal radiation exposure; however, small and poorly calcified stones may not be readily visualized. Plain film is most useful in cases of suspected submandibular sialolithiasis using an occlusal film positioned 90 degrees from the floor of the mouth, or using panoramic film. Other calcified entities, some of which have a similar appearance to sialoliths, such as phleboliths (stones that lie within blood vessels), tonsoliths, calcified cervical lymphadenopathy, and arterial atherosclerosis of the lingual artery, can also appear on these films.[99]

Stones in the parotid gland can be difficult to visualize on plain film due to superimposition of anatomic structures and their tendency to be poorly calcified. The choice of radiographic views is important to minimize overlap: an AP view of the face, an occlusal film placed intraorally adjacent to Stensen's duct, or a panoramic film may be useful in these cases.

Computed Tomography (CT)

Of all the available imaging modalities, conventional CT demonstrates the highest accuracy in detection of salivary stones and is often the method of choice where it is readily available. It is capable of detecting very small and semicalcified calculi, but is associated with a high radiation exposure. In cases of suspected sialolithiasis, noncontrast imaging with a slice thickness of 0.2–0.5 mm is used since this can help distinguish sialoliths from similarly-appearing, small opacified blood vessels.[41] Studies have indicated, however, that the majority of calcifications detected on CT scans of the salivary glands represent incidentally-discovered parotid parenchymal calcifications not associated with sialadenitis, but rather due to etiologies such as alcoholism, chronic kidney disease, HIV infection, and autoimmune disease, among others.[101]

Cone Beam Computed Tomography (CBCT)

CBCT can be of great diagnostic value in the initial imaging of patients with suspected sialolithiasis as it is helpful not only in detection of sialoliths, but it can also provide accurate information on stone size and position. As it is relatively inexpensive, is increasing in availability, and has limited radiation exposure, it is often used as first-line imaging (or second-line after plain film) for patients with signs and symptoms consistent with sialolithiasis.[41]

The use of CBCT for the detection of sialoliths is associated with high specificity, sensitivity, positive and negative predictive values.[41] CBCT also has reduced superimposition and distortion of anatomic structures and higher sensitivity over two-dimensional radiography, and reduced radiation exposure, cost, and greater availability in offices and clinics over conventional CT.[102] The sensitivity and specificity of CBCT for this indication is also considered comparable or superior to conventional CT.[40]

Ultrasonography

Ultrasonography (US), typically transoral sonography using an intraoral transducer, is widely used as first-line imaging in cases of suspected sialolithiasis, especially in emergency and urgent care settings, since it allows rapid visualization of the course of the main ducts and body of the major salivary glands. Sialoliths characteristically produce hyperechoic areas with distal signal loss (posterior acoustic shadowing) and there may be accompanying dilatation or inflammation of the ductal system and enlargement of the involved gland.[103]

While noninvasive and less costly than other imaging, US may not always allow for accurate determination of the number of calculi where there are multiple stones. Stones that are semi-calcified and calculi less than 2 mm in diameter also may not be accurately depicted as they may not produce an acoustic shadow. Scarring or calcifications in the duct or adjacent blood vessels, adjacent normal anatomic structures, and even air bubbles within saliva, may erroneously be interpreted as sialoliths.

The reported sensitivity (77–94%) and specificity (80–100%) of US in identification of sialoliths varies widely among studies, and therefore the use of US alone may not be sufficient for definitive diagnosis.[104,105] Sensitivity may be enhanced with sonopalpation (digital palpation of the floor of mouth with simultaneous placement of the ultrasound probe extraorally), and concurrent administration of a sialogogue such as ascorbic acid, which promotes filling of the ducts with salivary secretions.[106]

Sialography

Conventional sialography, using panoramic, occlusal, and periapical radiographs, can be an appropriate first-line imaging approach where there is strong clinical suspicion of sialolithiasis.[39] It can help distinguish between mucus plugs, salivary stones, and ductal strictures, which are the most common findings in patients with obstructive salivary signs and symptoms. Contrast sialography, using an iodinated contrast media, can help visualize the parotid and submandibular glands' ductal systems and aid in differentiating calcified phleboliths from sialoliths since the former lie within a blood vessel while the latter occur within the duct or gland.

CBCT sialography is another supplementary noninvasive diagnostic technique which may be superior to conventional sialography with respect to imaging salivary gland parenchyma and sialoliths.[107] It may be especially useful where plain film sialography has been inadequate, such as in more complex cases of salivary duct obstruction.[108] Similar to CT or CBCT, CBCT sialography can determine the number and location of salivary stones, including those smaller than 2 mm in diameter.[56]

MR sialography provides high sensitivity, specificity, and positive and negative predictive values with respect to the detection of salivary gland stones.[109] It does not require ductal cannulation and does not employ a contrast medium, and can therefore be used in patients with iodine or contrast media allergies. It also does not employ ionizing radiation and can be used in patients with acute sialadenitis.

Sialendoscopy

Sialendoscopy can be employed for direct visualization and, often, simultaneous treatment of sialoliths of the parotid and submandibular glands. Mobile and smaller stones may be relatively easily removed, whereas larger stones may require prior fragmentation (see below).[110]

Management

During the acute phase of sialolithiasis, initial therapy is primarily supportive. Standard treatment often involves the use of analgesics, hydration, antibiotics, and antipyretics, as indicated. Sialogogues, massage, and heat applied to the affected area may also be beneficial. Smaller stones at or near the duct orifice can often be removed transorally by milking the gland, but deeper and larger stones may require sialendoscopy or surgical intervention.

The mainstay of treatment has shifted away from open surgical procedures such as gland resection to endoscopic-based, gland preservation methods such as interventional sialendoscopy. Preservation of glandular structure maintains normal facial fullness and contour and diminishes the risk of injury to adjacent nerves. This approach is also supported by several studies that have shown that glandular function is regained after stone removal, with few cases of recurrent sialolithiasis or complications.[111]

A series of CBCT scans may be performed on the day of surgery. A preoperative CBCT provides superior intraoperative orientation by allowing for determination of spatial topography, size, number, and location of calculus relative to the surrounding anatomic structures, and it minimizes the risk of calculus migration between CBCT evaluation and the beginning of surgery. A postoperative CBCT provides a means of confirming removal of all sialoliths.[112]

Interventional sialendoscopy is employed for removal of stones up to 4–5 mm in diameter and cases involving multiple smaller stones, especially those that lie freely in the

duct lumen. Larger stones may require fragmentation with shock wave impulses via intracorporeal lithotripsy (i.e., laser or pneumatic lithotripsy), or extracorporeal shock wave lithotripsy (ESWL), which facilitate retrieval or may permit passage of the fragments with physiologic salivary flow.[113,114] Treatment of sialoliths by ESWL may require multiple treatments and is contraindicated where there is complete distal duct stenosis, acute sialadenitis, or other acute inflammatory processes of the head and neck, in pregnancy, and in patients with cardiac pacemakers.[115]

To prepare for interventional sialendoscopy, dilation of the ductal opening or papillotomy is performed to allow introduction of surgical instruments such as the Dormia basket, graspers, or lasers. Saline or steroid instillation is performed to flush out debris and treat ductal inflammation.[116] Following removal of the stone, the endoscope is used to explore the duct and ensure all calculi have been removed. A stent may be placed to maintain ductal patency.[117]

Failing gland-sparing techniques and where there are fixed intraparenchymal stones, sialoadenectomy, such as superficial parotidectomy or transcervical submandibulectomy, may be required.[118] Very large stones and a longstanding history of recurrent sialadenitis may also be an indication for gland removal.

Some postoperative complications associated with parotidectomy include transient (2–76%) or permanent (1–3%) facial nerve injury, sensory loss of the greater auricular nerve (2–100%), and Frey's syndrome (8–33%). Risks associated with submandibular gland removal include temporary (1–2%) or permanent (1–8%) injury to the marginal mandibular nerve, temporary (1–2%) or permanent (3%) hypoglossal nerve palsy, or temporary (2–6%) or permanent (2%) lingual nerve damage. Other complications include hematomas, salivary fistulas, sialoceles, wound infection, hypertrophic scars, and inflammation caused by residual stones.[115]

Mucoceles and Ranulas

Mucoceles

Etiology and Pathogenesis

Mucocele is a clinical term that describes a swelling caused by the accumulation of saliva at the site of a traumatized or obstructed minor salivary gland duct. Although often called a "mucous retention cyst", this is a misnomer as the mucocele does not have an epithelial lining. Mucoceles can be classified histologically as extravasation types or retention types. Extravasation mucoceles develop secondary to trauma to a minor salivary gland excretory duct resulting in pooling of saliva in the adjacent submucosal tissue, whereas retention mucoceles are caused by obstruction of a duct, often by a sialolith, periductal scaring, or tumor, resulting in the accumulation of saliva and ductal dilation.[119]

Superficial mucoceles are a rare variant of mucocele that are typically smaller and more often appear as multiples. Development of superficial mucoceles has been attributed to the accumulation of sialomucins at the epithelial–connective tissue interface occurring idiopathically or secondary to trauma.[120] They have also been reported associated with oral lichen planus and lichenoid reactions, chronic graft-versus-host disease (cGVHD) following allogeneic bone marrow transplant, chronic minor oral trauma (e.g., use of an orthodontic splint), use of tartar-control toothpastes and alcohol-containing mouth rinses, smoking, taking alginate impressions, and in patients with oral cancer following chemoradiation therapy.[121,122] Superficial mucoceles have also been reported at the margins of excised oral cancer specimens.[123]

Epidemiology

The true incidence of mucoceles is difficult to definitively state since the term "mucocele" has been used to refer to both the extravasation and retention types and often it is unclear whether epidemiologic data has been reported for each type separately or in aggregate.[124] Mucoceles in general occur most commonly in patients aged 10 to 29 years which may reflect a higher prevalence of exposure to trauma or presence of parafunctional oral habits in this age group.[125] There is no significant gender predilection for the extravasation and retention type mucoceles. The extravasation type of mucocele is the more common histological subtype and it mainly affects the lower lip. The floor of mouth, ventral tongue, and buccal mucosa are other common sites of mucoceles, with the palate and retromolar area representing less frequent sites of involvement.[124]

Determination of the true incidence of superficial mucoceles is also challenging as these lesions are uncommon, and, because of their transient nature, they are often not biopsied or reported. They most commonly arise in women 30 years of age or older. The most commonly involved sites include the soft palate, retromolar pad, and buccal mucosa.[124]

Clinical Manifestations

Mucoceles present as discrete, smooth surfaced swellings that may or may not be painful. They range in size from a few millimeters to a few centimeters in diameter. Mucoceles occurring closer to the mucosal surface often have a characteristic blue hue, whereas deeper lesions are more diffuse and are usually covered by normal-appearing mucosa. The lesions may vary in size over time; superficial mucoceles in particular are frequently traumatized, causing them to drain and deflate. Mucoceles that continue to be traumatized are most likely to recur and may develop surface ulceration (Figure 9-14).

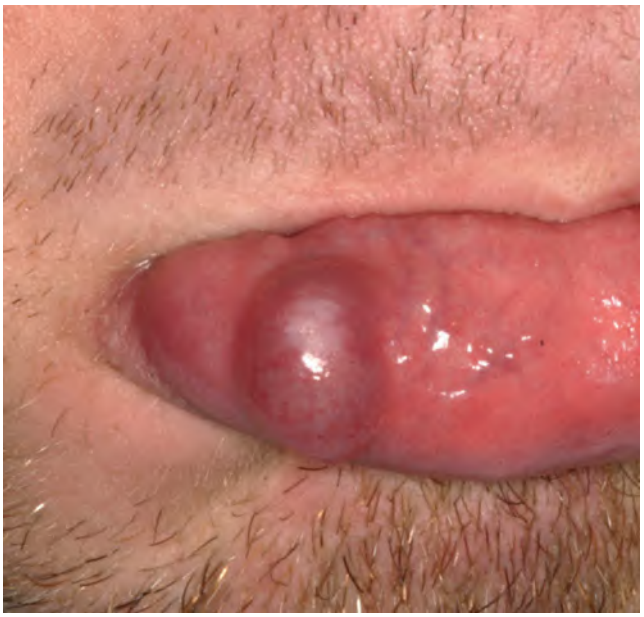

Figure 9-14 Mucocele of the lower right labial mucosa with surface ulceration.

Extravasation mucoceles appear most frequently in areas where trauma occurs: the lower lip, buccal mucosa, tongue, floor of the mouth, and retromolar region. These types of mucoceles are most common in children and teenagers. Retention mucoceles are more commonly found on the upper lip, palate, buccal mucosa, floor of the mouth, and rarely the lower lip, and usually afflict an older patient population. Distinctive-appearing mucoceles can also arise in the glands of Blandin and Nuhn on the ventral surface of the tongue. These have a characteristic appearance of a soft, fluctuant polypoid mass.[126] Superficial mucoceles typically appear as multiple, smaller (usually < 3mm) lesions of the soft palate and buccal mucosa. They are short-lived, burst easily, leaving an ulcerated surface, and have a tendency to recur. Diagnosis can often be made clinically.

Differential Diagnosis

Although the development of a bluish lesion after trauma is highly suggestive of a mucocele, other lesions (including salivary gland neoplasms, soft tissue neoplasms, and vascular malformations) should be considered in the differential diagnosis. Differential diagnoses to consider for superficial mucoceles include vesiculobullous diseases, including mucous membrane pemphigoid and bullous lichen planus. Biopsy for definitive diagnosis may be warranted.

Management

Small or superficially located mucoceles may spontaneously resolve whereas persistent lesions may require treatment. Conventional definitive surgical treatment of mucoceles involves removal of the entire lesion along with the feeder salivary glands and duct. Incomplete removal of the mucocele may result in recurrence. Surgical management can be challenging since it can cause trauma to adjacent minor salivary glands (leading to the development of a new mucocele), or to adjacent nerves, such as the branches of the mental nerve. Alternative treatments that have been used with varying degrees of success include electrosurgery, cryosurgery using liquid nitrogen, laser therapy and micromarsupialization, intralesional injections of corticosteroids, and sclerotherapy with pingyangmycin.[127–129]

Since the natural course of superficial mucoceles is typically self-limited, no treatment is usually necessary. Identification of a source of trauma or inciting agent and its elimination may prevent recurrence. Additional treatments that have been used include topical corticosteroids and laser therapy.[130] Persistence of the lesions or atypical appearance may prompt biopsy.[121]

Ranulas

Etiology and Pathogenesis

A form of mucocele located in the floor of the mouth is known as a ranula (Figure 9-15), named due to its resemblance to the underbelly of a frog (Latin rāna ["frog"]). Ranulas are believed to arise from the sublingual gland usually following mechanical trauma to its ducts of Rivinus, resulting in extravasation of saliva. Other proposed causes include an obstructed salivary gland duct (e.g., due to sialolith) or ductal aneurysm. The tendency of ranulas to develop in the sublingual gland is thought to be due to the gland's continuous salivary secretion which precludes effective sealing of mucous extravasation via fibrosis.

Ranulas are categorized anatomically as being oral ("simple," "superficial," "nonplunging"), plunging ("cervical," "diving"), or mixed, having both oral and plunging

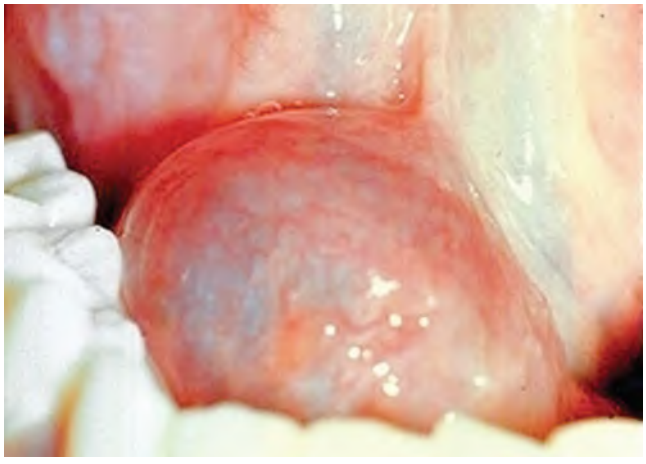

Figure 9-15 Ranula of the right floor of mouth. *Source:* Courtesy of Dr. Michael D. Turner, New York University.

components.[131] The oral ranula remains confined to the sublingual space, while in the plunging ranula, extravasated mucus from ruptured sublingual gland acini passes around the posterior border of the mylohyoid muscle or through a hiatus in the muscle, and dissects along facial planes beyond the sublingual space.[132] There is also the rare congenital ranula, which may be detected *in utero*, which is speculated to develop due to narrowing and obstruction of the main sublingual duct or acini causing extravasation of mucous into the surrounding tissues.[133]

Epidemiology

Ranulas appear most commonly in the second and third decades of life but have been reported in a wide age range of patients including infants and the elderly. The incidence of ranulas appears to vary between populations. Studies indicate that those of Maori and Pacific Island Polynesian descent are 10 times more likely to develop plunging ranulas than Europeans. There is also a significantly greater incidence of plunging ranula in those of Asian descent, especially those with familial origins in China.[131]

While the oral ranula is more common in females, the plunging ranula has a distinct male predilection.[131] This too, however, appears to vary between populations. Studies from Asia and Finland indicate a male predominance, whereas in New Zealand, there appears to be an equal gender distribution.[134] Interestingly, oral ranulas tend to form on the left side, whereas plunging and mixed ranulas occur more often on the right side.[131] The reason for these patterns is unclear.

Trauma, surgery, or other manipulation of the floor of the mouth are risk factors for the development of ranulas. A congenital predisposition toward ranulas has been suggested associated with anatomic variation in the sublingual gland ductal system, dehiscence of the mylohyoid muscle, and presence of ectopic sublingual gland tissue.[135,136]

Clinical Manifestations

An oral ranula typically appears as a painless, slow-growing, fluctuant, movable mass in the floor of the mouth. Ranulas in the area of the sublingual caruncle may obstruct Wharton's duct causing a temporary swelling in the submandibular region upon gustatory stimulus. Usually, oral ranulas form to one side of the lingual frenulum, but if the ranula extends deeper into the soft tissue, it can cross the midline. As with mucoceles, oral ranulas located more superficially can have a bluish hue. Oral ranulas vary in size; most are less than 1 cm in diameter but they may reach up to and beyond 5 cm with larger lesions causing elevation or deviation of the tongue.

The plunging component of a ranula will present as a soft, fixed swelling of the neck often involving the submandibular space or deeper cervical fascial spaces. While most are painless, some patients experience pain. The lesions may undergo intermittent spontaneous drainage but never fully resolve. In a patient with an early mixed ranula, the intraoral swelling may present prior to the cervical swelling becoming clinically evident.[131] Congenital ranulas in a newborn present clinically in a similar manner to other ranulas. Additional signs in an infant may include feeding difficulties, airway compromise, failure to thrive, dysphagia, snoring, and obstructive sleep apnea.[137]

Differential Diagnosis

The diagnosis of a ranula is based on clinical examination, imaging, and, ultimately, excisional biopsy. The characteristic clinical appearance of the oral ranula makes its identification easy, but imaging is indicated to determine the extent of the lesion, for surgical planning purposes, and to help rule out other similarly appearing lesions such as a hemangioma, lymphangioma, dermoid cyst, or benign or malignant salivary gland neoplasm. Where there is a cervical swelling consistent with a plunging ranula, the differential diagnosis includes other causes of neck swelling such as a thyroglossal duct cyst, epidermoid cyst, and cystic hygroma, for example. Presence of both an oral and cervical swelling is highly suggestive of a mixed ranula.

Fine-needle aspiration biopsy, ultrasound, CT with contrast, and MRI have been used to characterize ranulas. Fine-needle aspiration biopsy will demonstrate inflammatory cells and mucus while biochemical analysis of aspirated fluid will show a high protein content and amylase. Ultrasound is often used for oral ranulas and to diagnose congenital ranulas *in utero*, while CT with contrast and MRI are suggested modalities for evaluation of suspected plunging ranulas.[138] MRI, in particular, allows for superior localization of the lesion and allows for evaluation of the associated ductal anatomy. Ultimately, definitive diagnosis requires excisional biopsy.

Management

While no standard treatment for ranulas has been established, for both oral and plunging ranulas, transoral resection of the sublingual gland is associated with the highest cure rate overall and is most likely to prevent recurrences.[119,139] While a transoral resection is the preferred approach for the isolated oral ranula, in the mixed ranula, a combined transcervical and transoral approach is often used to access the lesion below the mylohyoid muscle as this can be difficult using a transoral approach alone.[140]

Since resection of the sublingual gland is an invasive procedure requiring general anesthesia and is associated with complications such as nerve injury, damage to Wharton's duct, or bleeding, other treatments have been investigated. These include micromarsupialization or marsupialization to

form a drainage tract, injection of a sclerosing agent (e.g., OK-432) to induce fibrosis, aspiration only, and laser excision or cryosurgery, all of which are associated with varying degrees of success, recurrence, and complications. Reports of spontaneous regression of ranulas also exist and, therefore, some would advocate an initial period of surveillance.[137]

Congenital ranulas may be discovered on routine obstetric ultrasound allowing for optimal treatment planning. Management of the congenital ranula may involve the *ex utero* intrapartum (EXIT) procedure in which there is controlled partial delivery of the fetus, while maintaining placental circulation, to allow the airway to be secured. Once this has been accomplished, the neonate is delivered. A postnatal assessment is made once the patient's condition has stabilized to determine the appropriate definitive management of the ranula.[141]

Inflammatory and Reactive Conditions

Necrotizing Sialometaplasia

Etiology and Pathogenesis

Necrotizing sialometaplasia (NS) is a benign, self-limiting, reactive inflammatory disorder most frequently affecting minor salivary glands and, rarely, the major salivary glands and mucoserous glands of the upper respiratory tract. NS has also been reported associated with both benign and malignant neoplasms.[142] Clinically and histopathologically, NS can resemble malignancy and its misdiagnosis has resulted in unnecessary radical surgery.

Although the definitive etiology is undetermined, NS likely represents a local ischemic event leading to infarction, subsequent tissue necrosis, repair, and metaplasia. Infectious processes or an immune response to an unknown allergen have also been proposed to play a role.[143]

Epidemiology

NS has been reported to constitute about 0.03% of all biopsied oral lesions; however, as it is often self-limiting, it may not be biopsied and reported and therefore the true incidence is unknown. It has been reported in patients ranging in age from 17 to 80 years and has a male predominance especially in those older than 40 years.[144,145] The sites most often involved with respect to NS arising in the oral minor salivary glands are the palate, retromolar pad, gingiva, labial mucosa, tongue, and buccal mucosa.

Development of NS has been associated with smoking, local injury, blunt force trauma, denture wear, dental and surgical procedures, and administration of local anesthesia. It has been reported in pregnant patients and those with diabetes mellitus, sickle-cell disease, histories of cocaine or alcohol abuse, anorexia, bulimia, and chronic vomiting.[144]

Clinical Manifestations

Most often, NS presents as a painful, rapidly progressing swelling of the hard palate with central ulceration and peripheral erythema. The associated pain is often described as sharp and may precede mucosal changes. Numbness or anesthesia in the associated area may be an early finding. The lesions typically are of rapid onset and range in size from 1 to 3 cm.[146] They may develop anywhere salivary gland tissue exists, most frequently on the hard palate, retromolar pad, gingiva, labial mucosa, tongue, and buccal mucosa, but also on the tonsils, in the nasal cavity, trachea, maxillary sinus, and, rarely, the parotid gland.[144] Although the lesions are usually unilateral, bilateral cases have been reported. Lesions often develop shortly after trauma but there are reports of NS developing weeks after an inciting event or even in the absence of trauma.

Differential Diagnosis

NS of the hard palate clinically resembles salivary gland malignancies, particularly the mucoepidermoid carcinoma and adenoid cystic carcinoma, although the rapid onset of NS may be a distinguishing feature. At other sites, it may resemble other malignancies, such as squamous cell carcinoma or metastatic cancer, or other causes of ulceration, such as major aphthous stomatitis, secondary syphilis, and primary oral tuberculosis.

Pathology

Histopathologically, NS may present with an array of findings. Typically, there is necrosis of the salivary glands with preservation of the lobular architecture. Granulation tissue, and a mixed inflammatory cell infiltrate including lymphocytes, histiocytes, neutrophils, and eosinophils is often present. There may be pseudoepitheliomatous hyperplasia of the mucosal epithelium and squamous metaplasia of the salivary ducts. Most significantly, there are no malignant cells. In more chronic lesions, pseudoepitheliomatous hyperplasia and ductal metaplasia are more prominent and necrosis may not be as evident.[146]

Management

NS is usually a self-limiting condition resolving within 3 to 12 weeks. During this time, supportive and symptomatic treatment is usually adequate. Appropriate analgesics combined with use of an antiseptic mouthwash, such as 0.12% chlorhexidine gluconate, is recommended. Surgical intervention is typically not required; however, there are reports of resolution following debridement for particularly large lesions and those secondarily infected with bacterial species and *Candida*.[146]

Cheilitis Glandularis

Etiology and Pathogenesis

Cheilitis glandularis (CG) is a rare, chronic inflammatory disorder affecting the minor salivary glands and their ducts in which mucous and/or purulent discharge is secreted from dilated ductal openings. Although the etiology of CG is still undetermined, it has been suggested that it is an autosomal dominant hereditary disease. There is evidence that the expression and possibly the function of some of the aquaporin proteins in the minor salivary glands may be altered in CG, resulting in abnormalities in water flow leading to production of the characteristic thick discharge.[147]

Epidemiology

Because of its rarity, the true incidence and prevalence of GC is unknown. Most reports of CG have been in middle-aged and elderly men with fewer cases reported in women and children. The condition occurs more frequently in fair-skinned adults and patients with albinism. Proposed predisposing factors include poor oral hygiene, chronic exposure to sunlight (i.e., UV radiation) and wind, smoking, and an immunocompromised state.

Clinical Manifestations

CG presents with secretion of mucoid material or purulence from dilated ostia of swollen minor salivary glands. It most commonly affects the lower lip, but may involve both upper and lower lips, upper lip alone, buccal mucosa or palate, and in some cases, multiple sites simultaneously.[148] The discharge often adheres to the vermilion causing discomfort. Edema and focal ulceration may also be present.

CG has been subclassified into three clinical types: simple, superficial suppurative, and deep suppurative. In simple CG, there are multiple painless lesions, dilated ductal openings, and numerous small nodules that may be palpable. There is a lack of inflammation but mucinous material can be expressed on application of pressure. Infection of the simple type lesions may result in progression to the superficial or deep suppurative types. Superficial suppurative CG is characterized by superficial ulceration, painless crusting, swelling, induration and a mucinous exudate is often apparent at the ductal openings. In the deep suppurative type, infection of the deeper tissues results in abscess formation and fistulae.[149]

Differential Diagnosis

CG may present a diagnostic challenge to clinicians since its appearance is akin to orofacial granulomatosis and actinic cheilitis. The differential diagnosis of CG also includes multiple mucoceles, chronic sialadenitis, factitious cheilitis, and benign and malignant neoplasms of the minor salivary glands.

Pathology

The characteristic clinical and histopathologic presentation are used to make the diagnosis of CG. The histopathologic appearance may vary depending on the severity of disease but is generally nonspecific. Variably dilated and tortuous minor salivary gland ducts, accumulation of mucous in the ductal lumina, chronic sialadenitis, glandular fibrosis, oncocytic metaplasia, and mucous metaplasia may be present to variable degrees.[150]

Management

Where possible, predisposing factors should be addressed. Neutral lip balms, emollients, and sunscreens should be applied to vulnerable areas. Excessive exposure to sun and wind should be avoided. Conservative treatment of CG may involve use of topical, intralesional, or systemic steroids, systemic anticholinergics, systemic antihistamines, topical tacrolimus, and/or antibiotics. Refractory cases may require surgical intervention such as cryosurgery, vermillionectomy, and/or labial mucosal stripping.

Several reports document the development of squamous cell carcinoma in areas affected by CG, leading some to call CG a premalignant lesion.[148] Currently, the association between CG and squamous cell carcinoma is not well defined, but it does appear that co-occurrence of lower lip CG with actinic changes represent an increased risk of development of squamous cell carcinoma and therefore close clinical monitoring, with biopsy as warranted, is advised.[151]

External Beam Radiation-Induced Pathology

For a complete discussion on the effects of external beam radiation on the salivary glands, please refer to Chapter 8 "Oral Complications of Nonsurgical Cancer Therapies: diagnosis and Treatment".

Internal Radiation-Induced Pathology

Etiology and Pathogenesis

Radioactive iodine (^{131}I) [RAI] is standard treatment for papillary and follicular thyroid carcinomas following thyroidectomy, or in cases of suspected or known metastases to the thyroid. It may also be indicated for treatment of hyperthyroidism due to Graves' disease and hyperactive thyroid nodules. A significant portion of the RAI taken up by thyroid tissue is concentrated and secreted through the salivary glands resulting in radiation exposure and potential damage.[152] In contrast to external beam radiotherapy, RAI's effects within the oral cavity are limited to salivary gland tissue, where it causes relatively less glandular destruction.

Salivary gland toxicity due to RAI is related to cumulative dose.[153] Standard doses of RAI often cause obstructive

symptoms, while hyposalivation from parenchymal damage is more often observed with larger doses or repeated treatments. RAI can also lead to glandular fibrosis and permanent salivary gland hypofunction.[154] Acute side effects associated with RAI include ageusia, salivary gland swelling, and pain, while long-term side effects include recurrent and chronic sialadenitis with xerostomia, hyposalivation, stomatitis, and dental caries.[155]

Clinical Manifestations

The effect of RAI on the salivary glands can be mild to severe and is gland dependent. Patients may be asymptomatic or complain of parotid gland swelling (usually bilaterally), pain, xerostomia, and decreased gland function, as early as after the first treatment.[156] Signs and symptoms of the effects of RAI on salivary flow may initially go unnoticed as the more radioresistant submandibular and sublingual glands compensate for the decreased function of the parotid glands.[157]

Symptoms of acute, early sialadenitis usually abate within a few days after RAI but salivary gland swelling may persist. This may be accompanied by obstructive symptomatology with swelling and pain during salivary stimulation, not unlike that associated with sialolithiasis. The patient may also complain of a salty taste.[156] Ageusia or dysgeusia immediately following RAI may be temporary or, at higher doses, permanent.

Diagnosis

Diagnosis of RAI-induced salivary gland pathology can be established in a patient with a history of ^{131}I administration along with symptoms of chronic salivary gland dysfunction. Salivary gland scintigraphy using IV technetium 99m pertechnetate can be used to determine the extent of parenchymal damage and assess the acinar and ductal function of both the parotid and submandibular glands.[157,158]

Prevention and Management

RAI-induced salivary gland injury is irreversible; however, residual functioning salivary gland tissue is often present and responsive to therapy.[157] Following administration of ^{131}I, patients should undergo an aggressive salivary stimulation routine employing sugar-free lozenges, sour candies, and gums to stimulate salivary flow and aid in clearing the ^{131}I, thereby potentially decreasing damage.[156] Stimulation of salivary flow by these means should not be initiated within the first 24 hours after ^{131}I therapy, however, as this may increase the salivary gland side effects.[159]

Pilocarpine and cevimeline used before and after RAI may decrease transit time through the salivary glands, thereby diminishing exposure. Avoidance of anticholinergic medications during RAI, where possible, is also helpful. In cases of RAI-associated sialadenitis, external massage of the gland or use of duct probing to encourage outflow of retained saliva and debris may be indicated. Antibiotics may be necessary if infection is suspected due to the presence of suppuration or fever.[156]

Sialendoscopy has shown some promise in relieving obstructive symptoms and improving salivary flow in patients with early ^{131}I-induced sialadenitis by means of duct dilation and removal of mucus plugs and debris.[155] Following completion of RAI, patients with persistent xerostomia and/or hyposalivation should be counselled and managed appropriately (see section: Management of Xerostomia and Hyposalivation).

IgG4-Related Disease

Etiology and Pathogenesis

In 2003, Kamisawa and Okamoto proposed the existence of a new clinicopathologic entity: IgG4-related disease (IgG4-RD). The basis of their proposal was the observation that there were several multiorgan, inflammatory, mass-forming lesions with increased IgG4-positive plasma cells and shared histopathologic findings. These conditions have since been observed in nearly every organ system including the salivary and lacrimal glands.

The features common to all IgG4-RDs are elevated serum and tissue levels of IgG4, a characteristic histologic appearance, and response to immunosuppressive treatment. Chronic sclerosing sialadenitis (previously known as the "Küttner Tumor") and Mikulicz's disease (bilateral parotid and lacrimal gland enlargement) are now considered manifestations of IgG4-related disease.[160] The definitive etiopathogenesis of IgG4-RD is not known. Both IgG4 and T cells have been implicated, but their exact role is not established.[161]

Epidemiology

Because of its relatively recent recognition, the true incidence and prevalence of IgG4-RD have not been established. IgG4-RD typically presents in adults in their fifth, sixth, and seventh decades, although IgG4-RD has been reported in children.[161] Men tend to be affected more often than women overall, but studies indicate that Asian patients and women are at increased risk for head and neck disease. Risk factors have also not been well established. Antecedent malignancy, tobacco and asbestos exposure, and other environmental exposures, especially occupational antigens (e.g., solvents), have been suggested.[162]

Clinical Manifestations

IgG4-RD can present in a myriad of ways, but at its onset, it often appears in an indolent fashion and may be discovered incidentally. Patients may present with manifestations isolated to a single organ, or in multiple organ systems

simultaneously or metachronously.[162] The majority of patients will present with a nonpainful mass of the head and neck region but some will present with systemic signs and symptoms such as weight loss, fever, and malaise.[163] Lymphadenopathy, when present, is often symmetric with mildly enlarged, well-defined lymph nodes around the affected organ or organs.[162] The most common sites of lymphadenopathy are the supraclavicular, cervical, and submandibular regions.[164]

IgG4-RD of the salivary glands presents in the following decreasing order of prevalence: submandibular, parotid, sublingual, and minor salivary glands.[165] A typical presentation is a single nontender, persistently (> 3 months) enlarged gland, but involvement of bilateral glands has been described. The saliva secretory function of the gland may be normal or slightly reduced.

Differential Diagnosis

IgG4-RD of the head and neck has numerous mimics depending upon the organ system involved. Differential diagnosis with respect to salivary gland involvement may include salivary gland neoplasms including lymphoma, systemic diseases such as Sjögren's syndrome and sarcoidosis, infectious sialadenitis, metastatic cancer, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome).[164]

Imaging and Pathology

The diagnosis of IgG4-RD can be challenging as the extent of disease may be variable, there can be a wide spectrum of presentation, and it can clinically mimic many other pathoses. Diagnosis is dependent upon clinical examination, imaging, serological and histopathologic findings. Proposed diagnostic criteria suggest that definitive diagnosis can be reached only when three criteria are fulfilled: evidence of diffuse/localized swelling or mass in one or more organs, elevated serum IgG4, and a marked lymphoplasmacytic infiltration and fibrosis with IgG4+ plasma cells upon histopathologic examination.[166,167]

Imaging, particularly US, CT, and MRI, can be helpful in diagnosis and determining the extent of disease, while 18F-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT may be useful for staging patients and for evaluating response to treatment.[164] It has been recommended that patients with IgG4-related disease also undergo a systemic workup at diagnosis to determine the extent of disease and to screen for non-Hodgkin lymphoma, as IgG4-RD may be a predisposing condition.[168]

Management

Treatment for IgG4-RD is dependent upon the extent and severity of disease. Close clinical observation only may be appropriate for patients with mild submandibular swelling or asymptomatic lymphadenopathy. Surgery may be considered where disease is confined to a single gland. High-dose corticosteroid therapy is often the first-line medical treatment and can help improve salivary gland function. Steroid-sparing agents, such as mycophenolate mofetil, tacrolimus, cyclophosphamide, azathioprine, and 6-mercaptopurine, are also used along with the anti-CD20 antibody rituximab.[164]

Viral Diseases

The viruses responsible for the majority of virally-induced salivary gland enlargement are the mumps paramyxovirus, cytomegalovirus (CMV), HIV, and hepatitis C virus (HCV). Echoviruses, the Epstein–Barr virus (EBV), parainfluenza viruses, and choriomeningitis virus infections have also been linked to reports of nonsuppurative salivary gland enlargement. Here we will highlight the more common viral salivary gland diseases.

Paramyxovirus Mumps (Epidemic Parotitis)

Etiology and Pathogenesis

Mumps is an acute viral infection caused by an enveloped, single stranded RNA-containing paramyxovirus. The virus can be found in saliva and urine and is transmitted by inhalation of infectious droplets, by direct contact, or by autoinoculation (i.e., interaction with virus-laden fomites followed by contact with the nose or mouth). The mechanism behind the development of mumps parotitis is unknown but it has been hypothesized that it results from lymphocytic infiltration and destruction of periductal cells leading to obstruction of salivary gland ducts.[169]

The Centers for Disease Control and Prevention (CDC) began recommending mumps vaccination for children in 1977. Live-attenuated mumps vaccines are currently provided as the MMR (measles, mumps, and rubella) vaccine and more recently combined with the varicella vaccine (MMRV).[170] Current guidelines call for initial vaccination at 12–15 months of age and a second dose at 4–6 years of age. All persons born during or after 1957 are advised to receive between one and three doses.[171]

Prior to the development of the vaccine, viral mumps was among the most common infectious salivary gland diseases. Despite widespread vaccination campaigns, mumps has made a comeback in many countries including those that had previously reported good control. Recent outbreaks have occurred in the United States, the United Kingdom, Sweden, the Netherlands, Canada, Australia, Belgium, and a number of other countries.[170] Therefore, viral mumps should be considered in all cases of acute nonsuppurative salivary gland

inflammation in both vaccinated and unvaccinated patients. Outbreaks among vaccinated populations may be due to declining immunity and may prompt health authorities to recommend additional doses of vaccine among susceptible patients. Postexposure prophylaxis with the MMR vaccine is not recommended, however.

Complications of mumps include meningitis and encephalitis; mumps encephalitis has an approximately 1.5% mortality rate.[172] Deafness, myocarditis, thyroiditis, pancreatitis, hepatitis, and oophoritis are additional complications. Males may develop epididymitis and orchitis, resulting in testicular atrophy and diminishment in fertility if the disease occurs in adolescence or later.

Epidemiology

Mumps only became a nationally reportable disease in the United States in 1968, but there were an estimated 212,000 cases in the United States in 1964. A vaccine was recommended for routine use in the United States in 1977, after which time, reports of mumps decreased rapidly; approximately 3000 cases were reported annually in 1983 to 1985. Since then, several mumps outbreaks among highly vaccinated populations have been reported. Most recently, from January 2016 to June 2017, US health departments reported 150 outbreaks involving 9200 cases.[171]

In the absence of preventive measures, mumps typically occurs most frequently in childhood, especially in children between 5 and 9 years of age. Although mumps can occur in any age group, adolescents, young adults, and, generally, those in close-contact settings (e.g., on college campuses, in dormitories, prisons, summer camps, military garrisons, and ships) are considered at increased risk, and have mainly been involved in outbreaks.[173] Prolonged, close contact with an infected patient, underimmunization, or lack of immunization are risk factors.

Clinical Manifestations

Viral mumps typically presents with a 1 to 2 day prodrome of headache, fever, fatigue, anorexia, myalgia, and malaise followed by nonpurulent salivary gland enlargement. About 25% of cases present with unilateral salivary gland swelling, with swelling eventually developing in the contralateral gland; 95% of symptomatic cases involve the parotid gland only, while about 10% of cases involve the bilateral submandibular and sublingual glands concomitant with parotid gland involvement.[172] A minority of cases involve the submandibular glands alone.

Onset of glandular enlargement is sudden and the gland is painful to palpation with edema of the overlying skin and duct orifice. Glandular swelling increases over the next few days, lasting about 1 week. Trismus and pain with salivation, particularly if there is partial duct obstruction, is common. Where parotid enlargement is severe, the mandibular angle may be obscured and there may be superolateral lifting of the ear.[173]

Differential Diagnosis

An odontogenic infection causing facial swelling should be ruled out. The location and configuration of the swelling can help distinguish the cause (Figure 9-16). Other causes of parotitis, including other forms of viral parotitis (e.g., due to CMV, HIV, and hepatitis C virus), must also be considered.

Laboratory Findings

The CDC advises collection of both a buccal swab and blood specimen as soon as possible in all patients with clinical signs and symptoms consistent with mumps. Viral detection can be performed using molecular assays, such as real time reverse transcription quantitative PCR (RT-qPCR), and culturing in cell lines. To obtain a buccal swab specimen during

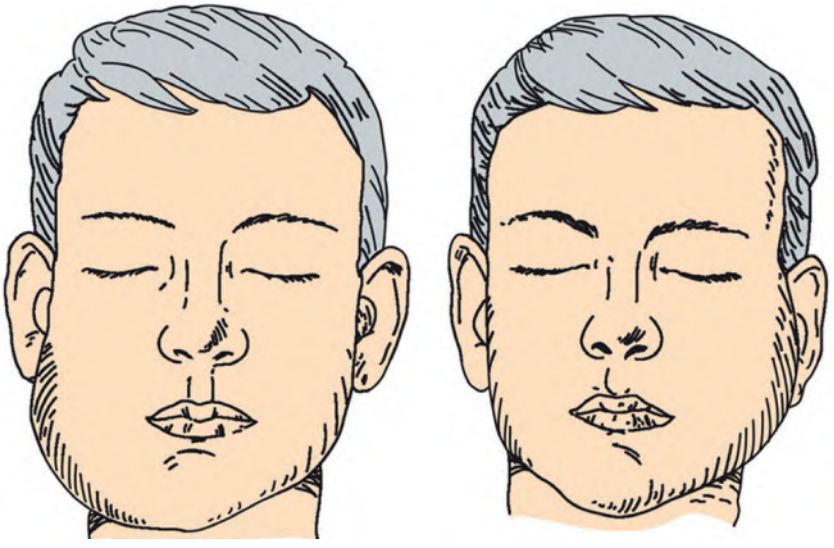

Figure 9-16 Left: right-sided facial swelling of typical location and configuration associated with abscessed mandibular molars. Right: Left-sided facial swelling of typical location and configuration associated with viral mumps affecting the parotid gland.

an acute infection, the patient's parotid gland is massaged for 30 seconds to express infected saliva and a swab is rubbed along the buccal mucosa near Stensen's duct. The swab is placed in 2 mL of a standard viral transport medium and shipped to the laboratory at 4 °C.[171]

Management

Treatment of viral mumps is supportive and may involve the use of analgesics, antipyretics, and antiemetics. Mumps is considered contagious 2 days prior to and 5 days after the onset of parotid swelling.[174] To prevent spread of infection, the CDC recommends that mumps patients are isolated and standard and droplet precautions are followed for 5 days after parotitis onset. Mumps is a nationally reportable disease in the United States and the CDC advises reporting of all cases to the appropriate state or local health department.[171]

CMV Infection

Etiology and Pathogenesis

Human cytomegalovirus (CMV) is a genus in the order *Herpesvirales*. The human betaherpesvirus 5 (HHV-5), commonly referred to as CMV, is the species which commonly infects salivary glands and is the major cause of non-EBV infectious mononucleosis in the general population. Infection presumably occurs as a result of exposure of mucosal surfaces to infectious virus. The virus attaches to and enters susceptible epithelial cells where it undergoes lytic replication. The resulting progeny virions are then released to infect the adjacent submucosal cells. Persistent infection occurs due to dissemination of these virions into tissues that support and harbor them, including the salivary glands. Tissue damage occurs due to direct viral cytopathic effects and host response. As with other members of the *Herpesvirales*, CMV can become latent after initial infection and may reactivate when favorable conditions present.

The majority of CMV infections are asymptomatic, especially in healthy individuals; however, in immunocompromised patients and neonates, infection can be life threatening. Transmission from children to adults or between children typically occurs through fomites, urine, saliva, and respiratory secretions. Between 11% and 24% of children attending daycare centers have CMV in their saliva and a large percentage of healthy adults have serum antibodies to the virus.[175,176]

CMV can be cultured from blood, saliva, feces, respiratory secretions, urine, and other body fluids. Horizontal transmission can occur through blood transfusion, solid organ transplant, hematopoietic stem cell transplant, and sexual contact. High rates of seropositivity are found in men who have sex with men, intravenous drug users, sex workers, and individuals who have undergone multiple transfusions.[177]

Transplacental transmission in the neonate can result in a congenital syndrome involving prematurity, low birth weight, and various congenital malformations. The mortality rate has been estimated at less than 5% of cases in symptomatic neonates.[178] Perinatal infection occurs in 1–3% of all live births and is thought to be due to transmission from breast milk, saliva, fomites, or urine.[179]

Clinical Manifestations

In the young, otherwise healthy adult, acute CMV infection presents as a mild, self-limiting, mononucleosis-like disease. Patients will commonly experience fever, malaise, and myalgia but pharyngitis and cervical lymphadenopathy are seen less frequently than in EBV-associated mononucleosis. Acute sialadenitis, presenting as diffuse, painful swelling of the parotid and submandibular glands with associated xerostomia, may also occur. CMV infection in immunocompetent patients has been associated with colitis, encephalitis, myocarditis, and other organ-specific complications.[180]

In the acute infection in neonates, the child will appear ill within days of infection. The child may develop a sepsis-like syndrome with associated hepatosplenomegaly, abnormal blood counts with lymphopenia, neutropenia, and thrombocytopenia, abnormal transaminases, and pneumonitis.[181] Acute CMV infection can also cause parotitis in infants.[182]

Long-term sequelae of early postnatal CMV infection include neurological problems such as sensorineural hearing loss. Developmental tooth defects may also be a consequence including diffuse enamel hypoplasia, attrition, enamel hypomaturation, and yellow discoloration of dentin.[183]

In immunocompromised adults, the impaired immune system permits viral replication resulting in a disseminated infection. Patients taking immunosuppressive medications and patients with hematologic abnormalities or HIV infection are particularly susceptible to severe CMV infections. Infection may result from reactivation of endogenous virus or receipt of an infected transplanted organ or blood product. Oral and maxillofacial manifestations of CMV in immunosuppressed patients include persistent oral ulcerations and major salivary gland infections, with or without concomitant alterations in salivary flow. In patients with HIV, the degree of CMV-induced sialadenitis and/or xerostomia has been found to be proportional to the HIV load and inversely proportional to the CD4+ T-cell count.[182]

Laboratory Findings

Several diagnostic modalities for CMV are available, including serology, qualitative and quantitative PCR, and histopathology. The choice of test may be based on the status of the patient's immune system. Diagnosis of primary CMV infection in immunocompetent hosts is usually made using serologic studies using an ELISA to detect the presence of CMV-specific IgG or IgM. Diagnosis in immunocompromised patients relies on clinical history, presentation, and

quantitative PCR tests for detecting viral DNA. Histopathologic examination of CMV-infected tissue may show large, atypical cells with inclusion bodies, resulting in a characteristic "owl eye" appearance. However, as these cells may be scarce and undetectable, CMV-specific immunohistochemistry staining is recommended.[184]

Management and Prevention

Most cases of primary CMV infection in immunocompetent adults present with minimal or no symptoms. In those with a symptomatic, mononucleosis-like infection, the disease typically lasts a few days to weeks and therefore only supportive, symptomatic care (i.e., analgesics, rest, and hydration) is required. Antiviral therapy is usually not indicated.[180]

Immunocompromised patients, including transplant recipients, are at particular risk for CMV infection and reactivation. CMV prophylaxis in patients undergoing transplant may involve the use of valganciclovir or ganciclovir. In November of 2017, letermovir, a CMV-terminase inhibitor, was approved by the FDA for CMV prevention in hematopoietic cell transplant recipients.[185]

Transplant recipients who develop CMV disease may be required to discontinue immunosuppressive therapy and start antiviral treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir. Adjunctive treatment may involve the use of cytomegalovirus immune globulin or intravenous immune globulin (IVIG). The choice of antiviral agents is influenced by the severity of disease, level of viremia, patterns of drug resistance, and response to treatment, among other factors. The length of treatment is dependent on CMV viral load (monitored on a weekly basis) and clinical signs and symptoms. Treatment continues until clinical signs and symptoms of CMV disease have completely resolved and at least two consecutive negative samples are obtained.[185,186]

HIV-Associated Salivary Gland Disease

Etiology and Pathogenesis

The term HIV-associated salivary gland disease (HIV-SGD), coined by Schiødt et al. in 1989, has been used to describe major salivary gland enlargement and/or xerostomia in HIV patients in the absence of xerogenic agents, medications, and diseases known to cause xerostomia.[187]

Both neoplastic and non-neoplastic salivary gland lesions occur with increased frequency in HIV-positive patients. Neoplasms include Kaposi's sarcoma and lymphoma of the salivary glands, which have a predilection for the parotid glands and intraparotid lymph nodes.[188] Non-neoplastic conditions often involve lymphocytic enlargement, particularly of the parotid gland, and may be referred to as cystic lymphoid hyperplasia (CLH), benign lymphoepithelial lesions (BLELs), benign lymphoepithelial cysts (BLECs), and diffuse infiltrative lymphocytosis syndrome (DILS). Many of these conditions present clinically in a similar fashion. Salivary gland swelling in the setting of HIV or AIDS can also arise due to bacterial, fungal, or viral (e.g., Hepatitis C, mumps) infections, and in patients undergoing antiretroviral therapy.[189]

Since the advent of highly active antiretroviral therapy (HAART) in the mid-1990s, the prevalence of AIDS and many HIV-associated oral lesions has decreased; with respect to HIV-SGD, however, the findings are variable. Some studies indicate an increase in HIV-SGD, particularly in developed countries, other studies show no change, and yet further studies indicate a decrease.[190,191] It is speculated that these disparities could be related to variations in HAART protocol, patient response, or an increase in life expectancy due to improved medical management. There is a male predilection for HIV-SGD; a finding consistent in both the pre-HAART and HAART eras.[188]

Clinical Manifestations

Typically, HIV-SGD presents as a unilateral or a bilateral diffuse swelling of the major salivary glands, which may or may not be painful, and which may be accompanied by generalized lymphadenopathy. When the labial minor salivary glands are affected, features of sialadenitis are present. The patient may also experience xerostomia/hyposalivation, keratoconjunctivitis sicca, and arthralgias.

Cystic lymphoid hyperplasia (CLH) is the most common HIV-associated salivary gland lesion and has been variably termed benign lymphoepithelial lesions (BLEL) or benign lymphoepithelial cysts (BLEC). CLH most commonly affects the parotid glands where it will present as bilateral nontender, slowly progressing swellings. It may also occur in the other major salivary glands, minor salivary glands, tonsils, and cervical lymph nodes.[192] As it can be the initial presentation of HIV infection, prompt identification is important.

Diffuse infiltrative lymphocytosis syndrome (DILS) is a multisystem syndrome in HIV-infected patients in which sicca syndrome occurs with extraglandular manifestations typically involving the lung, gastrointestinal tract, kidney, liver, muscle, or nerves. Because of its clinical presentation, it is often referred to as "Sjögren-like syndrome". Patients with DILS may present with sicca syndrome coupled with bilateral parotitis, lymphadenopathy, and, if the nervous system is involved, unilateral or bilateral facial nerve palsy. DILS typically occurs in patients with uncontrolled or untreated HIV infection, but it can occur independently of CD4+T-cell counts.[193] The diagnostic criteria for DILS, as initially defined by Itescu et al., require the patient to demonstrate all of the following: HIV-1 seropositivity, bilateral salivary gland enlargement or xerostomia persisting for > 6 months, and histologic confirmation of salivary or lacrimal

gland lymphocytic infiltration in the absence of granulomatous or neoplastic involvement.[194]

Imaging and Pathology

Persistent salivary gland enlargement in a patient with HIV warrants further investigation by imaging and possibly biopsy. Imaging modalities employed for evaluation of salivary gland enlargement where HIV-SGD is suspected may include US, CT, and/ or MRI. Pathologic findings on US of parotid glands affected by HIV may be of one of four recognized patterns: lymphocytic aggregations, lymphoepithelial cysts, fatty infiltration, or lymphadenopathy only.[195]

Differential Diagnosis

Since the clinical presentation of DILS, Sjögren's syndrome, and IgG4-RD are often similar, appropriate salivary, ophthalmologic, and serologic evaluation may be required to allow for differentiation. While salivary flow may be compromised in all three disorders, anti-SSA and anti-SSB autoantibodies are usually negative in DILS and IgG4-RD.

Biopsy may be indicated to help differentiate DILS from other causes of salivary gland enlargement, such as Kaposi's sarcoma, IgG4-RD, Sjögren's syndrome, and lymphoma. Indeed, patients with HIV have a higher incidence of non-Hodgkin lymphoma and DILS can resemble lymphoma histopathologically.[196] In DILS, there is a preponderance of CD8+ T-cells in contrast to CD4+ infiltrates that predominate in Sjögren's syndrome or IgG4 positive plasma cells predominant in IgG4-RD.

Management

HIV-SGD-related xerostomia and hyposalivation can be managed with optimized hydration, use of sugar-free lozenges, candies, and gums, dry mouth products and saliva substitutes, or other pharmacologic agents such as sialogogues (see section: Management of Xerostomia and Hyposalivation). Patients with salivary hypofunction should also be encouraged to follow a rigorous daily oral hygiene regimen incorporating the use of topical neutral fluoride and to maintain a regular schedule of dental examinations and hygiene appointments.

Treatment with HAART can result in the resolution of the histologic changes associated with DILS and CLH, but use of systemic steroids may be necessary for DILS unresponsive to HAART.[193] Other approaches and treatments for CLH have included: (1) close observation; (2) repeat aspiration; (3) antiretroviral medication; (4) sclerosing therapy (e.g., with bleomycin, sodium morrhuate, alcohol, tetracycline, or doxycycline); (5) radiation therapy; and (6) surgery.[197,198] Use of external beam radiation therapy (24 Gy in 1.5 Gy doses) has been reported with some success, but it is associated with acute mucositis, radiation dermatitis, altered taste, and xerostomia.[199]

Hepatitis C Virus Infection

Etiology and Pathogenesis

The hepatitis C virus (HCV) is an enveloped, single-stranded RNA virus of the family Flaviviridae. Infection with the virus is associated with extrahepatic manifestations such as sialadenitis and sicca syndrome. HCV is also a known oncogenic virus; chronic infection is associated with the development of hepatocellular carcinoma and there is a convincing link between chronic HCV infection and B-cell non-Hodgkin lymphoma (NHL).[200]

HCV is sialotropic, as well as being hepatotropic and lymphotropic. The virus appears to infect and replicate in the epithelial cells of the salivary gland acini. Sialadenitis is thought to develop due to a host response against ductal cells expressing viral antigens.[201] Chronic antigenic stimulation by the virus is speculated to trigger B-cell proliferation resulting in the development of lymphoma.

The majority of HCV-associated lymphomas are extranodal and involve the gastrointestinal tract and salivary glands, most commonly the parotid glands.[202,203] MALT lymphoma is the most common histotype among the primary lymphomas of the salivary glands and represents 1.7–8.6% of all salivary gland tumors and about 1% of all NHL cases.[204,205]

Clinical Manifestations

HCV infection has many extrahepatic manifestations, including sialadenitis and chronic enlargement of the salivary glands. Xerostomia, hyposalivation, and sicca syndrome are common among patients with chronic infection.[206] The reported prevalence of xerostomia ranges from 10% to 35.3% and that of hyposalivation ranges from 13% to 33%.[207] The prevalence of HCV-related sicca syndrome in patients with chronic HCV infection ranges from 4% to 57%; the large range may reflect differences in diagnostic criteria.[208]

Acute HCV infection is defined by the presence of clinical signs or symptoms of hepatitis within 6 months of presumed HCV exposure. These symptoms can include jaundice, nausea, dark urine, and right upper quadrant pain. Most patients who are acutely infected, however, are asymptomatic. Chronic HCV infection is slowly progressive and may not result in clinically apparent liver disease. Patients may be asymptomatic or present with mild, nonspecific symptoms including fatigue, nausea, anorexia, myalgia, arthralgia, weakness, and weight loss.

Because of the attendant increased risk of NHL in patients with HCV infection, any persistent glandular swelling despite treatment or the presence of salivary glands that feel indurated or nodular should undergo imaging and biopsy to rule out lymphoma or other pathology.

Laboratory Findings

The diagnosis of HCV infection is established by serologic detection of anti-HCV antibodies by ELISA and HCV RNA

by PCR. HCV RNA is first detectable in serum within days to eight weeks following exposure, while development of antibodies may be delayed up to several years in patients who have subclinical infection.

Management

The introduction of oral direct-acting antiviral agents (DAA) for hepatitis C in 2011 has changed treatment significantly. Cure rates of greater than 95% have been reported with a favorable safety profile and fewer contraindications for treatment than previous regimens. Duration of treatment is typically between 8 and 12 weeks. Prior to the use of DAA, patients with HCV received interferon alone, interferon with ribavirin, or pegylated-interferon with ribavirin for up to 48 weeks. The sustained virological response rate was inferior to DAA and was associated with numerous side effects and a reduction in quality of life.[209]

While there are no studies on the impact of DAA on HCV-associated salivary gland disease, it is speculated that rates will decline. In addition, pegylated interferon/ribavirin therapy was associated with xerostomia and temporary salivary gland hypofunction, while no such side effects with DAAs have been reported.[210] When present, hepatitis C-associated sialadenitis and xerostomia are treated symptomatically while treatment for HCV-associated lymphoma of the salivary glands is dependent on the histotype, and may be treated with chemotherapy, including DAAs.[209]

Bacterial Sialadenitis

Acute and Chronic Bacterial Sialadenitis

Etiology and Pathogenesis

Acute bacterial sialadenitis refers to a sudden-onset swollen and painful infected salivary gland, while chronic bacterial sialadenitis indicates a persistent, recurrent, or refractory infection. Bacterial sialadenitis is most common in patients with salivary gland hypofunction or with conditions that inhibit salivary flow.[211] Reduced salivary flow results in diminished mechanical flushing permitting bacteria to colonize the oral cavity where they may invade the salivary duct in a retrograde fashion and establish an infection. Recurrent infections can occur in a susceptible gland where ductal strictures developed following an episode of acute bacterial sialadenitis.[99]

Risk factors for bacterial sialadenitis include dehydration, use of xerogenic drugs, salivary gland diseases, nerve damage, ductal obstruction, irradiation, and chronic systemic diseases such as diabetes mellitus and Sjögren's syndrome; however, the majority of bacterial infections occur in patients with disease- or medication-induced salivary gland hypofunction. Poor oral hygiene can also increase the risk of infection. Elderly and infirm adults are particularly susceptible to bacterial sialadenitis due to the frequent combination of medication-induced salivary hypofunction and poor oral hygiene. Thus, although suppurative parotitis can affect persons of any age, it is predominately a disease of the middle aged and elderly.[99]

A retrograde bacterial parotitis can also occur as a complication of general anesthesia. It develops secondary to markedly decreased salivary flow during anesthesia, often because of the use of anticholinergic drugs and relative dehydration. Although the incidence has decreased significantly in the era of perioperative antibiotics, parotitis still complicates between 1 in 1000 and 1 in 2000 operative procedures. It usually occurs within 2 weeks of the procedure, with major surgeries comprising the greatest risk.[99]

Although bacterial sialadenitis occurs most frequently in the parotid glands, it can occur in any of the salivary glands. The antimicrobial activity of certain mucins, found in the saliva of the submandibular and sublingual glands, may competitively inhibit bacterial attachment to the ductal epithelium, thereby decreasing the risk. The serous parotid gland saliva also contains fewer protective lysozyme and IgA antibodies.[99] Anatomy may also play a role: tongue movements tend to clear the floor of the mouth and protect Wharton's duct, whereas the orifices of Stensen's ducts are susceptible to heavy bacterial colonization.[212]

Complications of bacterial sialadenitis include facial nerve palsy, sepsis, mandibular osteomyelitis, internal jugular vein thrombophlebitis, and respiratory obstruction.[99]

Clinical Manifestations

Patients with acute bacterial sialadenitis usually present with a sudden onset of salivary gland enlargement. Approximately 20% of cases are bilateral. The involved gland is enlarged, warm, painful, indurated, and tender to palpation, and there may be erythema of the overlying dermis.[213] If Stensen's duct is involved, it may appear erythematous and edematous. These findings may be accompanied by fever, chills, malaise, trismus, and dysphagia. The presence of dry oral mucosa may indicate systemic dehydration.

Clinical examination of the involved glands should include bimanual palpation along the path of the excretory duct. In approximately 75% of cases, purulent discharge may be expressed from the ductal orifice (Figure 9-17). Drainage from the gland may be absent, however, if there is ductal obstruction (e.g., by sialolith) or in early-stage disease.

Rarely, an abscess may develop in the setting of chronic bacterial sialadenitis. Due to the dense capsule surrounding the submandibular and parotid glands, it is difficult to determine based on physical exam alone whether an abscess has formed. A maxillofacial CT with intravenous contrast is the

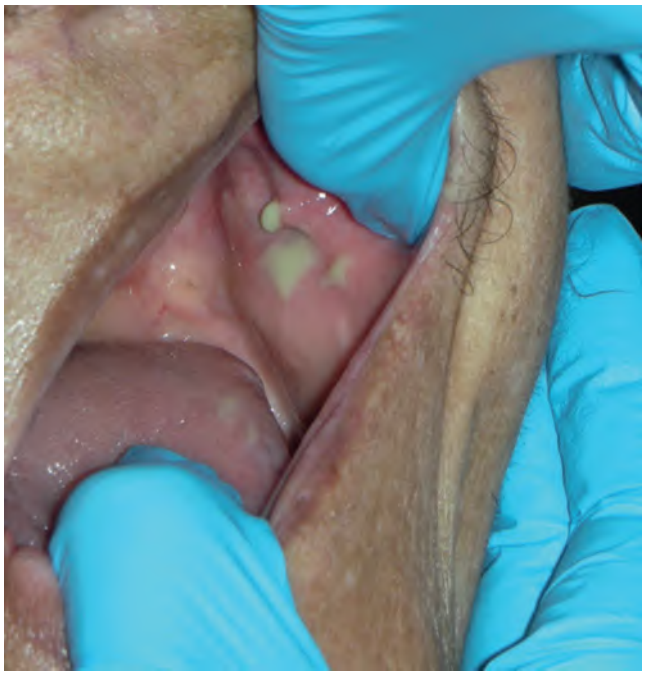

Figure 9-17 Acute bacterial sialadenitis with purulent discharge from the left Stensen's duct expressed upon massage of the left parotid gland.

most sensitive and commonly used imaging modality for differentiating an abscess from other salivary gland pathology.

Differential Diagnosis

Differentiating between viral and bacterial parotitis can be challenging. In general, viral infections are bilateral, affect younger patients, have prodromal symptoms, do not involve purulent drainage, and patients appear less unwell. Although systemic symptoms follow the development of a symptomatic gland in bacterial suppurative parotitis, the order is usually reversed in viral parotitis. Sialendoscopy, US, CT, MR sialography, or percutaneous aspiration may be helpful to rule out other causes of salivary gland infections, cysts, obstructions, and neoplasms.[99]

Laboratory Findings

Bacterial parotitis is largely a clinical diagnosis. If purulent discharge can be expressed from the duct orifice, samples should be collected to undergo culture and sensitivity assays for aerobes, anaerobes, fungi, and mycobacteria, taking care to avoid contamination with intraoral flora, and a second specimen should be sent for Gram staining.[214] A complete blood count with differential may show leukocytosis with neutrophilia.

Infections are often polymicrobial; however, *Staphylococcus aureus* is by far the most commonly isolated pathogen in bacterial parotitis; institutionalized patients are particularly susceptible to infections caused by methicillin-resistant *S. aureus* (MRSA). Other common aerobes include *Haemophilus influenzae*, *Streptococcus viridans*, *Streptococcus pneumoniae*, and *Escherichia coli*. Typical anaerobes are the Gram-negative bacilli (including pigmented *Prevotella* and *Porphyromonas* species), *Fusobacterium* and *Peptostreptococcus* species.[214] *Actinomyces* species, *Mycobacterium tuberculosis*, and atypical mycobacteria are rarer causes of infection.[99]

Management

Treatment for bacterial sialadenitis involves addressing the signs and symptoms of infection, eliminating the causative bacteria, rehydration, and resolving glandular obstruction where present. Initially, this may involve the use of analgesics, fluids, heat application, glandular massage, oral hygiene products, and sialogogues. Glandular massage can be performed by instructing the patient to empty the affected parotid or submandibular gland several times a day by gently pressing the skin overlying the gland and proceeding in a forward (ventral) direction. Once the gland is no longer painful, the patient may begin to stimulate the gland using, for example, a sugar-free lemon candy, in between massaging sessions.

Antibiotic therapy may be necessary if there are signs and symptoms of systemic spread of infection. This is typically started empirically and modified later based on culture results or if there is no response to treatment. Appropriate regimens should include coverage for *S. aureus* as well as oral polymicrobial aerobic and anaerobic infections. It is estimated that up to 75% of infections are caused by β-lactamase-producing bacteria, and, therefore, treatment with antistaphylococcal penicillin, a combination β-lactamase inhibitor, or a first-generation cephalosporin is appropriate. Macrolides such as azithromycin with metronidazole can be used for those with a penicillin allergy. Intraductal instillation of penicillin or saline may also be considered for chronic bacterial parotitis or submandibular sialadenitis.[215]

Anti-inflammatory agents including steroids may help to reduce pain and swelling. Where possible, medications implicated in salivary gland hypofunction should be discontinued. With the above measures, significant improvement should be observed within 24 to 48 hours. If this does not occur, or where abscess formation is evident, incision and drainage may be considered, but this is typically reserved for exceptional cases.[99,213]

Neonatal Suppurative Parotitis

Etiology and Pathogenesis

Neonatal suppurative parotitis (NSP), also known as acute suppurative parotitis, is a rare condition in the neonate often attributed to infection by *S. aureus* or other Gram-positive cocci, Gram-negative bacilli, or anaerobic bacteria. Several

reports have also implicated MRSA. Risk factors include dehydration, male gender, low birth weight, immune suppression, ductal obstruction, oral trauma, and structural abnormalities of the parotid gland.[216]

Clinical Manifestations

NSP may affect neonates between the ages of 2 to 4 weeks. Presentation includes swelling of the affected gland or glands with overlying erythema which may be accompanied by systemic signs including fever, poor oral intake, and irritability.[216]

Diagnosis

Diagnosis of NSP is reliant on the presence of parotid swelling, which may be unilateral or bilateral, and expression of a purulent exudate from Stensen's duct with identification of pathogenic bacteria on culture. Diagnosis may be aided by ultrasound examination which may show an enlarged gland and hypoechoic areas characteristic of parotitis. Ultrasound may also help determine whether there is an additional glandular mass or abscess.[212]

Management

Treatment of NSP involves antibiotics with supportive therapy including optimizing hydration. Antimicrobial therapy is based on culture and sensitivity assays of the exudate. If an intraglandular abscess is present, surgical drainage may be necessary.[212] Complications associated with NSP include facial palsy, recurrent infection, bacteremia, sepsis, and respiratory distress. Although potential morality has been associated with NSP, no deaths have been reported in the English-language literature since 1970, possibly due to improvement in antibiotic therapy.[216]

Juvenile Recurrent Parotitis

Etiology and Pathogenesis

Juvenile recurrent parotitis (JRP) is a nonobstructive, recurrent inflammatory parotitis in children of unknown etiology. It is characterized by recurrent episodes of painful parotid gland swelling, most commonly unilateral, often accompanied by fever and malaise, hyposalivation, and xerostomia. Although most cases of JRP are idiopathic, recurrent episodes of parotitis may in fact represent an underlying variable immunodeficiency, HIV infection, or Sjögren's syndrome and therefore distinguishing JRP from these aforementioned conditions is paramount.

There is no standard definition of JRP. Multiple criteria sets have been proposed but none are universally accepted. Some have proposed including children up to the age of 16 years and those with 2 or more episodes of unilateral or bilateral swelling over the previous 6 months while excluding patients with dental malocclusion, Sjögren's syndrome, congenital IgA deficiency, and obstructive causes of swelling (i.e., sialolithiasis), as these are believed to be associated conditions with an etiopathogenesis distinct from that of JRP.[217]

The definitive etiology behind the inflammation central to JRP is unknown. It appears, however, that this inflammation leads to decreased salivary flow, which promotes ductal metaplasia resulting in a more mucinous secretion, which further decreases salivary flow. Thus, factors that diminish salivary flow (e.g., systemic dehydration) or otherwise perturb flow (e.g., congenital duct abnormalities, autoimmune duct destruction), and those that promote inflammation (e.g., infection), are thought to be contributory and result in a reinforcing cycle of glandular inflammation and decreased salivary flow.

Because the etiology of JRP is ultimately unknown and there is no standard definition of the disease, there is no agreement on risk factors and associated conditions. Factors that are proposed to increase susceptibility to JRP include a congenital malformation of Stensen's duct, dental malocclusion, poor oral hygiene, IgA deficiency, and/or an IgG subclass deficiency, and HIV infection. Allergies, diseases such as sarcoidosis, or an autoimmune process have also been proposed to increase the risk of JRP. It is unclear, however, which of these represent true risk factors and which are associated, rather than causative, conditions.[217]

Epidemiology

After mumps, JRP is the most common inflammatory disease of the salivary glands in childhood. However, due to the lack of defining criteria, it is not possible to determine its true incidence and prevalence. There are two peak ages of onset: one at 2–5 years and the other at 10 years, and there appears to be a male predominance. Recurrence rates vary tremendously depending upon the study but have been reported to be up to 30 times per year with a mean of 1.5 episodes per year.[218]

Clinical Manifestations

The patient with JRP may present with unilateral or bilateral painful parotid gland swelling and fever and may complain of malaise, xerostomia, and dysphagia due to hyposalivation. The swelling may cause blunting of the mandibular angle and there may be discharge of white, mucinous saliva upon compression of the involved gland. These signs and symptoms typically last 2–7 days, with a median of 3 days, or may persist for weeks.[218]

A patient with a long history of JRP or one who has suffered from many recurrent episodes may manifest signs and symptoms of chronic hyposalivation such as xerostomia, dry, cracked, or atrophic lips, desiccated oral soft tissues, and an increase in dental caries and oral fungal infections. The patient may be intolerant of coarse, salty, or spicy foods due to the condition of the dry oral mucosa.

The diagnosis of JRP is based on presenting medical and dental history, physical exam, laboratory findings, and supportive imaging findings. Imaging modalities may include ultrasound, MRI, MR sialography, computed tomography, and sialendoscopy (see below). Culture and sensitivity assays of discharge from the affected gland should also be performed to help rule out an infectious cause.

Differential Diagnosis

Differential diagnoses include causes of bacterial and viral parotitis, especially mumps—even in the vaccinated patient. Diffuse infiltrative lymphocytosis syndrome (DILS), associated with HIV in particular, has a similar clinical presentation. Other causes to consider include other immune deficiencies such as an IgA deficiency, autoimmune disorders such as Sjögren's syndrome, and systemic diseases such as sarcoidosis and IgG4-RD. Sialolithiasis should also be considered along with salivary gland neoplasms. Eating disorders such as anorexia nervosa and bulimia may also present with similarly enlarged glands due to a noninflammatory sialadenosis.

Imaging and Laboratory Findings

Ultrasonography, because of its availability, ease of use, noninvasiveness and lack of radiation exposure, is often the first imaging modality used in the evaluation of a patient suspected of having JRP. Findings supportive of JRP include heterogeneous glandular enlargement, with areas of hypoechogenicity of 2 to 4 mm representing sialectasis or lymphocytic infiltration. There may be enlarged intraglandular lymph nodes and microcalcifications. These findings may be present even when the disease is quiescent. Sialography can also be employed to diagnose JRP since it allows visualization of fine branches of Stensen's duct and can highlight anatomic abnormalities.

Once ultrasound or sialography have been used to initially evaluate the patient, sialendoscopy is often used to confirm the diagnosis and provide treatment. Sialendoscopy allows for assessment of the anatomy over the course of Stensen's duct as well as detection of sialoliths, sialectasis, and ductal stenoses. Findings supportive of JRP include pale-appearing ductal walls, diminished ductal vascularity, areas of stenosis, and fibrinous debris or mucus plugs.[218]

Magnetic resonance imaging and magnetic resonance sialography have also been used. They represent noninvasive methods of evaluating the ductal and parenchymal portions of the parotid gland. MR sialography in particular allows for differentiation between the inflammation present in JRP from infiltrative diseases such as lymphoma. Computed tomography (CT) or CT sialography can be employed to evaluate the glandular parenchyma and adjacent structures and are superior at depicting calcifications such as sialoliths. CT, however, comes at the expense of radiation exposure.

Laboratory exams are important for ruling out other causes of recurrent parotitis including Sjögren's syndrome and HIV-related salivary gland disease. In addition to standard lab tests such as a complete blood count with differential, an HIV test and/or autoantibody panel may be warranted. A swab of expressed discharge from the affected gland may also allow differentiation from an infectious cause of parotitis.

Management

There is currently no standard treatment for JRP. There is a tendency for spontaneous remission of the disease near the onset of puberty or late adolescence; however, some patients will continue to experience swelling episodes into adulthood.

Treatment for acute episodes aims to relieve symptoms and prevent parenchymal damage and may include glandular massage, optimization of hydration, application of heat to the affected gland, mouth rinses, sialogogues, or chewing gum. Medical therapy may include analgesics, non-steroidal anti-inflammatory drugs, corticosteroids, and antibiotics.

Sialendoscopy has quickly become the first-line interventional approach and can be performed under local or general anesthesia. It provides a means of washing out intraductal debris, including sialoliths, addressing stenotic Stensen's ducts where present, and allows for installation of antibiotics or steroids into the ductal system. Parotidectomy and duct ligation have also been suggested in select cases.[218]

Systemic Conditions with Salivary Gland Involvement

Diabetes Mellitus

Diabetes mellitus (DM) is a common endocrine disorder that produces multiple metabolic abnormalities and may lead to microvascular and macrovascular complications. Many patients with uncontrolled diabetes report dry mouth and experience salivary hypofunction. In general, patients with poorly controlled DM tend to experience greater salivary gland dysfunction than well-controlled patients or controls.[219]

The etiology of diabetic salivary gland dysfunction may be related to multiple issues, including an underlying salivary gland pathology, such as alterations in salivary gland basement membranes or the microcirculation to the glands.[219] Poor glycemic control, poor hydration, autonomic nervous system dysfunction, and the effect of certain medications may also result in salivary gland dysfunction. Xerostomia in those with DM could also be attributed to thirst (polydipsia), a common, and sometimes presenting, manifestation of diabetes.

Anorexia Nervosa and Bulimia Nervosa

Salivary gland enlargement (sialomegaly), especially of the parotid glands, can occur in patients with the eating disorders anorexia nervosa and bulimia nervosa. The glandular enlargement is noninflammatory and non-neoplastic in nature and may be termed sialadenosis. It is speculated that this enlargement occurs due to nutritional deficiencies and/or the habit of repeated induced vomiting or other factors. Sialomegaly secondary to bulimia occurs in 10–68% of patients with bulimia and correlates directly with the number of daily episodes of vomiting.[220]

These eating disorders can also influence salivary flow and composition. Patients may suffer from hyposalivation and xerostomia, which may be related to dehydration secondary to vomiting or withholding food and drink. Hyposalivation and xerostomia may also occur due to the use of certain medications, such as antidepressants, used not only in treatment of the disorders but also for mood disorders—a common comorbidity.

Sialomegaly due to bulimia may resolve spontaneously when patients return to an optimal weight and re-establish healthy dietary habits, but this may take a long time. Conversely, in anorexia nervosa, salivary gland enlargement can persist despite a return to normal weight.[221] Relapse of the eating disorder can also lead to a recurrence of sialomegaly.

Conservative treatments for eating disorder-associated sialomegaly include the use of salivary stimulation in the form of sugar-free sour candy, application of heat, and optimizing hydration. Pilocarpine hydrochloride (5–15 mg/day) has also been used with limited success. When sialomegaly persists, it can be of cosmetic concern and negatively affect the patient's self-esteem. Superficial parotidectomy has been used in select cases although its use is controversial.[222]

Eating disorders are often difficult to diagnose because of the secretive nature of the conditions. To facilitate early diagnosis and treatment, clinicians should be aware of the common associated clinical findings (i.e., dental erosion, xerostomia, salivary gland enlargement, mucosal erythema, and cheilitis). Patients should be queried diplomatically if an eating disorder is suspected and an appropriate medical referral made.

Chronic Alcoholism

Chronic alcoholism is one of the primary causes of sialadenosis, an asymptomatic, bilateral, noninflammatory, persistent enlargement of the salivary glands, usually affecting the parotid glands. Salivary gland enlargement in these patients is thought to result from an ethanol-induced peripheral autonomic neuropathy resulting in disordered salivary gland metabolism and secretion.[223] Interestingly, sialadenosis attributable to alcohol occurs only in the presence of some form of liver disease and therefore its presence should prompt medical referral.[224] Chronic alcoholism is also associated with a reduction in parotid gland salivary flow and saliva-buffering capacity.[225] The exact etiology of decreased salivary flow is not definitively known but is thought to be due to dehydration and poor nutrition.[226]

Dehydration

Dryness of the oral cavity can be a result of suboptimal levels of salivary flow or excess evaporation of saliva, which can occur due to mouth breathing, for example. Hyposalivation, and concomitant xerostomia, may reflect systemic dehydration since normal salivary output requires movement of water from the systemic circulation through acinar cells into the salivary ductal system and into the mouth. Both stimulated and unstimulated parotid salivary flow rates were shown to decrease in studies in which healthy subjects underwent a controlled 24-hour dehydration followed by rehydration.[227]

Clinical signs of dehydration include dryness of the mucous membranes of the nose and mouth and longitudinal furrowing of the oral tongue.[227] When systemic dehydration is suspected, patients should be questioned regarding their daily fluid intake and urine output (taking into account dehydrating beverages such as coffee and alcohol) their daily sodium intake, and the use of dehydrating medications such as diuretics, laxatives, and antihistamines.

Requirements for daily water intake will vary based on an individual's body size, activity level, and additional factors. Risk of dehydration tends to be greater in the elderly for a number of reasons, including decreased fluid intake secondary to impaired thirst mechanisms and increased likelihood of use of dehydrating medications. Patients may also restrict fluid intake where there is fear of incontinence.[228] Patients with xerostomia should be counseled that reliance on thirst sensation alone to stimulate water intake may be inadequate. Rather, they should be advised to take frequent sips of water throughout the day to prevent dehydration and alleviate xerostomia.

Medication-Induced Salivary Dysfunction

Medications can have a number of adverse effects on salivary gland function. The most well-known of these are hyposalivation and xerostomia. More than 400 drugs with xerogenic potential have been identified, including antidepressants, anticholinergics, antispasmodics, antihistamines, antihypertensives, sedatives, bronchodilators, and newer targeted therapies and immunotherapies (e.g., immune checkpoint inhibitors). Attempts have been made to compile a comprehensive list of medications with documented effects on salivary

Table 9-3 Common drug categories associated with salivary hypofunction.

Analgesics
Anticholinergics
Antidepressants
Antihistamines
Antihypertensives
Antiparkinsonian
Antipsychotics
Antiseizure
Cytotoxic agents
Diuretics
Muscle relaxants
Sedatives and anxiolytics

gland function.[15] Table 9-3 summarizes the drug categories most commonly associated with salivary hypofunction.

Due to insufficient clinical investigations, relatively few drugs have been shown definitively to reduce salivary gland function. Some drugs may not actually cause impaired salivary output but produce alterations in saliva composition that lead to the perception of oral dryness. Other medications may affect only the unstimulated output, leaving stimulated function intact.

The pathogenesis of medication-induced salivary dysfunction differs with different classes of drugs. Anticholinergic drugs, the most well-recognized drug class associated with hyposalivation, inhibit acetylcholine binding to muscarinic receptors on salivary gland acinar cells preventing water movement through the ductal system and into the mouth. Other medications such as antihistamines and the alpha- and beta-blocker antihypertensives also inhibit neurotransmitter binding to the salivary gland acinar cells or perturb ion transport pathways, resulting in changes in the quantity and/or composition of salivary secretion.[229]

Medication-induced salivary hypofunction is more common in the elderly and they are more likely to be engaged in polypharmacy (generally defined as taking five or more medications), which further increases the likelihood of salivary hypofunction. A critical review of a patient's medications (both prescribed and over the counter), supplements, and herbal preparations is warranted to identify xerogenic agents and determine if the drug in question is still appropriate. Perhaps due to a lack of follow-up or if a patient has seen multiple health-care providers, the initial indication for a medication may no longer be applicable or there may be other redundancies in their prescribed medications. Communication with the patient's health care providers, therefore, can help optimize their medication regimen and diminish side effects.

Ideally, medication-induced salivary dysfunction would be alleviated by discontinuation of the drug(s) or substitution with a similar drug with little or no effect on the salivary glands. Additional strategies may include altering when the drug is administered. For example, if nocturnal xerostomia disrupts sleep, medications could be taken earlier in the day when xerostomia may be managed. Alternatively, if xerostomia is problematic during the day, taking a medication at night might resolve this issue. Lowering or dividing drug doses where possible may also help to minimize salivary gland effects. All proposed changes should be discussed with the prescribing clinician to determine the optimal strategy. Where change in medications is not feasible, the patient should be counselled in the management of hyposalivation and xerostomia (see section: Management of Xerostomia and Hyposalivation).

Drug-Induced Parotitis

Drug-induced parotitis, although rare, has been reported with numerous drugs but has only been definitively linked with a few. The most commonly associated medicines are iodine-containing drugs such as those used as imaging contrast media: hence the term "iodide mumps".[230] Other drugs include the antineoplastic drug L-asparaginase, clozapine, and phenylbutazone.[231]

Most cases of drug-induced parotitis are bilateral due to the systemic distribution of the drug, but unilateral cases have been reported. With respect to the antipsychotic clozapine, there are two competing theories as to the pathogenesis of reported parotitis. One theory proposes that it is the immunomodulating properties of clozapine that sensitize mononuclear blood cells leading to a sialadenitis. The second hypothesis posits that clozapine-induced hypersalivation results in a chronic inflammatory state leading to parotid sialolithiasis and subsequent parotitis.[232] In the majority of cases of drug-induced parotitis, the condition resolves with discontinuation of the causative agent.

Parotid Lipomatosis

Parotid lipomatosis is the salivary gland manifestation of lipodystrophy syndrome associated with long-term highly active antiretroviral therapy (HAART) for HIV/AIDS. It has been associated specifically with the first-generation protease inhibitors indinavir, nelfinavir, ritonavir, fosamprenavir, and saquinavir mesylate.[233]

Parotid lipomatosis presents as a painless, progressive enlargement of the parotid glands which can become a cosmetic concern. MRI of the parotids will show fatty replacement without cystic changes or masses. Histologically, there will be an infiltration of the normal glandular parenchyma with benign-appearing adipocytes. Case reports on treatment for parotid lipomatosis describe the use of bilateral

total superficial parotidectomy via a facelift approach. Long-term follow-up is advised due to the likelihood of recurrence.[234]

End-Stage Renal Disease

Patients undergoing hemodialysis for end-stage renal disease are likely to experience xerostomia and/or hyposalivation for a number of reasons. It is estimated that salivary flow is decreased in these patients typically by 20–55%.[235] The identified causes of hyposalivation include salivary gland atrophy and fibrosis, polypharmacy (it is estimated that a patient on hemodialysis takes an average of twelve daily medications, many with xerogenic potential), fluid intake restrictions, and the effects of the dialysis procedure. The cause of the salivary gland atrophy and fibrosis is unknown but salivary flow was found to be inversely related to the degree of atrophy and fibrosis. Optimal fluid management is paramount in the treatment of hemodialysis patients since both fluid overload and dehydration are linked to increased morbidity. With these factors in mind, management of xerostomia and hyposalivation should be closely coordinated with the patient's nephrology care team.[236]

Immune Conditions

Sjögren's Syndrome

Etiology and Pathogenesis

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by oral and ocular dryness, lymphocytic infiltration, dysfunction, and destruction of exocrine glands. Although the salivary and lacrimal glands are most commonly affected, SS can have widespread and diverse manifestations. Dryness may also affect other mucosal areas such as the skin, nasopharynx, throat, trachea, and vagina. Signs of systemic autoimmune disease with musculoskeletal, pulmonary, gastric, hematologic, dermatologic, renal, hepatic, and neurologic manifestations may also be evident in patients with SS. SS patients also frequently experience fatigue, arthralgias, myalgias, peripheral neuropathies, and dermatoses.

The definitive etiology of SS is unknown. There appear to be genetic and nongenetic, immune and nonimmune, environmental, and epigenetic factors involved in disease susceptibility and the disease process. Genetic studies have identified an association with HLA haplotypes and genes involved in both innate and adaptive immunity. Many studies have also explored the role of hormonal factors and viral infections in a genetically susceptible host. While it is unlikely that one unifying theory will account for all facets of this complex disease, there is developing evidence that salivary gland epithelial cells stimulated by interferons and other cytokines trigger and maintain chronic immune activation resulting in a vicious cycle of autoimmunity in a genetically susceptible host. This results in an autoimmune epithelitis which affects exocrine glands as well as various other organs. It is hoped that a greater understanding of its etiopathogenesis will generate future targeted therapeutics, preventive measures, and possibly even a cure. [237]

SS is classified as primary or secondary. Primary Sjögren's syndrome (pSS) occurs in the absence of another autoimmune disease, whereas secondary SS occurs in conjunction with another autoimmune disease such as systemic lupus erythematosus, rheumatoid arthritis, or scleroderma. It is for this reason that secondary Sjögren's syndrome may be referred to as "Sjögren's syndrome associated with another autoimmune disease" or polyautoimmunity. Recently, there have also been cases of Sjögren's syndrome/sicca syndrome reportedly triggered by the class of cancer immunotherapies known as immune checkpoint inhibitors. The phenotype observed in these cases is distinct from that of idiopathic cases and further study into the etiopathogenesis is warranted (see section: Sjögren's Syndrome/Sicca Syndrome Triggered by Cancer Immunotherapies).

Epidemiology

SS is now considered the second most common autoimmune disease after rheumatoid arthritis. Epidemiologic studies indicate some geographic variation in SS incidence and prevalence. A systematic review and meta-analysis of population-based studies from Europe, North America, and Asia indicates a pooled incidence rate for pSS of 6.92 per 100,000 person-years.[238] pSS predominantly affects women between the ages of 30 and 70 years of age, with a peak incidence between the ages of 55 and 65 years. pSS often appears in men after the age of 65 years resulting in the average overall age at diagnosis for men and women of 56.2 years. The female/male ratio incidence rate for pSS is 9.15; however, the rate of SS is likely higher in males than currently estimated since males tend to develop a different pattern of autoantibodies and are often missed using current classification criteria.[238,239] Although there is no clear consensus that disease severity is worse in males, several studies have reported more frequent extraglandular manifestations in men.[240]

Younger individuals and children may also be affected. In children, in particular, SS can initially present as recurrent episodes of parotitis which may be attributed to juvenile recurrent parotitis (JRP). Women with SS are also at an increased risk of having offspring with congenital heart block due to autoantibody-mediated damage to the atrioventricular node. This occurs in approximately 2% of infants born to women with anti-Ro/SSA antibodies and 3% of infants born to women with anti-La/SSB antibodies. Thus,

counseling seropositive women with SS of childbearing age regarding this risk becomes necessary.[241]

Clinical Manifestations

Patients with SS may experience the full spectrum of oral complications resulting from decreased saliva production.[242] Virtually all patients complain of dry mouth and attendant difficulties in speaking, tasting, and swallowing, and report the need to drink liquids throughout the day or to swallow foods. Xerostomia may first become evident with nocturnal awakening with thirst and the need to have chewing gum or lozenges to stimulate saliva production. Other associated complaints include dysgeusia or hypogeusia, coughing episodes, a globus sensation, dysphagia, and choking. The mucosa may be painful and sensitive to spices, heat, and coarse foods. Patients often have dry, cracked lips and angular cheilitis or oral candidiasis may be present.

Intraorally, the mucosa may be pale and dry, friable, or furrowed. Minimal salivary pooling is seen, and the saliva that is present tends to be thick and ropy. The tongue is often smooth (depapillated), but may be deeply fissured and painful. Mucocutaneous candidal infections are common, particularly of the erythematous form. Due to the lack of lubricating saliva, traumatic or frictional injury is increased and removable prostheses are not as well tolerated due to a reduction in retention usually afforded by saliva.

Reports of swollen salivary glands are common in the SS population (Figure 9-18) and indeed the 2002 American-European Consensus Group (AECG) criteria for SS by Vitali et al. contains within its patient questionnaire inquires as to whether the patient has experienced swollen salivary glands.[64] Glandular enlargement can be unilateral or bilateral, acute, intermittent or chronic and may occur due to one of many causes. Retrograde salivary gland infection due to stasis, inflammation, or obstruction due to sialolithiasis or mucus plugging can all result in glandular swelling. If the swelling is due to a stone or mucus plug, it often subsides if the patient passes calculus or a mucus plug into the mouth—in which case they may describe encountering a piece of sand or gravel in the mouth or experience a sour taste from the mucus plug.

Intermittent or persistent salivary gland swelling may also represent an inflammatory sialadenitis from lymphocytic infiltration of the salivary glands. Sialadenosis or fatty infiltration of the glands will also present as salivary gland swelling and can develop in SS patients on chronic or frequent intermittent corticosteroids or with metabolic disorders. Finally, glandular swelling may represent a lymphoma; 5–10% of patients with SS will develop this malignancy, most commonly a mucosa-associated lymphoid tissue (MALT) lymphoma.[243] A patient with persistent glandular swelling or the presence of salivary glands that feel indurated or nodular should undergo imaging and likely biopsy to rule out lymphoma.[244]

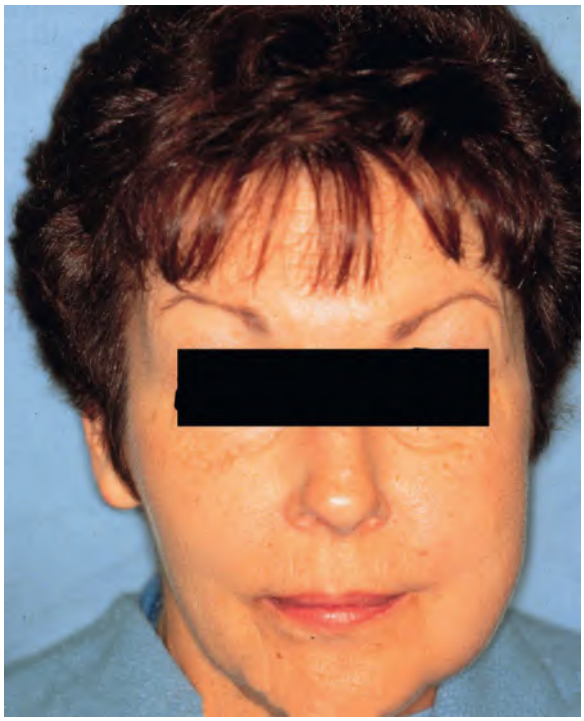

Figure 9-18 Chronic unilateral parotid salivary gland enlargement in a patient with Sjögren's syndrome.

An oral burning sensation, stomatitis, or glossodynia is a common complaint in SS patients and is most likely secondary to a fungal infection. However, it may be due to a parafunctional habit, hematinic deficiencies, allergies, oral lesions, burning mouth syndrome, or SS-associated neuropathy. The prevalence of peripheral nervous system involvement in SS has been estimated at 5–20% and is most commonly reported as an excruciating, burning pain of the extremities, or, when the cranial nerves are involved, may present as a trigeminal sensory neuropathy which can manifest as oral or facial numbness, paresthesia or dysesthesia, or, conceivably, a burning sensation of the mouth and/or tongue.[245]

Changes in volume and composition of saliva may lead to a significantly increased caries index which may be the initial sign alerting a clinician to suspect SS. The saliva of patients with SS has a much lower pH and buffering capacity, which, coupled with delayed sugar clearance due to diminished salivary flow, leads to an increased rate of decay. Patients with SS also tend to have higher levels of cariogenic and acidophilic bacteria such as *Lactobacillus acidophilus* and *Streptococcus mutans*. The decay pattern in patients with SS is also distinctive: caries develop at root and facial surfaces and cusp tips (locations usually more resistant to decay), as well as tooth-restoration interfaces.

Gastro-esophageal reflux disease (GERD) is a common comorbidity in SS patients and may result in, or contribute to, heartburn, hoarseness, chronic cough, nausea, chest pain, and dysphagia. Uncontrolled or unrecognized GERD also places the patient at increased risk of dental erosion, which, coupled with the already increased risk of dental decay, places the patient at an even greater risk of tooth structure loss.

Primary biliary cholangitis [PBC] (formerly known as primary biliary cirrhosis) is an autoimmune disease of the bile ducts leading to bile duct destruction, cholestasis, and liver failure which frequently occurs in patients with SS. PBC and SS share a number of common features. They have similar pathogenic mechanisms involving apoptosis leading to organ-specific, immune-mediated injury directed against the small bile ducts and salivary gland epithelia, respectively and they both have a female predominances. In the early phase of PBC, pruritus and fatigue are common complaints and there may be skin hyperpigmentation. End-stage signs include jaundice, ascites, hepatic encephalopathy, and upper GI bleeding.[246] Clinicians should be aware of these presenting signs and symptoms in order to make the appropriate prompt referrals.

Diagnosis

Currently, there is no set of clinical, laboratory, histopathologic, or imaging findings that serve as a gold standard for diagnosis of SS, rather classification criteria, intended for research purposes, have been proposed which may serve to guide further diagnostic testing. A variety of classification criteria sets have been developed and newer sets continue to be proposed to reflect our changing understanding of the disease. These classification criteria are not universally applied, however, and a patient may be diagnosed with SS without fulfilling them.

The most recognized of these criteria are the 2002 American-European Consensus Group (AECG) criteria by Vitali et al.,[64] the 2012 American College of Rheumatology classification criteria of the Sjögren's International Collaborative Clinical Alliance (SICCA) [ACR-SICCA] by Shiboski et al.,[65] and the joint collaboration of the ACR and the European League Against Rheumatism (EULAR) which established the 2016 ACR/EULAR criteria (Table 9-4).[66] The latter criteria set is currently considered the leading one.

The criteria sets share three common goals: to demonstrate objective evidence of: (1) dry eyes; (2) salivary gland involvement; and (3) provide proof of autoimmunity in order to differentiate SS from other causes of dryness and salivary gland dysfunction. Some key differences between these classification criteria involve whether sicca symptoms are taken into account, recommendations for autoantibody testing, evaluation of dry eyes, and assessment of salivary gland involvement. The 2016 ACR/EULAR criteria recognizes that patients may not always present with oral or ocular symptoms and that this should not result in automatic dismissal from further evaluation where there is a high index of suspicion. In addition, criteria for salivary gland imaging was included in the 2002 criteria set but omitted from more recent sets.[244]

Table 9-4 The 2016 American College of Rheumatology/European League Against Rheumatism Sjögren's syndrome classification criteria.[66] (Used with permission from John Wiley and Sons)

Item	Weight/score
The classification of primary Sjögren's syndrome (SS) applies to any individual who meets the inclusion criteria[a], does not have any of the conditions listed as exclusion criteria[b] and has a score of ≥4 when the weights of the five criteria items below are summed	
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm[c]	3
Anti-SSA/Ro-positive	3
Ocular staining score ≥5 (or van Bijsterveld score ≥4) in at least one eye[d, e]	1
Schirmer's test ≤5 mm/5 min in at least one eye[d]	1
Unstimulated whole saliva flow rate ≤0.1 mL/min[d, f]	1

[a] These inclusion criteria are applicable to any patient with at least one symptom of ocular or oral dryness, defined as a positive response to at least one of the following questions: [1] Have you had daily, persistent, troublesome dry eyes for more than 3 months? [2] Do you have a recurrent sensation of sand or gravel in the eyes? [3] Do you use tear substitutes more than three times a day? [4] Have you had a daily feeling of dry mouth for more than 3 months? [5] Do you frequently drink liquids to aid in swallowing dry food?—or in whom there is suspicion of SS from the European League Against Rheumatism Sjögren's syndrome Disease Activity Index questionnaire[247] (at least one domain with a positive item).

[b] Exclusion criteria include prior diagnosis of any of the following conditions, which would exclude the diagnosis of Sjögren's syndrome and participation in Sjögren's syndrome studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: [1] history of head and neck radiation treatment; [2] active hepatitis C infection (with confirmation by PCR), [3] acquired immunodeficiency syndrome, [4] sarcoidosis, [5] amyloidosis; [6] graft-versus-host disease; [7] immunoglobulin G4-related disease.

[c] The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and focus score count, using the protocol described by Daniel et al.[248]

[d] Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval without these medications in order for these components to be a valid measure of oral and ocular dryness.

[e] Ocular Staining Score described by Whitcher et al.[249] or by the van Bijsterveld score described by van Bijsterveld.[250]

[f] Unstimulated whole saliva flow rate measurement described by Navazesh and Kumar.[20]

Definitive diagnosis of SS can present a challenge. According to the Sjögren's syndrome foundation, there is an average lag of 2.8 years between onset of symptoms and diagnosis. Some reasons for delay include under-recognition of the signs and symptoms (particularly the extraglandular [systemic] manifestations, and in the absence of sicca symptoms), and under-referral to relevant specialists.[244]

In the evaluation of patients, salivary flow is usually measured in the office by calculation of a whole mouth unstimulated salivary flow rate as described above (see section: Sialometry). Assessment of stimulated salivary flow should also be performed as this indicates the relative functional capacity of the salivary glands and can help determine whether sialogogues are likely to be of benefit.

Ocular signs are assessed using the Schirmer's test in which normal tear production should result in wetting of ≥ 15 mm of a paper strip inserted under the lower eyelid for 5 minutes where wetting of ≤ 5 mm in at least one eye is considered to be a positive (abnormal) test. Alternative tests using vital dyes may be performed by an ophthalmologist and include the use of fluorescein to determine the integrity of the corneal epithelium, and rose bengal or lissamine green used for evaluating the integrity of the conjunctiva. Ocular symptoms consistent with dry eyes include complaints of a burning sensation, grittiness, itching, redness, mucous exudate, photophobia and glare, with symptoms typically worsening throughout the day.

The labial MSGB is considered to be the best sole diagnostic criterion for the salivary component of SS (Figure 9-19).[72] There is growing evidence to suggest that a histological examination should be performed in all SS patients (even those who otherwise fulfil the criteria), as it provides additional prognostic information with respect to the development of severe systemic involvement and lymphoma as well as allowing for monitoring disease and treatment response.[251,252]

A grading system for quantifying the salivary histologic changes seen in the minor glands is as follows: (1) the numbers of infiltrating mononuclear cells are determined, with an aggregate of 50 or more cells termed a focus; (2) the total number of foci and the surface area of the specimen are determined; and (3) the number of foci per 4 mm^2 is calculated which generates the focus score (FS).[253] The FS ranges from 0 to 12 with a FS of ≥ 1 considered positive for salivary gland involvement consistent with SS and 12 denoting confluent infiltrates. Acinar degeneration, with the relative preservation of ductal structures, may also be observed (Figure 9-20).

Parotid gland biopsy has been proposed as an alternative to the MSGB. The parotid gland biopsy presents several advantages over the MSGB including facilitating monitoring

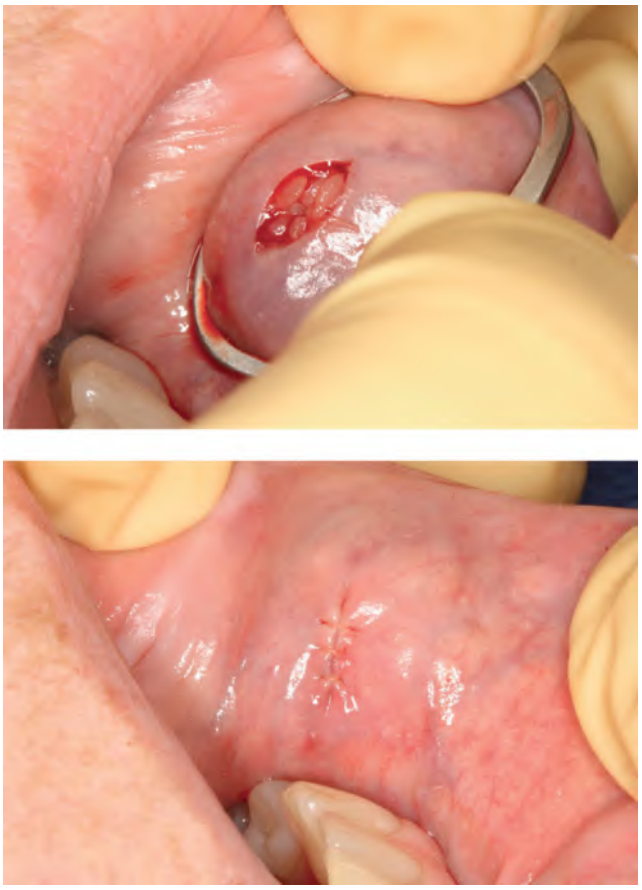

Figure 9-19 Top: Minor salivary gland biopsy of the lower labial mucosa illustrating how the minor salivary glands are readily accessible under the mucosal surface. Bottom: Primary closure after dissection and removal of the superficial minor salivary glands.

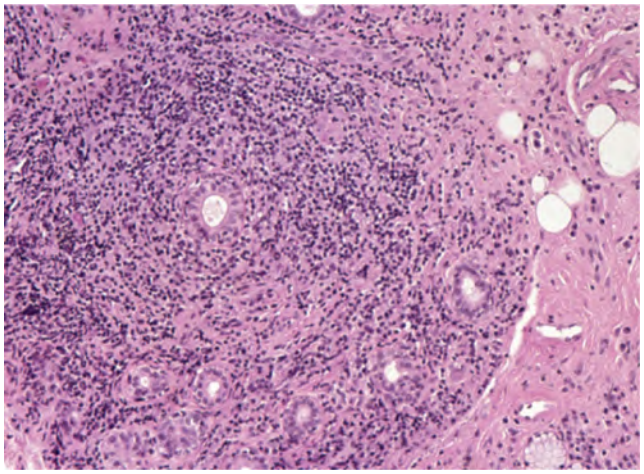

Figure 9-20 Histomicrograph of a biopsy of a labial minor salivary gland with features supportive of a diagnosis of Sjögren's syndrome including generalized chronic lymphocytic sialadenitis with fibrosis, atrophy of the gland parenchyma, and cystic dilatation of ducts.

of disease progression and treatment effect because it permits procuring multiple specimens or repeat biopsy from the same gland. Histopathologic results can also be compared with other data derived from the same gland (e.g., ultrasound, computed tomography, MRI). Furthermore, parotid gland biopsies permit detection of benign lymphoepithelial lesions (LELs), a characteristic histologic feature seen in the major salivary glands in SS, lymphomas, or other salivary gland pathology.[254] Finally, the parotid gland biopsy is considered a relatively simple procedure and there have been no reports of permanent morbidity, in contrast to the relatively high morbidity rate associated with the MSGB due to the risk of permanent damage to the sensory nerves of the lower lip.[71]

Histopathologically, in the affected parotid gland, epimyoepithelial islands with lymphoid stroma and LELs may be present in addition to the characteristic lymphocytic infiltration. Histologic criteria for diagnosis of SS using a parotid gland biopsy requires one of the following two criteria: (1) a FS ≥ 1 per 4 mm^2 of glandular parotid tissue (including adipose tissue) regardless of the presence of benign LELs; or (2) small lymphocytic infiltrates not fulfilling the criterion of a FS of ≥ 1, in combination with the presence of benign LELs.[255]

Imaging

Although both sialography and scintigraphy were included as part of the 2002 AECG classification criteria, both the 2012 ACR-SICCA and 2016 ACR/EULAR classification criteria have no imaging component. Sialography remains the best performing diagnostic imaging technique with respect to SS. It has an accuracy greater than that of MRI and ultrasound and will highlight characteristic changes associated with SS. MRI or CT can also be helpful, particularly in the assessment of enlarged glands and lymphadenopathy. MRI is preferable to CT unless a stone is suspected or other calcified structure requires visualization since it provides superior soft tissue resolution. Tc 99m radionuclide scintigraphy studies may also be used to determine salivary gland function; however, scintigraphy, in spite of being an optional part of the 2002 AECG criteria, scored poorly when compared with sialography, MRI, and ultrasound.[256]

Examination by ultrasound may be useful in a patient with SS to characterize the extent of salivary gland involvement, and to identify patients at risk for complications such as lymphoma.[36] A number of abnormalities detected by ultrasound have been associated with pSS, most significantly parenchymal inhomogeneity, especially when observed in bilateral salivary glands. Ultrasound can also reliably distinguish pSS from conditions that may have a similar clinical presentation such as IgG4-RD.[257] While the role of ultrasound in the diagnosis and response to treatment in SS is still being established, research groups have proposed its inclusion into classification criteria, and there are international efforts underway to optimize and standardize a scoring system.[258–260]

Serology

Primary and secondary SS patients often have prominent serologic signs of autoimmunity and other serologic abnormalities including the presence of certain autoantibodies, hypergammaglobulinemia, an elevated sedimentation rate, decreased white blood cell count, hypocomplementemia, and monoclonal gammopathies.[261]

The marker antibodies, anti-Ro/SSA and anti-La/SSB, are detected in 50–70% of patients with SS and can occur in one of three patterns: anti-SSA with anti-SSB, anti-SSA alone, or anti-SSB alone. Anti-SSB most frequently occurs with anti-SSA, since they share epitopes, but isolated anti-SSB is rare. As such, the presence of anti-SSB antibodies alone is not considered serologic proof of autoimmunity using the 2016 ACR/EULAR criteria. Since anti-SSA may occur in 1.7–17.5% of normal individuals, and may be present with other autoimmune conditions such as SLE, additional objective measures for diagnosis are required.[262]

The presence of these autoantibodies is associated with a higher rate of extraglandular manifestations and more active immunological status when compared with seronegative SS cases. Anti-SSA/SSB-positive patients with SS are more likely to have severe hypergammaglobulinemia and cryoglobulinemia, and are at an increased risk of developing lymphoma. Circulating levels of anti-SSA/SSB do not correlate with disease activity but the IgA anti-SSA titer appears to be associated with the rate of lymphocyte glandular infiltration.[263]

The association between vitamin D levels and SS has been explored. Vitamin D deficiency is relatively frequent in patients with primary SS and there is speculation that this deficiency plays a role in the pathogenesis of the disease.[264] Low levels of vitamin D in patients with SS might also play a significant role in the development of extraglandular manifestation such as lymphoma and peripheral neuropathy. Since patients with primary SS are at an increased risk of non-Hodgkin B cell lymphoma (NHL) and there is some evidence that a low dietary intake of vitamin D is also associated with an increased risk of NHL, it is recommended that patients with SS undergo evaluation of vitamin D levels and appropriate supplementation.[263]

Because monoclonal gammopathy is predictive of a poor outcome in primary SS patients, screening should be included in both the diagnostic and follow-up laboratory profiles. Monoclonal gammopathy is associated with a higher prevalence of parotid enlargement, extraglandular features, hypergammaglobulinemia, cryoglobulinemia and related

markers (e.g., rheumatoid factor, hypocomplementemia), and an overall poor prognosis due to development of neoplasia and death.[265]

Lymphoma

The development of a non-Hodgkin B cell lymphoma (NHL) is the most important hematologic complication of pSS. This type of lymphoma is estimated to develop in 5–10% of SS patients with the lifetime risk accumulating over time.[266] pSS patients have somewhere between a 7- and 20-fold increased relative risk of lymphoma over the general population, although some studies suggest this may be an overestimation.[267,268] There is a particularly significantly increased incidence of NHL observed among men with SS as well as in patients with persistent salivary gland swelling. Additional recognized risk factors include having a salivary gland biopsy focus score of $\geq 3/4\ mm^2$ or the presence of ectopic germinal centers (GC) within the biopsy.[269] The presence of these GCs has also been correlated with increased clinical disease severity, and increased positivity for anti-SSA/Ro and anti-SSB/La antibodies.[270]

The most common NHL affecting SS patients is a low-grade marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT). However, the more aggressive diffuse large B-cell lymphoma (DLBCL) is also found in SS patients. Some studies have found up to 10% of SS-associated MALT lymphomas transform into DLBCL. NHL in these patients tends to arise where SS is most active, often in the parotid and submandibular glands. Here, NHL most commonly presents as a unilateral, persistent, sometimes indurated and nodular swelling of the gland. The lymph nodes, orbits, nasopharynx, stomach, thyroid, and lungs are other common sites of development. Typically, the course of NHL is more indolent and without B symptoms (e.g., fever, weight loss, or night sweats) in the majority of patients.[267]

Since salivary gland lymphomas associated with SS often progress slowly, close clinical monitoring of all SS patients is necessary. This involves periodic physical examination (including a thorough head and neck examination) and assessment of immunoglobulin levels. Suspicious signs associated with NHL lymphoma in SS patients in addition to unilateral or bilateral salivary gland enlargement include lymphadenopathy, palpable purpura, splenomegaly, leg ulcers secondary to vasculitis, mixed cryoglobulinemia, and low C4 (complement component 4) levels.[270]

Clinical suspicion for lymphoma warrants a biopsy for further investigation. Incisional biopsy of extranodal tissue should be performed along with excisional lymph node biopsies if appropriate. Where salivary gland lymphoma is suspected, histopathologic analysis is often combined with techniques such as flow cytometry and fluorescence *in situ* hybridization for definitive diagnosis and characterization. Diagnosis of lymphoma requires prompt referral to an oncologist where further assessment will likely include evaluation of Waldeyer's ring, full body imaging, blood work including a complete blood count and chemistry panel, among other examinations.[271]

Management

There is currently no cure for SS and are no effective means of inducing remission. Goals of treatment are focused on alleviation of symptoms, prevention of sequelae of oral and eye dryness, and, where present, addressing systemic manifestations. As there is often a poor correlation between the severity of ocular symptoms and the results of objective tests for keratoconjunctivitis sicca, regardless of symptom severity, every patient should see a cornea or dry eye specialist at least once for a comprehensive evaluation.[244]

Treatment depends upon disease extent and symptom severity taking into account their effect on quality of life. Although there are no data from large randomized controlled trials to support use of any currently available pharmacologic therapy that effectively modifies the course of the disease, symptomatic management should be offered to every SS patient.[244] Comprehensive management requires a collaborative multidisciplinary approach involving referral to specialists to address the glandular and extraglandular manifestations specific to the patient and to tailor treatment to the organs or systems involved.

Agents used in the treatment of SS can be categorized as topical, for which there is strong supporting evidence, and systemic, for which there is limited data from randomized controlled trials to guide use.[272] Agents may include topical oral products (saliva substitutes), topical ocular agents (artificial tear drops, topical nonsteroidal anti-inflammatory drugs, topical corticosteroids, topical cyclosporine A, serum tear drops), oral muscarinic agonists (pilocarpine, cevimeline), hydroxychloroquine, oral glucocorticoids, immunosuppressive agents (cyclophosphamide, azathioprine, methotrexate, leflunomide, mycophenolate mofetil), and biological therapies (rituximab, abatacept, belimumab).[273] Here, we will highlight some common approaches to treatment, focusing on oral signs and symptoms. For a more comprehensive overview of treatment, please refer to the Suggested Reading list.

Management of Hyposalivation and Xerostomia in SS

Prior to the initiation of treatment for hyposalivation and xerostomia, baseline evaluation of unstimulated and stimulated whole salivary flow is recommended (see section: Sialometry). Management in SS patients revolves around the use of symptomatic therapies such as secretagogues, oral rinses and gels, mouthwashes, artificial saliva, and water

sipping (see section: Management of Xerostomia and Hyposalivation), and prevention of the sequelae of hyposalivation (e.g., dental caries), such as by the use of high-potency fluoridated toothpastes.

Mechanical stimulation (e.g., chewing gum) can provide some increased saliva production in SS patients with residual salivary gland capacity. In a systematic review investigating the safety and efficacy of treatments in pSS patients, there was no evidence that chewing gum had any more or less efficacy than saliva substitutes in reducing dry mouth symptoms. There was also no strong evidence to support any one specific oral topical therapy (e.g., lozenges, sprays, mouth rinses, gels, oils, chewing gum, and/or toothpastes) over another. As there are no definitive effective topical treatments, the focus of treatment should be on improving the patient's xerostomia rather on increasing saliva production.[272] Patients should be encouraged to try a number of different agents since response may differ between individuals.

Trial of nonpharmacologic agents should be attempted prior to consideration for systemic agents. There are two FDA-approved medications for dry mouth in SS: pilocarpine and cevimeline. These parasympathomimetic secretagogues have demonstrated the greatest reduction in xerostomia in SS patients with residual gland function. Both pilocarpine and cevimeline are muscarinic agonists which induce a transient increase in salivary output. Cevimeline is reported to have increased specificity to M3 muscarinic receptors compared with pilocarpine, which might result in a lowered potential for side effects. Cevimeline also tends to have a faster onset of effect than pilocarpine.[274]

In a retrospective study comparing side effect profiles and discontinuation rates of pilocarpine and cevimeline in patients with pSS, patients were more likely to continue with cevimeline than pilocarpine long term, mostly due to fewer reported side effects (primarily sweating). It was also found that therapeutic failure of one secretagogue did not necessarily predict similar results with the other and, in fact, those who had changed from one secretagogue to the other were more likely to continue treatment for the long term. This implies that it is reasonable to encourage patients to consider trying the alternative agent after initial treatment failure.[275] Common side effects of these medications include sweating, flushing, urinary urgency, nausea, and gastrointestinal discomfort. Although these side effects are frequent, they are rarely severe or serious, but they may be significant enough to be intolerable to patients.

Pilocarpine and cevimeline are contraindicated in patients with uncontrolled asthma, narrow-angle glaucoma and acute iritis, and in patients who are pregnant or breastfeeding. They should be used with caution in patients with significant cardiovascular disease, Parkinson's disease, asthma, or chronic obstructive pulmonary disease. Pilocarpine is recommended at 20–30 mg per day, and cevimeline up to 90 mg per day, both in divided doses. When introducing these medications, one approach to minimize side effects is to start with a low dose taken after meals and increase slowly on a weekly basis until the target dose is achieved.[244] To further minimize side effects, a patient may even start with a very low dose, for example using a 2.5 mg dose of pilocarpine, by dividing a 5 mg tablet.

Although a systematic review concluded that there was very limited evidence to support the use of these medications in pSS patients, it was deemed that a trial for up to 12 weeks (given the potential for delayed response), should be offered to all patients where response to nonpharmacologic therapy is inadequate. Interestingly, although these oral secretagogues are not indicated for keratoconjunctivitis sicca, there is some evidence that they may be effective in alleviating dry eye symptoms as well.[276,277]

Interventional Sialendoscopy

A few studies have demonstrated that sialendoscopy, including irrigation of the ductal system with saline or a saline/corticosteroid solution, may improve salivary gland function and alleviate symptoms such as xerostomia in SS patients. Ductal strictures and mucus plugs (common findings and major causes of obstruction and recurrent sialadenitis among patients with SS) can also be addressed with interventional sialendoscopy.[69]

Systemic Treatments

Systemic glucocorticoids Systemic glucocorticoids (e.g., methylprednisolone) are used at the minimum dose and length of time necessary to control active systemic disease in SS patients; their frequent use is not supported by reliable scientific data. Glucocorticoids at high doses are believed to downregulate the immune inflammatory process within the salivary and lacrimal glands.

Immunosuppressive agents Immunosuppressive agents, such as leflunomide, methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide can act as steroid-sparing agents in patients systemic disease who may require long-term therapy. Since there are no clinical trials comparing the safety and efficacy of these agents, there are no standard treatment recommendations.[273]

Antimalarial Agents The antimalarial agent hydroxychloroquine has been used in SS patients to address acute musculoskeletal pain based upon its comparable use in other autoimmune diseases such as systemic lupus erythematosus. Some studies have demonstrated the efficacy of hydroxychloroquine in reducing sicca and constitutional symptoms such as fatigue and arthromyalgia. However, in a randomized, placebo-controlled trial, the use of hydroxychloroquine in

pSS patients did not improve symptoms during 24 weeks of treatment compared with a placebo.[278]

Hydroxychloroquine has been reported to increase salivary flow rate and reduce some inflammatory indices such as ESR and C-reactive protein, and results in an improved immunologic profile with respect to rheumatoid factor, anti-Ro/SSA, and anti-La/SSB. Owing to its antineoplastic properties, hydroxychloroquine also has the potential to reduce the risk of lymphoma development in those with SS.[263] It may be prescribed during pregnancy in women with SS as it is considered safer than many alternative treatments.

Biological Therapies It is now well established that both B- and T-cells are involved in the pathogenesis of SS hence the use of biological therapies such as rituximab, a monoclonal antibody developed against the surface B-cell molecule CD20. Rituximab is the most frequently used biological agent and the most widely studied B-cell targeted therapy for SS.[279] The majority of studies have indicated that rituximab demonstrated at least some systemic effect and therefore, it may be considered for patients with severe, refractory systemic disease.[280] Belimumab is another B-cell targeted therapy which inhibits B-cell activating factor (BAFF). Studies have indicated that belimumab resulted in improvements in parotid swelling and was effective in patients with disease refractory to rituximab.[273]

Therapeutic investigation is now shifting from focusing on B-cell depletion to biologicals targeting cytokines, T-cells, and intracellular signaling pathways. Studies are now exploring the effect of monoclonal antibodies targeting the BAFF-receptor and the association between B-cell depletion and BAFF inhibition. Research is also focused on treatment for lymphomas related to SS, searching for predictive factors of biological response and identification of biomarkers which will help identify predictors of poor outcomes.[273,281]

Sjögren's Syndrome/Sicca Syndrome Triggered by Cancer Immunotherapies

Recently, there have been reports of cases of Sjögren's syndrome/sicca syndrome triggered by the class of cancer immunotherapies known as immune checkpoint inhibitors (ICIs) (e.g., PD-1 inhibitors nivolumab and pembrolizumab, PD-L1 inhibitor durvalumab, and CTLA-4 inhibitor ipilimumab) used to treat melanoma, lung cancer, and kidney cancer, among other neoplasms.[282] This phenomenon is considered an immune-related adverse event: side effects associated with the increased activity of the immune system by ICIs that can involve multiple organ systems including the skin, liver, and lungs, gastrointestinal tract, endocrine, nervous, and musculoskeletal systems. Up to 80% of patients receiving ICIs experience adverse events; the overall prevalence of all types of systemic immune-related adverse events is reported as less than 1%; however, the reported prevalence is much higher (2.5%) in patients receiving combination therapy compared with those treated with a single ICI.[283]

The etiopathogenesis of this phenomenon is unknown but it is suspected there may be a genetic predisposition. It is possible that some cases represent a latent SS, especially in women of middle age, and that the cancer diagnosis and initial development of SS was coincidental. This highlights the importance of evaluation of pre-existing autoimmune signs and symptoms prior to initiating biological therapy. The presence of a pre-existing autoimmune disease does not necessarily preclude treatment with an ICI, but the patient must be made aware of the risk of exacerbation or development of new signs and symptoms and should be under the close collaborative clinical care of their rheumatologist, oncologist and oral medicine specialist.[284]

The phenotype observed in cases of Sjögren's syndrome/sicca syndrome triggered by ICIs is distinctly different from that of idiopathic cases of SS. In the former, 50% occurred in males, the mean age at diagnosis is approximately 10 years older, and there is often an abrupt onset within the first 3 months of ICI treatment.[282] There is also a lower frequency of both oral and ocular dryness and a lower frequency of abnormal ocular tests. With respect to MSGB histopathology, the typical focal lymphocytic sialadenitis seen in the idiopathic form of SS was observed in half of cases biopsied. However, this infiltrate was composed mainly of CD3+ T cells with a slight predominance of CD4+ over CD8+ T cells and a virtual absence of B cells, in contrast to the lymphocytic infiltrate in idiopathic Sjögren's syndrome, which is composed mainly of CD20+ B cells, with variable germinal center formation and number of CD3+ T cells, and a slight predominance of CD4+ over CD8+ T cells.[283] There is also a much lower prevalence of SS-associated serum autoantibodies (52% antinuclear antibody, 20% anti-Ro/SSA, 9% rheumatoid factor, 8% anti-La/SSB), when compared with idiopathic primary SS.[282]

Patients who developed Sjögren's syndrome/sicca syndrome triggered by ICIs were also more likely to require treatment for severe symptoms and systemic disease manifestations including the use of second- and third-line therapies. Management may also include discontinuation of the ICI(s), especially where there is significant involvement of internal organs, corticosteroids, and/or limited use of immunosuppressive/immunomodulatory agents. Although, with treatment, some patients reported a subjective improvement, none reported complete resolution of their sicca symptoms and few patients returned to normal salivary flow rates. It is likely that many of these patients will experience long-term salivary hypofunction and will therefore require ongoing close follow-up.[285]

Chronic Graft-Versus-Host Disease (cGVHD)

cGVHD is a complex clinical entity that occurs following bone marrow transplantation. It develops within several months of hematopoietic stem cell transplantation (HSCT) in approximately 25–80% of patients.[286] Hyposalivation, xerostomia, and keratoconjunctivitis sicca, some of the more common manifestations of cGVHD, occur due to infiltration of the salivary and lacrimal glands respectively by autoreactive T lymphocytes.[287]

Salivary gland involvement in cGVHD tends to develop rapidly and be very severe, while recovery often does not occur until at least 1 year following transplantation. Changes in both saliva composition and quantity have been observed. The histopathologic changes observed in cGVHD can resemble those seen in Sjögren's syndrome: lymphocytic infiltration of the minor salivary glands, parenchymal destruction, and fibrosis. In general, treatment of cGVHD consists of the use of immunosuppressive agents such as methylprednisolone and cyclosporine. Treatment of hyposalivation and xerostomia with pilocarpine has also been reported.[288]

Granulomatous Conditions

Tuberculosis

Tuberculosis (TB) is a bacterial infection, usually caused by *Mycobacterium tuberculosis*, characterized by granulomatous inflammation with variable degrees of necrosis. Although the lungs are most commonly affected, other tissues, including the salivary glands, may be involved. Salivary gland tuberculosis has been reported in both the major salivary glands, most commonly the parotid and submandibular glands, and in the minor salivary glands.[289] Salivary gland TB is usually confined to the intraglandular and periglandular lymph nodes; involvement of the salivary gland parenchyma is rare and usually represents spread from the adjacent lymph nodes.[290]

TB of the major salivary glands has a varied clinical appearance. Most commonly, it presents as a slow-growing, firm mass with a variable degree of fixation. Diffuse glandular enlargement and acute sialadenitis may be seen if there is parenchymal involvement. It may alternatively present as a peri-auricular fistula, abscess or with cyst formation.[291] Salivary gland enlargement may occur as part of a characteristic symptom complex (i.e., weakness, weight loss, and cough) or in the absence of systemic symptoms, and the patient may complain of xerostomia.

Salivary gland TB may present a diagnostic challenge in the absence of additional signs and symptoms of TB. The clinical appearance is sometimes indistinguishable from that of some salivary gland neoplasms and sarcoidosis.[289] Where TB of the salivary gland is suspected, investigation requires review of the patient's medical and dental history, physical examination, imaging, microbiologic tests, molecular biologic assays, and histological evaluations such as fine-needle aspiration cytology (FNAC). Imaging and FNAC are often inconclusive, however, necessitating an open biopsy.[290]

Definitive diagnosis of TB requires the isolation and identification of mycobacteria. PCR when applied to FNAC specimens can enhance specificity and sensitivity. Using PCR-based salivary assays, evidence of *M. tuberculosis* was found in 98% of infected patients, representing a detection rate significantly better than culture (17%), suggesting that in the future, salivary tests may be helpful for the diagnosis of TB.[292]

Treatment of salivary gland TB requires standard multidrug chemotherapy using a combination of antibiotics including isoniazid, rifampicin, pyrazinamide, and ethambutol. Additional chemotherapy and salivary gland surgery may be required to treat persistent salivary gland disease.[293,294]

Sarcoidosis

Sarcoidosis is a chronic granulomatous condition of unknown etiology in which T lymphocytes and mononuclear phagocytes cause destruction of affected tissue. It most commonly first appears in the lungs, skin, and lymph nodes, but any organ system can be affected. Salivary gland involvement is seen in an estimated 5–10% of those with sarcoidosis.[295]

With respect to the salivary glands, clinical presentation varies from a complete lack of symptomatology to xerostomia or painful glandular swelling, which may be unilateral, bilateral, or synchronously affect multiple glands. Parotid gland swelling is the most common presentation while clinically silent disease is most often discovered in the minor salivary glands upon biopsy.

Because there are numerous pathoses that can clinically mimic sarcoidosis of the salivary glands, such as tuberculosis, Sjögren's syndrome, lymphoma, and salivary gland tumors, evaluation to rule out other processes is warranted. In particular, when sarcoidosis affects both the salivary and lacrimal glands, patients may present with xerostomia/hyposalivation and keratoconjunctivitis sicca, not unlike that of Sjögren's syndrome.

Heerfordt's syndrome (uveoparotid fever) is a form of sarcoidosis that involves parotid gland swelling, inflammation of the uveal tract of the eye (uveitis), chronic fever, and facial nerve palsy. The typical glandular presentation of Heerfordt's syndrome is bilateral, painless, and firm enlargement of the parotid glands with diminished salivary output. Unilateral salivary gland enlargement has also been reported.[296]

The diagnosis of sarcoidosis is based upon supporting clinical features and the presence of non-necrotizing granulomas in a biopsy specimen; the imaging features of salivary gland sarcoidosis are nonspecific.[295] Examination of a minor salivary gland biopsy specimen and laboratory assays including calcium levels, autoimmune serologies, and serum

angiotensin-converting enzyme (ACE) levels, can confirm or refute the diagnosis of sarcoidosis and help differentiate it from other similarly presenting pathoses such as Sjögren's syndrome.[297]

Treatment of sarcoidosis may range from observation only to the use of systemic corticosteroids and/or immunosuppressive steroid-sparing agents such as methotrexate, azathioprine, leflunomide, and mycophenolate mofetil. The tumor necrosis factor-alpha (TNF-alpha) antagonists infliximab and adalimumab may be used in cases refractory to steroids or immunosuppressive therapy.[298] Salivary gland involvement of sarcoidosis is usually responsive to systemic treatment but surgical excision of granulomatous tissue may be required. Sarcoidosis-associated xerostomia may be treated symptomatically (see section: Management of Xerostomia and Hyposalivation).

Crohn's Disease

Crohn's disease is an inflammatory condition of the gastrointestinal tract which can present with oral signs that may precede intestinal manifestations. Apart from the more commonly known serpiginous lesions of pyostomatitis vegetans, there are reports of Crohn's disease involving the minor salivary glands of the oral cavity, clinically appearing as a saliva-draining cutaneous fistula associated with the parotid gland duct, or as multiple submucosal nodules.[299,300] Histopathologically, these nodules were composed of non-necrotizing granulomas within the walls of the minor salivary gland ducts. Additional findings in the minor salivary glands were foci of lymphocytes within the stromal connective tissue and signs of acinar atrophy and ductal hyperplasia.[301]

Often, both the oral lesions and gastrointestinal symptoms of Crohn's disease resolve after appropriate therapy, which may include the use of antibiotics, glucocorticoids, sulfasalazine, azathioprine, 6-mercaptopurine, methotrexate, or biological agents, such as the TNF-alpha inhibitors infliximab or adalimumab.

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is an immune-mediated vasculitis of the small- and medium-sized vessels characterized by necrotizing granulomatous inflammation. It most commonly affects the upper and lower respiratory tracts, lungs, and kidneys.

The head and neck are involved in nearly 90% of GPA cases with the most commonly affected areas being the nose, eyes, ears, and mouth. Although rare, salivary gland enlargement may be the initial manifestation of GPA allowing for prompt treatment and thereby possibly preventing irreversible organ damage. Salivary gland involvement is typically accompanied by manifestations in other organs, but there are reports of isolated parotid gland involvement. With respect to the major salivary glands, GPA usually affects the parotid or submandibular glands in a unilateral or bilateral fashion. A combination of parotid and submandibular gland involvement has been reported in a few cases.[302]

GPA affecting the salivary glands will present as a painful or painless glandular swelling and there may be accompanying neurologic manifestations such as facial nerve weakness or hearing loss. A cutaneous fistula overlying the parotid gland has been reported in many cases. Depending on the extent of disease, the patient may also present with rhinitis, severe rhinorrhea, epistaxis, sinusitis, a "saddle nose" deformity, nonspecific oral ulcerations, or hyperplastic gingival lesions with petechial hemorrhages known as "strawberry gingivitis." Related constitutional symptoms include fever, migratory arthralgias, malaise, anorexia, and weight loss. Where there is lung involvement, hoarseness, cough, and dyspnea may be present.

Diagnosis of GPA is made through a combination of clinical, laboratory, and histopathologic analyses. An open biopsy is indicated if a fine-needle aspiration biopsy is nondiagnostic. Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) levels are highly specific but have variable sensitivity dependent on disease activity. c-ANCA may be negative in 15–33% of patients, especially where there is renal involvement.[303] Effective management of GPA can result in resolution of salivary gland swelling and pain and may involve the use of glucocorticoids, methotrexate, cyclophosphamide, rituximab, and plasmapheresis.

Sialorrhea

Sialorrhea (hypersalivation or ptyalism) is defined as excessive salivation and is the result of either increased saliva production or decreased saliva clearance. Sialorrhea can lead to drooling (i.e., excess saliva beyond the lip margin). Drooling is considered normal in children less than 4 years of age prior to the development of oral neuromuscular control. Primary sialorrhea is defined as true salivary hyperfunction resulting in drooling. Secondary sialorrhea results in drooling due to impaired neuromuscular control (such as with a swallowing disorder) and/or a sensory processing disorder in which the presence of saliva is not properly detected and, as a result, not effectively cleared from the oral cavity. Impairment in the oral phase of swallowing may lead to anterior drooling (saliva leaving the oral cavity) while dysfunction of the pharyngeal phase of swallowing may lead to posterior drooling (saliva leaking into the hypopharynx), which increases the risk of aspiration.

Sialorrhea may be observed associated with neurological diseases such as amyotropic lateral sclerosis (ALS), cerebral palsy, and Parkinson's disease, or with neoplasms of the

upper aerodigestive tract. It can be associated with certain medications[15] (Table 9-5), hyperhydration, infant teething, the secretory phase of menstruation, heavy metal poisoning (e.g., mercury, selenium), organophosphorus (acetylcholinesterase) poisoning, nausea, obstructive esophagitis, neurologic changes such as in a cerebral vascular accident (CVA), and central neurologic infections.[304]

Sialorrhea as a manifestation of GERD is often referred to as "water brash" or "acid brash" and may be particularly evident during pregnancy. Sialorrhea may also be part of a constellation of signs and symptoms of autonomic dysfunction associated with infection with the rabies lyssavirus. Other conditions that can be associated with sialorrhea include Down syndrome, fragile X syndrome, and autism.[304] Minor hypersalivation may result from local oral irritations, such as aphthous ulcers or an ill-fitting oral prosthesis. Idiopathic paroxysmal sialorrhea is a rare condition in which there are paroxysms of increased salivary flow occurring 1 or 2 times per week for a duration of 2 to 5 minutes preceded by a prodrome involving nausea or epigastric pain.[305]

Table 9-5 Medications and conditions that can cause hypersalivation and drooling.

Medications
Pilocarpine
Cevimeline
Bethanechol
Clozapine[1]
Olanzapine[1]
Venlafaxine[1]
Clobazam[1]
Digoxin
Lithium[1]
Nitrazepam
Physostigmine
Risperidone[1]
Neurologic diseases
Parkinson's disease
Wilson's disease
Amyotrophic lateral sclerosis
Down syndrome
Fragile X syndrome
Autism
Cerebral palsy
Organophosphate poisoning
Heavy metals
Arsenic
Iron
Lead
Mercury
Selenium
Thallium
Hyperhydration
Ill-fitting dentures
Rabies
Secretory phase of menstruation

Key: 1- may also cause xerostomia.

Clinical Presentation

When sialorrhea results in drooling, it can result in social embarrassment and affect a patient's quality of life. In particularly severe cases and where there is impaired swallowing, partial or total airway blockage may lead to inhalation of oral contents and aspiration pneumonia. Sialorrhea can also lead to perioral irritations, malodor, and traumatic ulcerations that can become secondarily infected by fungal or bacterial organisms.

Diagnosis

As there is a multitude of causes of sialorrhea, it is essential to obtain the history of hypersalivation along with a complete medical history and review of medications. A systematic head and neck evaluation should be performed including a cranial nerve examination, noting the presence of any head/neck/oral masses and lesions, and neuromuscular dysfunction. An evaluation of the condition of removable intraoral prostheses should also be performed.

Salivary flow rates should be obtained to determine if the sialorrhea is due to an overproduction of saliva (see section: Sialometry). The normal rate of unstimulated salivary output from all glands is approximately 0.3–0.4 mL/minute. Collection of unstimulated whole saliva using a drainage method into a preweighed container that results in more than 1.0 mL/minute suggests a greater than normal production of saliva. If examination indicates that the cause of sialorrhea is due to a problem in secretion clearance or there is a complaint of dysphagia or odynophagia, further imaging to rule out an obstructive cause (e.g., esophageal stricture or tumor) is necessary and a swallowing study may be indicated.

Blood samples should be obtained and evaluated for heavy metals and organophosphate pesticides if there is suspicion of toxicity. Women of childbearing age should be evaluated for potential pregnancy. If the onset of sialorrhea is acute, a CT scan of the brain may be required to rule out a CVA or a central nervous system mass or infection.

Management

Treatment for sialorrhea should take into consideration the etiology, risks and benefits of treatment, and the effect on quality of life. There are several categories of treatments: physical therapy, medications, surgery, and radiation therapy. Additional strategies may involve changes in diet or medications, oral habits, and behavior modification.

The management of drooling may require a multidisciplinary approach incorporating speech-language pathologists, physiotherapists, or occupational therapists, for example. Physical therapy can be used to improve neuromuscular control (but requires patient cooperation) and may involve the use of oral-motor exercises and intraoral devices such as palatal training devices.

Drug-based treatments for sialorrhea are prescribed based on etiology. If the patient is experiencing sialorrhea secondary to a pharmaceutical agent, alternate medications should be considered. If the therapeutic regimen cannot be altered or in other circumstances, a compatible xerogenic agent (e.g., glycopyrrolate, scopolamine, benztropine, amitriptyline, atropine, or diphenhydramine hydrochloride) may be added.[306] A glycopyrrolate oral solution has been approved in the United States for drooling in children with neurologic conditions. Intraoral tropicamide films are also available, which provide short-term relief of sialorrhea and have been used in patients with Parkinson's disease experiencing sialorrhea.[307] The anticholinergic effects of these medications downregulate acetylcholine resulting in decreased saliva secretion via the parasympathetic nervous system. They have side effects, however, which may make them intolerable to some patients.

Sialorrhea that occurs secondary to chronic nausea (e.g., during chemotherapy) can be treated with an antiemetic. Sialorrhea due to GERD is a protective buffering response to acids encountered in the oral cavity. Under most circumstances, when the GERD is appropriately managed, the sialorrhea resolves.

Botulinum toxins (BoNT) A and B are also used for the management of sialorrhea. They have proven efficacy, fewer side effects than anticholinergic medications, and their use can decrease the risk of aspiration pneumonia in people with neurologic diseases.[308] BoNT works by inhibiting the presynaptic release of acetylcholine and other neurotransmitters at the neuroglandular junction. BoNT-A injections have been used to treat sialorrhea in adults with Parkinson's disease, head and neck cancer, stroke, and other neurodegenerative diseases. It is also used for sialorrhea in children with cerebral palsy or other neurologic diseases.

The therapeutic effects of BoNT-A when injected into the salivary glands can extend for 3 to 6 months. Since they are the greatest contributors to saliva volume, the submandibular and parotid glands are the most commonly injected sites. Injection into these glands is performed using ultrasound guidance but, currently, there is no consensus on dosage or injection technique. The commonly reported side effects include injection site pain, difficulty chewing, increased saliva thickness, xerostomia, and rarely a transient dysphagia. There is also a risk of facial nerve trauma. Some limitations to BoNT injection include cost, necessity for retreatment, and possible need for sedation in the pediatric or uncooperative patient. Repeat injection may lead to antibody formation and diminishing efficacy.[309]

Surgical intervention is reserved for the most severe cases of sialorrhea that are refractory to conservative and pharmacologic therapy. There are a number of surgical techniques that have been used to treat sialorrhea, particularly in patients with poor or deficient neuromuscular function, such as in children with cerebral palsy. Several surgical strategies have been used including decreasing nervous stimulation to the salivary glands by denervation, re-routing or blocking salivary flow by transposition or ligation of the salivary ducts respectively, or excision of salivary gland tissue. These techniques are successful in reduction of drooling approximately 80% of the time, with occasional postoperative complications such as ranula formation, pain, and numbness.[310] There is also the risk of hyposalivation, and its attendant complications, and severe xerostomia, particularly with gland excision.

Radiation therapy is rarely used for sialorrhea and is typically reserved for elderly patients or those who are not candidates for surgery or other medical therapies (e.g., patients with amyotrophic lateral sclerosis (ALS) or Parkinson's disease).[311] Side effects include hyposalivation and xerostomia, mucositis, dermatitis, pain, and increased salivary viscosity, and there is an increased risk of development of radiotherapy-associated neoplasia.[312]

MANAGEMENT OF XEROSTOMIA AND HYPOSALIVATION

Treatments for dry mouth may be divided into four main categories: (1) preventive therapies; (2) symptomatic (palliative) treatment; (3) local or topical salivary stimulation; and (4) systemic salivary stimulation. For treatment of the underlying disorder associated with hyposalivation, please see section: Specific Diseases and Disorders of the Salivary Glands. Successful management of xerostomia and hyposalivation often involves a combination of agents tailored to the patient's needs. Management approaches are summarized in Table 9-6.

Preventive Therapies

The use of topical fluorides in a patient with salivary gland hypofunction is critical to prevent dental caries since, where there is hyposalivation, there may be insufficient saliva to effectively remineralize the enamel. There are many different fluoride therapies available, from low-concentration over-the-counter fluoridated mouth rinses to more potent, highly concentrated prescription fluorides (e.g., 1.1% neutral sodium fluoride) that are applied by brush or in a custom

Table 9-6 Management of xerostomia.

Management Approach	Examples
Preventive therapies	Supplemental neutral fluoride; remineralizing agents
Symptomatic (palliative) treatments	Water; saliva substitutes
Local or topical salivary stimulation	Sugar-free gums and candies
Systemic salivary stimulation	Parasympathomimetic secretagogues (e.g., cevimeline and pilocarpine)

carrier. Oral health care practitioners may also apply fluoride varnishes in the office; the dosage, method, and frequency of application (from daily to weekly) should be determined based on the patient's ability to perform oral home care and caries risk.[313] In a patient with dry mouth, neutral fluoride, rather than acidulated phosphate fluoride (APF), should be used. The low pH of acidulated agents (pH ~ 3) may irritate dry, sensitive mucosa. In addition, assuming the patient has an extensive restorative history, APF will etch composite restorations, including glass ionomer cements, and corrode porcelain surfaces.

Patients with hyposalivation require frequent dental visits (at least every 3–4 months) and must work closely with their dentist and hygienist to maintain optimal oral health. Time should be allotted to review instructions in optimal brushing and flossing techniques, discuss the use of other devices such as oral irrigators and interdental brushes, and establish a personalized home care regimen. Recommended practices include brushing at least twice a day and at least daily use of floss or interdental devices. The antiseptic chlorhexidine, used as a mouth rinse twice daily, can reduce cariogenic microbial load and is effective as a chemical plaque control agent. It can be especially helpful in patients with high levels of *Streptococcus mutans* (i.e., $\geq 10^6$ colony forming units per mL of saliva). The dispensing pharmacy should be requested to provide the patient with a chlorhexidine solution formulated without alcohol.

In the absence of the remineralizing properties of saliva, tooth demineralization proceeds unchecked, speeding the loss of tooth structure. In the presence of lesions of demineralization, remineralizing products, such as those containing calcium and phosphate, may be of benefit. Increased salivary calcium and phosphate levels can reduce enamel solubility, enhance remineralization and thereby protect against caries development. Casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) complex is reported to have anticariogenic effects. It can reduce enamel demineralization and promote remineralization by buffering free calcium and phosphate ions. ACP is incorporated into plaque and dental surfaces and maintains a state of supersaturation with respect to tooth enamel. Remineralizing products can be applied by the patient or caregiver to cleansed teeth just prior to the application of a high-potency fluoridated product.

Patients with dry mouth may also experience an increase in oral infections, particularly mucosal candidiasis. This is often of the erythematous form where the patient may present with redness of the mucosa and complaints of a burning sensation or soreness of the intraoral soft tissues. Angular cheilitis, usually seen as persistent cracking and erythema at the corners of the mouth, is also common. A high index of suspicion should be maintained, and appropriate treatment should be instituted. Patients with salivary gland dysfunction, however, may require prolonged treatment and periodic retreatment to eradicate oral fungal infections.[242] Patients should also be advised of the potential increased risk of development of oral candidiasis if they are to undergo a course of treatment likely to promote a fungal overgrowth, such as with systemic antibiotics or intraoral steroids.

Symptomatic Treatment

Patients should be encouraged to sip water throughout the day to help moisten the oral cavity and clear debris from the mouth. Since wettability of the oral mucosa and enamel by water is poor, any relief of xerostomia is usually very temporary.[13] In addition, since drinking copious amounts of water may effectively wash away saliva and disrupt sleep due to nocturia, patients should be advised instead to use small sips of water frequently throughout the day. The use of water with meals can also make chewing and forming a food bolus easier, facilitate swallowing, and may improve taste perception. Patients may find a sugar-free beverage is more palatable than water but should be advised that frequent use of sugar-free carbonated drinks is not recommended as their acidity is high which may promote tooth demineralization.

As a function of normal diurnal variation and positional changes, salivary flow decreases significantly at night, when supine, and during sleep. In individuals with secretory hypofunction, desiccation of the mucosa may result in nocturnal awakening preventing restorative sleep. The use of room humidifiers may lessen discomfort markedly. Similarly, patients should be counseled to avoid low humidity and air-conditioned environments where possible. Mouth breathing, where present, will typically exacerbate nocturnal symptoms and may require a medical evaluation to determine if there is a correctable cause such as nasal congestion caused by allergies or sinus polyps.

Patients using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) machines may

find that their use causes or exacerbates oral dryness. Use of a humidifier with the device, changing from a nasal pillow or nasal mask to a full face mask, or use of a chin strap to prevent mouth breathing are some strategies that could be explored. Oral dryness with use of these machines can also be caused or exacerbated by an ill-fitting mask.

There are a myriad of products available for dry mouth (e.g., mouthwashes, gels, sprays, lozenges), but patients should be cautioned to avoid products containing alcohol, sugar, or strong flavors that may irritate sensitive, dry mucosa. Moisturizing and lubricating products may provide additional comfort and help prevent friction-associated lesions. Some commercially-available preparations contain aloe vera which has purported humectant properties. Alternatively, topical use of aloe vera juice alone may provide temporary relief of dryness. Patients may also find rinsing with a neutral edible oil such as flax seed, coconut, or olive oil before bedtime or around meals provides moisture and lubrication.

Salivary substitutes, also known as oral rehydrating agents, are topical agents that maintain lubrication of the mucosa and may or may not have a saliva-stimulating effect. Agents incorporating salivary substitutes may be found in a range of products including lubricating gels, mouthwashes, lozenges, toothpastes, and oral sprays. These are typically composed of a mix of buffering agents, cellulose derivatives (to promote adherence to the mucosa and provide moisture), and flavoring agents. Ingredients in these products may include animal mucin, carboxymethyl cellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, and polyglycerylmethacrylate. Other agents that have been investigated include xanthan gum, linseed (flax seed) extract, and aloe vera.[314]

Saliva substitutes may have a positive effect on nocturnal oral dryness without appreciable side effects. Clinical trial data have not shown a significant difference in efficacy between some salivary substitutes and a placebo although some randomized control trials show improvement in oral symptoms. Although there is no reported superiority in preparations with mucin versus carboxymethylcellulose-containing substitutes, mucin-containing agents tend to be preferred by patients. These agents tend to have at most a very transient effect and therefore require frequent re-application.[263]

Salivary Stimulation

Local or Topical Stimulation

Both chewing and taste (especially sour and sweet tastes), stimulate salivary flow and thus the use of sugar-free chewing gums, mints, or candies, can be effective in temporarily relieving symptoms in patients who have remaining salivary gland function. Patients with dry mouth must be advised to avoid products that contain sugar or other fermentable carbohydrates (e.g., honey, high fructose corn syrup) due to the increased risk of dental caries. Instead, patients should be encouraged to try products using xylitol, a sugar alcohol that inhibits *Streptococcus mutans,* or other sweeteners including those made from the botanical species *Stevia rebaudiana*, *Siraitia grosvenorii* (monk fruit or *luo han guo*), and the sugar alcohol erythritol.

Attempts to develop a "salivary pacemaker" to stimulate saliva flow has generated some intriguing devices. There are 2 FDA-approved neuroelectrostimulating devices: the Salitron™ system, which employs a handheld probe placed on the dorsal tongue for 5 minutes three times daily, and the Saliwell GenNarino™, a removable, remote-controlled mouth guard. The Salitron™ system, which was reported to be cumbersome due to its bulky size, is no longer manufactured but may still be in use. More recently, implantable devices, such as the Saliwell Crown™, constructed in the form of an oral osteointegrated implant with an embedded wetness sensor, have been developed. These devices monitor oral dryness and provide an automatic or patient-controlled stimulus to the adjacent tissue resulting in salivation.[315] While these "pacemaker" devices show promise without cholinergic side effects, their routine use has been hampered by cost and insurance limitations.[244]

Acupuncture-like transcutaneous electrical nerve stimulation (ALTENS) is a needle-free, noninvasive treatment involving application of mild electric currents to acupuncture points. It has shown similar reduction in xerostomia as oral pilocarpine, with fewer side effects, in a study of patients with radiation-induced xerostomia. Although this treatment may be well tolerated, ALTENS devices are not widely available and may require clinic visits twice weekly for 12 weeks.[316] A study using a similar commercially available device (which may allow patients to administer treatment at home) has recently shown promise, but further studies are required.[317]

Many studies have explored the effect of acupuncture on salivary flow, and while some studies report a small increase in saliva production in patients with dry mouth following radiotherapy with few reported adverse effects, comprehensive systematic reviews have yet to show any definitive, nonbiased results. Further well-constructed clinical trials are required before definitive recommendations for its use can be made.

Systemic Stimulation

Pilocarpine HCl (Salagen®) and cevimeline (Evoxac®) are FDA-approved oral sialogogues. They are muscarinic acetylcholine receptor agonists mainly targeting M1 and M3 receptor subtypes. These subtypes are found not only in salivary glands but are also widely distributed throughout the body.

As a result, use of these sialogogues may also result in side effects such as sweating, flushing, hypotension, blurred vision, nausea, and stomach ache.[274]

Pilocarpine HCl is indicated specifically for the relief of xerostomia following radiotherapy for head and neck cancers and for patients with Sjögren's syndrome. It is safe and effective for patients with diminished salivation who have some remaining secretory function. The recommended dose is 5.0 or 7.5 mg taken three or four times daily, but patients may benefit from starting with 2.5 mg (by dividing a 5 mg tablet) to minimize side effects. Salivary output increases within 20 minutes of administration, reaches a maximum within 1 hour, and the duration of action is approximately 3 to 5 hours. At least 12 weeks of uninterrupted therapy may be necessary to assess whether a beneficial response will be achieved. Pilocarpine is contraindicated in patients with uncontrolled asthma, narrow angle glaucoma, and acute iritis and should be used with caution in patients with significant cardiovascular or pulmonary disease, cholelithiasis, or biliary tract disease.

Cevimeline HCl is indicated for the treatment of oral dryness in Sjögren's syndrome patients. It has a stronger affinity for M3 receptors, which may account for its fewer reported side effects and lower failure rate in first time users.[275] It is typically prescribed at 30 mg taken three times daily. Cevimeline is contraindicated in patients with uncontrolled asthma, narrow angle glaucoma, and acute iritis and should be used with caution in patients with significant cardiovascular or pulmonary disease, a history of cholelithiasis, or nephrolithiasis.

SALIVARY GLAND TUMORS

Salivary gland tumors account for 3% to 10% of all head and neck tumors.[318] Approximately 75–80% of salivary gland tumors arise in the parotid glands, 10–15% arise in the submandibular glands, and the remaining tumors develop in the sublingual or minor salivary glands. Generally speaking, the relative proportion of malignant neoplasms is greater the smaller the gland: that is, a neoplasm in the parotid gland is more likely to be benign than one arising in a minor salivary gland. Around 15–32% of tumors of the parotid glands, 41–45% of tumors of the submandibular glands, and 70–90% of tumors of the sublingual glands are malignant. With respect to tumors of the minor salivary glands, the risk of malignancy is site dependent: approximately half of tumors arising on the palate are malignant whereas up to 90% of those of the floor of mouth are malignant.[319]

Table 9-7 A list of some common benign and malignant salivary gland tumors.

Benign	Malignant
Pleomorphic adenoma	Mucoepidermoid carcinoma
Papillary cystadenoma lymphomatosum (Warthin's Tumor)	Adenoid cystic carcinoma
Oncocytoma	Acinic cell carcinoma
Basal cell adenoma	Polymorphous adenocarcinoma
Canalicular adenoma	Epithelial-myoepithelial carcinoma
Myoepithelioma	Salivary duct carcinoma
Sebaceous adenoma	Carcinoma ex-pleomorphic adenoma
Ductal papilloma	Clear cell carcinoma

Overall, the pleomorphic adenoma is the most common benign salivary gland tumor while the mucoepidermoid carcinoma is the most common malignant salivary gland tumor. While 15% to 25% of salivary gland tumors in adults are malignant, 25% to 50% of those in children and adolescents are malignant.[320] A partial list of the most common benign and malignant salivary gland neoplasms is presented in Table 9-7.

Certain clinical signs and symptoms are more likely to be associated with a malignant neoplasm of the salivary glands. These include ulceration of the overlying mucosa, fixation of the mass to deeper tissue planes, multiple masses within a single gland, induration, and lymphadenopathy. Additional findings such as otalgia, dysphagia, odynophagia, trismus, paresthesia, a history of cancer or cachexia, may further raise suspicion for malignancy.

Treatments for salivary gland neoplasms include surgery, radiotherapy (including brachytherapy), chemotherapy, and biological therapy. Clinicians should be cognizant of the increased risk of development of second cancers in patients who have previously received radiotherapy to the head and neck.

The taxonomy of salivary gland tumors is dynamic. New entities and variant morphologies are proposed while other entities have been removed or collapsed into other categories. Clinicians are advised to consult an up-to-date publication for further details on the classification of salivary gland tumors.[321]

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10

Temporomandibular Disorders

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This chapter focuses on the assessment and management of disorders of the masticatory system. The masticatory apparatus is a specialized unit that performs multiple functions, including those of suckling, cutting and grinding food, swallowing, and communication. The loss of these functions, particularly in association with pain, is characteristic of masticatory system disorders and causes significant distress that can be severely disabling.

The term *temporomandibular disorder(s)* (TMD) used in this chapter is a collective term embracing a number of clinical problems that involve the masticatory muscles, the temporomandibular joints (TMJs), and associated structures.[1] These disorders are characterized by: (1) facial pain in the region of the muscles of mastication, TMJs, or both; (2) limitation or deviation in mandibular movements; (3) hyperalgesia of the musculoskeletal structures; and (4) TMJ sounds during jaw movement and function.[2] "TMD" is not a diagnosis, but refers to any of many different disorders. Differentiating subtypes of muscle and joint disorders according to validated diagnostic criteria has often been sidestepped in favor of ad hoc assessment methods and ad hoc diagnoses. Adequate evidence supporting valid diagnostic approaches now exists[3] and such approaches are recommended.[4] In the past, disorders of the masticatory system were generally treated as one condition or syndrome, with no attempt to identify different muscle or joint disorders and link those to the chief complaint as well as targeted therapy. Use of a validated approach should lead to a better understanding of the natural course, more accurate predictions of prognosis, and more effective treatments. This chapter

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presents a general but evidence-based approach to the diagnostic assessment and nonsurgical management of the most common TMDs. Some of the less common disorders are also considered in order to better draw attention to the salient characteristics of the common disorders and why the general therapeutic guidelines for the common disorders remain the most sensible.[4]

BACKGROUND

Anatomy

Temporomandibular Joint

The TMJ is a complex joint comprised of bone, ligament, and an articular disc. The bony components include the mandibular condyle and the glenoid fossa of the temporal bone. The mandibular condyle forms the lower part of the bony joint and is generally elliptical in shape, although variations are common.[5,6] The articulation is formed by the mandibular condyle occupying a hollow in the temporal bone (the mandibular or glenoid fossa). The S-shaped form of the fossa and eminence, as viewed sagitally, starts developing at about 6 years of age and continues into the second decade[7] (Figures 10-1 and 10-2). The bony elements are enclosed and connected by a fibrous capsule.

The fibrous joint capsule is lined with synovial tissue, a vascular connective tissue which extends to the boundaries of the articulating surfaces. The synovial membrane consists of macrophage-like type A cells and fibroblast-like type B cells identical to those in other joints. The macrophage-like type A cells react with antimacrophage and macrophage-derived substances, including the major histocompatibility class II molecule, and show a drastic increase in their number

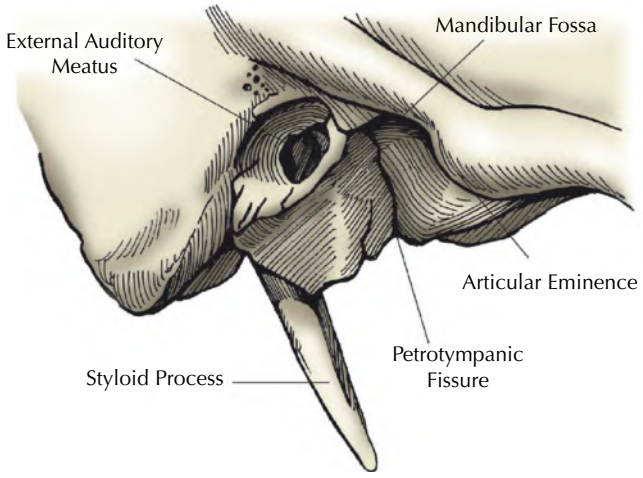

Figure 10-1 The S-shaped form of the fossa and eminence. The mandibular condyle occupies the space of the fossa, with enough room to both rotate and translate during mandibular movements.

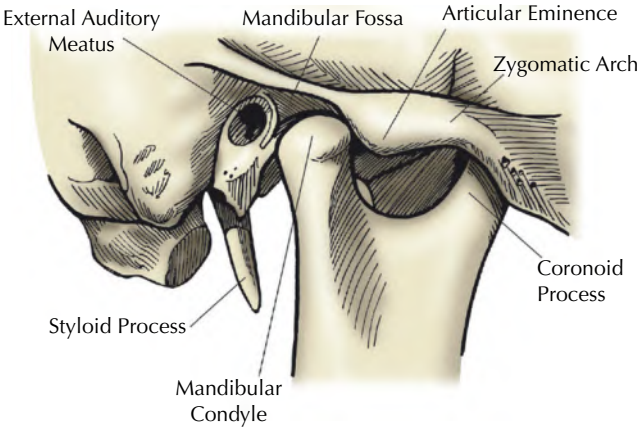

Figure 10-2 The articulation is formed by the mandibular condyle occupying a hollow in the temporal bone (the mandibular or glenoid fossa) during wide mouth opening; the condyle rotates around an axis and glides, causing it to move beyond the anterior border of the fossa, the articular eminence.

in the inflamed synovial membrane.[8] The joint cavity is filled with synovial fluid. Synovial fluid is a filtrate of plasma with added mucins and proteins. Its main constituent is hyaluronic acid. Fluid forms on the articulating surfaces and decreases friction during joint compression and motion.[9] Joint lubrication is achieved by mechanisms described as weeping lubrication and boundary lubrication. Weeping lubrication occurs as fluid is forced laterally during compression and expressed through the unloaded fibrocartilage.[10] As the adjacent areas become loaded, the weeping lubrication aids in reducing friction. Boundary lubrication is a function of water that is physically bound to the cartilaginous surface by a glycoprotein.[11] Collectively, the fluid dynamics depend on appropriate loading and unloading of the joint through normal function in order to maintain continuous lubrication as well as maintenance of the tissue health.[12]

Fibrocartilage, instead of the expected hyaline cartilage, covers the articulating surface of the joint. Fibrocartilage is less distensible than hyaline cartilage due to a greater number of collagen fibers including Type 1 collagen. The matrix and chondrocytes are decreased because of the larger irregular bundles of collagen fibers.[13] The fibrocartilage found on the articulating surfaces of the TMJ is thought to provide more surface strength against forces in many directions while allowing more freedom of movement than would be possible with hyaline cartilage. This covering is thickest on the posterior slope of the articular eminence and on the anterior slope of the condylar head; these are the areas thought to receive the greatest functional load. The thinnest part of the fibrocartilage covering is on the roof of the mandibular fossa. Fibrocartilage has a greater repair capacity than hyaline cartilage which may affect how the TMJ responds to degenerative changes.[13,14]

The TMJ articulation is a joint that is capable of both hinge-type movements and gliding movements. During wide mouth opening, the condyle rotates around a hinge axis and then translates as it glides, causing it to move beyond the anterior border of the fossa, which is identified as the articular eminence.[15]

Articular Disc

Dense fibrous connective tissue primarily made up of dense collagen of variable thickness is referred to as a disc and occupies the space between the fibrocartilage coverings of each of condyle and mandibular fossa (Figures 10-3 and 10-4). The disc consists of collagen fibers, cartilage-like proteoglycans,[16] and elastic fibers.[17] The disc contains a variable number of cells that resemble fibrocytes and fibrochondrocytes.[18] Collagen fibers in the center of the disc (often referred to as the intermediate zone) are oriented perpendicular to its transverse axis functionally aligned with loading on that zone. The collagen fibers become interlaced as they approach the anterior and posterior bands, and many fibers are oriented parallel to the mediolateral aspect of the disc. Cartilage-like proteoglycans contribute to the compressive stiffness of articular cartilage.[19] The disc is primarily avascular and has little sensory innervation. The disc is thinnest in the intermediate zone and thickens to form anterior and posterior bands represented as a "bow tie" in sagittal sections. This arrangement is considered to help stabilize the condyle in the glenoid fossa.[5] Over time, discs may exhibit changes in this conformation; the central intermediate zone may become elongated or nonexistent, the anterior band may become thinner, or the posterior band may become either thinner or thicker. These conformation changes, while presumably affecting the ideal function of the disc in stabilizing the condyle during loading, are currently regarded as a variation on normal in the absence of any clinical manifestation of disordered function.[20]

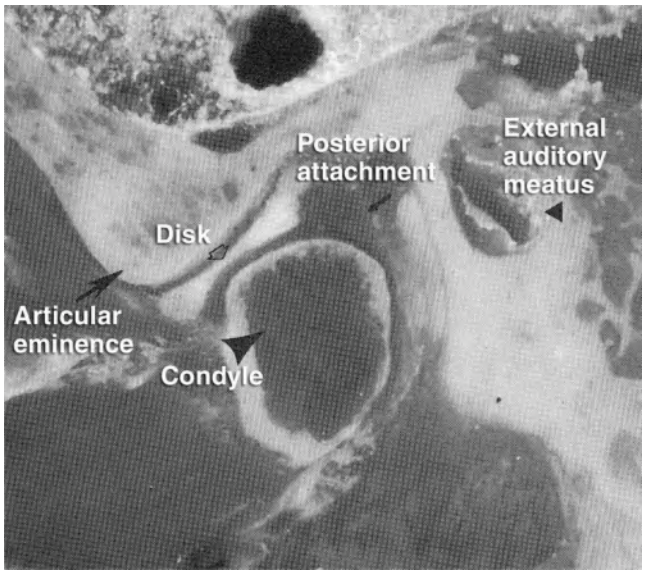

Figure 10-4 A cadaver section through the temporomandibular joint shows the relationship of the condyle, fossa, and articular disc.

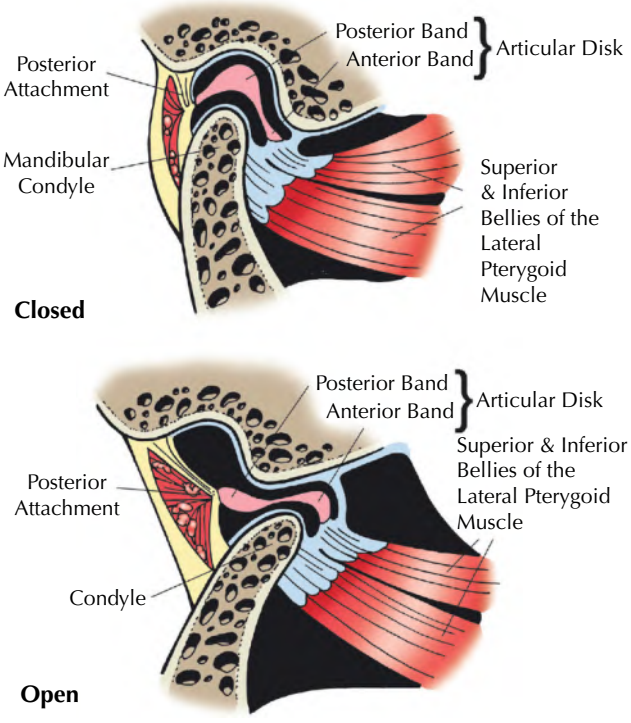

Figure 10-3 The temporomandibular joint is capable of hinge-type rotational movements and gliding translational movements. The articular disc has ligamentous attachments to the mandibular fossa and condyle. The disc's attachments create separate superior and inferior joint compartments.

The disc provides an interface for the condyle as it glides across the temporal bone. The disc is attached by ligaments to the lateral and medial poles of the condyle. The ligaments consist of both collagen and elastic fibers.[21] These ligaments permit rotational movement of the disc on the condyle during mouth opening and closing. The disc and its attachments divide the joint into upper and lower compartments that normally do not communicate. The passive volume of the upper compartment is estimated to be 1.2 mL and that of the lower compartment is estimated to be 0.9 mL.[21] The roof of the superior compartment is the glenoid (mandibular) fossa, whereas the floor is the superior surface of the disc. The roof of the inferior compartment is the inferior surface of the disc and the floor is the articulating surface of the mandibular condyle.[21] At its margins, the disc blends with the fibrous capsule. Muscle attachments inserting into the anterior aspect of the disc have been observed in a relatively small number of individuals.[22] Fibers of the posterior one-third of the temporalis muscle and of the deep masseter muscle may

attach on the anterolateral aspect, and fibers of the superior head of the lateral pterygoid have been observed to insert into the anteromedial two-thirds of the disc.[22]

Retrodiscal Tissue

Loose connective tissue occupies the space behind the disc and condyle. It is often referred to as the posterior attachment or retrodiscal tissue. The posterior attachment is a loosely organized system of collagen fibers, branching elastic fibers, fat, blood and lymph vessels, and nerves. Synovium covers the superior and inferior surfaces. The attachment has been described as being arranged in two lamina of dense connective tissue[23] but this has been challenged.[24] Between the lamina, a loose areolar, highly vascular, and well-innervated tissue has been described. Both superior and inferior lamina arise from the posterior band of the disc. The superior lamina attaches to the squamotympanic fissure and tympanic part of the temporal bone and consists primarily of elastin.[23,25] The inferior lamina inserts into the inferior margin of the posterior articular slope of the condyle and is composed mostly of collagen fibers.[23]

Temporomandibular Ligaments

Capsular Ligament

The capsular ligament is a thin inelastic fibrous connective tissue envelope that attaches to the margins of the articular surfaces (Figure 10-5). The fibers are oriented vertically and do not restrain joint movements. The medial capsule is composed of loose areolar connective tissue.[24] The capsule and the lateral discal ligament join and attach to the lateral aspect of the neck of the condyle.[26]

Lateral Temporomandibular Ligament

The lateral temporomandibular ligament is the main ligament of the joint, lateral to the capsule but not easily separated from it by dissection. Its fibers pass obliquely from bone lateral to the articular tubercle in a posterior and inferior direction and insert in a narrower area below and behind the lateral pole of the condyle (Figure 10-5). However, various studies were unable to confirm a distinct structure separate from the capsule.[21,26]

Accessory Ligaments

The sphenomandibular ligament arises from the sphenoid bone and inserts on the medial aspect of the mandible at the lingula. The stylomandibular ligament extends from the styloid process to the deep fascia of the medial pterygoid muscle. It is thought to become tense during protrusive movement of the mandible and may contribute to limiting protrusive movement.[5]

Muscles of Mastication

The primary muscles of mastication are the paired masseter, medial and lateral pterygoids, and temporalis muscles (Figures 10-6, 10-7, 10-8). Mandibular movements toward

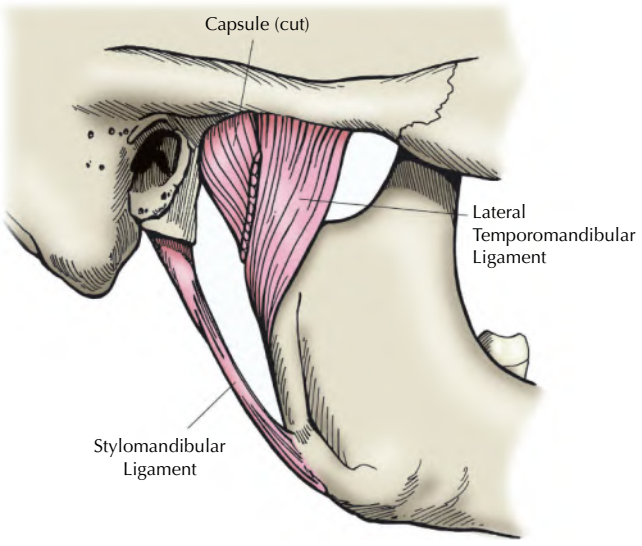

Figure 10-5 The capsular ligament is a thin, inelastic, fibrous connective tissue envelope, oriented vertically, that attaches to the margins of the articular surfaces. The temporomandibular ligament is lateral to the capsule. Its fibers pass obliquely from bone lateral to the articular tubercle in a posterior and inferior direction to insert in a narrower area below and behind the lateral pole of the condyle.

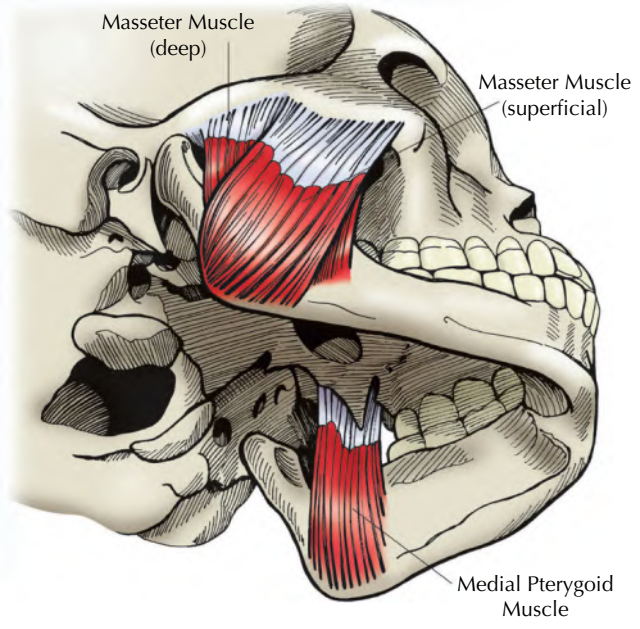

Figure 10-6 The masseter and medial pterygoid muscles have their insertions at the inferior border of the mandibular angle. They join together to form a sling that cradles the ramus of the mandible and produces the powerful forces required for chewing. The temporalis muscle is attached to the lateral skull. The muscle fibers converge to insert on the coronoid process and anterior aspect of the mandibular ramus.

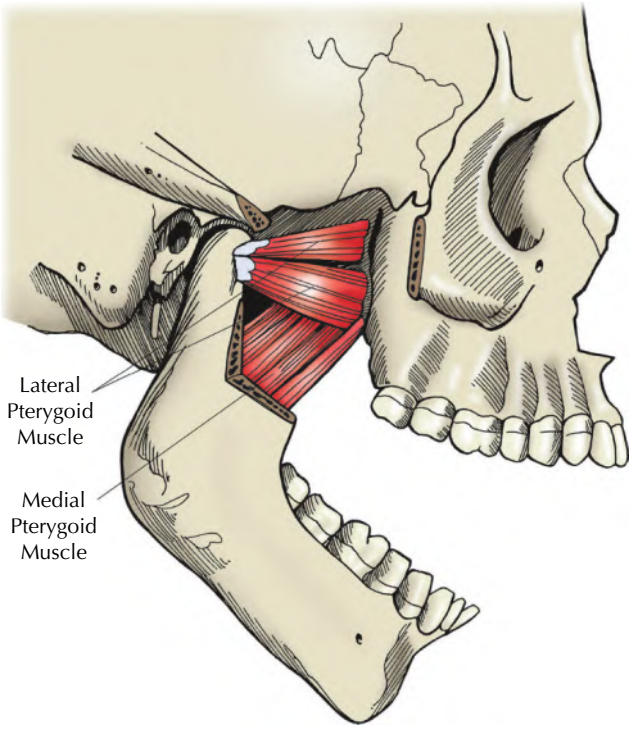

Figure 10-7 The lateral pterygoid muscle is the main protrusive and opening muscle of the mandible. The inferior part originates from the outer surface of the lateral pterygoid plate of the sphenoid and the pyramidal process of the palatine bone. The superior part originates from the greater wing of the sphenoid and the pterygoid ridge. They insert into the anteromedial aspect of the condylar neck. Some of the fibers insert into the most anterior medial portion of the disc.

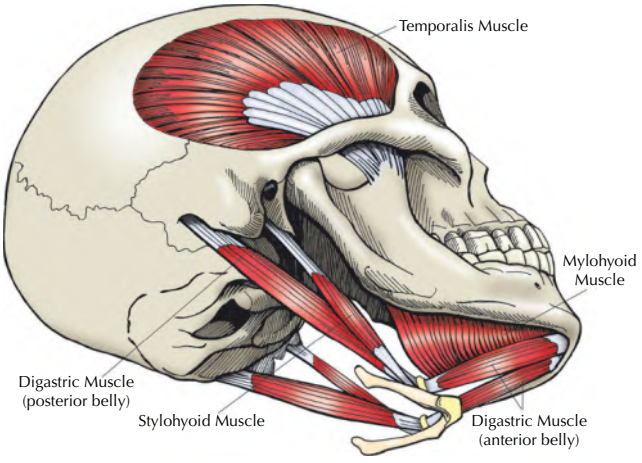

Figure 10-8 The digastric muscle is a paired muscle with two bellies. The anterior belly attaches to the lingual aspect of the mandible at the parasymphysis and courses backward to insert into a round tendon attached to the hyoid bone. The mylohyoid and geniohyoid muscles contribute to depressing the mandible, while the infrahyoid muscles stabilize the hyoid bone during mandibular movement.

the tooth contact position are performed by contraction of the masseter, temporalis, and medial pterygoid muscles.[27]

Masseter contraction contributes to moving the condylar head toward the anterior slope of the mandibular fossa (Figure 10-6). The posterior part of the temporalis contributes to mandibular retrusion. Unilateral contraction of the medial pterygoid contributes to a contralateral movement of the mandible. The masseter and medial pterygoid muscles have their insertions at the inferior border of the mandibular angle. They join together to form a sling that cradles the mandible and produces the powerful forces required for chewing. The masseter is divided into deep and superficial parts. The deep masseter in some individuals overlaps the anterior aspect of the TMJ, such that pain localized to the pre-auricular region may be associated with masseter, TMJ, or both structures. The temporalis muscle is attached to the lateral skull and has been divided into anterior, middle, and posterior parts. The muscle fibers converge into a tendon that inserts on the coronoid process and anterior aspect of the mandibular ramus. The anterior and middle fibers are generally oriented in a straight line from their origin on the skull to their insertion on the mandible. The posterior part traverses anteriorly and then curves around the anterior root of the zygomatic process before insertion.

The lateral pterygoid is the main protrusive and opening muscle of the mandible. The inferior head is the main section responsible for lateral jaw movements when the teeth are in contact.[28] The lateral pterygoid is arranged in parallel-fiber units, whereas the elevator muscles are multipennate in structure. This differential arrangement allows greater displacement and velocity in the lateral pterygoid vs. greater force generation in the elevator muscles.[29]

The lateral pterygoid muscle arises from two heads (Figure 10-7). The inferior head originates from the outer surface of the lateral pterygoid plate of the sphenoid bone and the pyramidal process of the palatine bone. The superior head originates from the greater wing of the sphenoid bone and the pterygoid ridge. The fibers of the upper and lower heads course posteriorly and laterally, fusing in front of the condyle,[30] and inserting into the anteromedial aspect of the condylar neck. Although some of the fibers insert into the most anterior medial portion of the disc (or capsule), most of the lateral pterygoid fibers insert into the condyle.[30] The superior part of the insertion consists of an identifiable tendon inserting through fibrocartilage. The inferior part of the insertion consists of muscle attached to periosteum.[31] Debate continues about the functional anatomy of the lateral pterygoid. The superior head is thought to be active during closing movements, and the inferior head is thought to be active during opening and protrusive movements.[32,33] However, substantial variability across individuals appears to account for some of the debate.[34,35] Translation of the condylar head

onto the articular eminence is produced by contraction of the lateral pterygoid.

The accessory muscles of mastication are relatively smaller and their function is more indirect and perhaps complex. The digastric muscle is a paired muscle with two bellies. The anterior belly attaches to the lingual aspect of the mandible at the parasymphysis and courses backward to insert into the hyoid bone. Contraction produces a depression and retropositioning of the mandible. The mylohyoid and geniohyoid muscles contribute to depressing the mandible when the infrahyoid muscles stabilize the hyoid bone. These muscles may also contribute to retrusion of the mandible. The omohyoid muscle arises from the scapula and inserts on the hyoid bone and serves to lower and stabilize the hyoid bone. Together with the digastric muscle, the omohyoid muscle lowers the jaw when active and is not active in a jaw resting position (Figure 10-8).[36] The buccinator attaches inferiorly along the facial surface of the mandible behind the mental foramen and superiorly on the alveolar surface behind the zygomatic process. The buccinator fibers are arranged horizontally; anteriorly, fibers insert into mucosa, skin, and lip. The buccinator helps position the cheek during chewing movements of the mandible and contracts in order to maintain the food bolus on the posterior teeth during chewing. The functional activity of these accessory muscles depends on simultaneous activation of the primary masticatory muscles for stabilizing the position of the mandible which, given the basal functions of the masticatory system, has implications with respect to the functional limitation and disability often associated with a TMD.

Vascular Supply of Masticatory System Structures

The external carotid artery (ECA) is the main blood supply for the structures of the masticatory system. The ECA leaves the neck and courses superiorly and posteriorly, embedded in the substance of the parotid gland, sending two important branches, the lingual and facial arteries, to the region. At the level of the mandibular condylar neck, the external carotid bifurcates into the superficial temporal artery and the internal maxillary artery. These two arteries supply the muscles of mastication and the TMJ. Arteries within the temporal bone and mandible also send branches to the capsule.[5]

Nerve Supply of Masticatory System Structures

The masticatory structures are innervated primarily by the trigeminal nerve, but cranial nerves VII, IX, X, and XI and cervical nerves 2 and 3 also contribute. The peripheral nerves synapse with nuclei in the brainstem that are associated with touch, proprioception, and motor function. The large spinal trigeminal nucleus occupies a major part of the brainstem and extends to the spinal cord. The spinal trigeminal nucleus is thought to be the main site for the reception of impulses from the periphery involved in pain sensation. The mandibular division of the trigeminal nerve supplies motor innervation to the muscles of mastication and the anterior belly of the digastric muscle. The auriculotemporal nerve, a branch of the mandibular portion (V3) of the trigeminal nerve, provides innervation of the TMJ (Figure 10-9). The deep temporal and masseteric nerves supply the anterior portion of the joint. About 75% of the time, the masseteric nerve, a branch of the maxillary division of the trigeminal nerve (V2), innervates the anteromedial capsule of the TMJ. In about 33%, a separate branch from V2 comes through the mandibular notch and innervates the anteromedial capsule.[37] These nerves are primarily motor nerves, but they contain sensory fibers distributed to the anterior part of the TMJ capsule. The autonomic nerve supply is carried to the joint by the auriculotemporal nerve and by nerves traveling along the superficial temporal artery.[38]

Epidemiology

Between 65 and 85% of people in the United States experience one or more symptoms of a TMD during their lives, but the symptoms are self-limiting for most individuals and resolve without professional intervention.[39] Incidence of first lifetime onset of a painful TMD appears to be between 2–4% per annum.[40–43] Although the prevalence of one or more signs of mandibular pain and dysfunction is high in the population, only about 5 to 7% have symptoms severe enough to require treatment.[39,44,45]Among those who

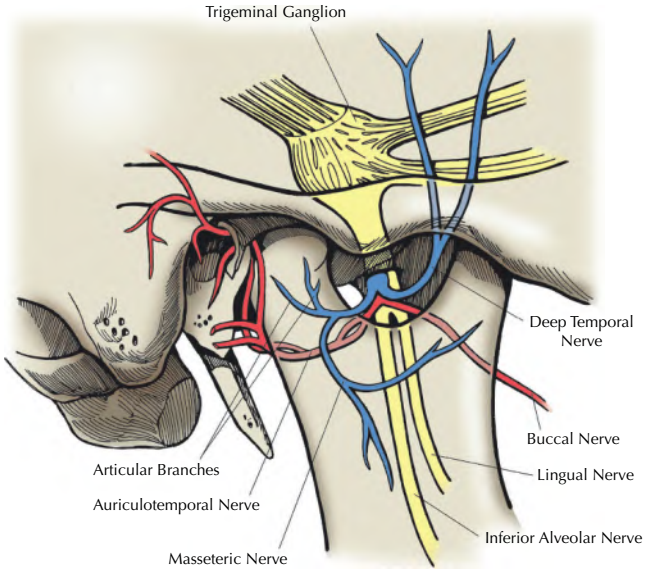

Figure 10-9 Branches of the auriculotemporal nerve supply sensory innervation of the TMJ. This nerve arises from the mandibular division in the infratemporal fossa and sends branches to the capsule of the joint.

develop a TMD, approximately 12% experience prolonged pain that results in disability,[39] and more recent estimates indicate that between 25–50% of individuals with acute painful TMD develop chronic pain in the absence of appropriate intervention.[46,47] In terms of symptom profile, individuals with a painful TMD are similar to those with headache and back pain with respect to pain intensity, frequency, chronicity, psychosocial distress, and pain-related disability.[48,49] These profiles appear to be similar in individuals with TMDs across cultures; for example, Asian, Swedish, and American populations with TMDs share similar characteristics.[50]

Available evidence indicates that TMDs are most prevalent between the ages of 20 and 40 years, and that prevalence then decreases by age 60, after which it decreases substantially.[51] The lower prevalence of TMDs in older age groups suggests that the disease course in a significant proportion of individuals with TMDs is strongly influenced by situational factors that resolve with aging. TMDs in the community occur at about twice the rate in females vs. males, yet females are eight times more common in the clinic population, compared to males. The reason why women make up the majority of patients presenting for treatment remains unclear. While the natural course of TMDs is poorly understood, gender apparently affects the disease course as well.[52] For example, oral contraceptives and estrogen replacement in women over 40 years of age substantially increases the risk of developing a painful TMD.[53]

Signs and symptoms of masticatory muscle and TMJ dysfunction are also commonly observed in children and adolescents.[54–56] Among adolescents in Sweden between the ages of 12 and 19 years, 4.2% reported TMD pain, and girls reported TMD pain approximately twice more frequently than boys, 6% compared with 2.7%.[57] Surprisingly, a wide variety of painful TMD characteristics observed in adults also occur to largely the same extent in children and adolescents. For example, among a group of 40 children aged 10 to 16 years and presenting with signs and symptoms of a painful TMD, 14 (35%) were diagnosed as having acute reactive depression.[58] Arthrography and computed tomography (CT) were performed on 31 children complaining of TMJ pain and dysfunction: 12 (39%) exhibited disc displacement with reduction, and 17 (55%) exhibited disc displacement without reduction.[59] Among the 29 individuals with internal derangement, causation was attributed to previous injury in 12 individuals. Yet, in a survey of 1000 12-year-old children, only 1% had a maximum mouth opening of less than 40 mm, indicating that the norm for expected opening range is established prior to the final growth phase in adolescents. Despite this extent of abnormal findings, only a small proportion of children presented with clinical findings severe enough to warrant treatment.[60]

Etiology

Etiology of the most common TMDs is unknown. The literature has been dominated by several hypothesized causes: occlusal disharmony, muscle hyperactivity, central pain mechanisms, psychological distress, and trauma.

Occlusal Disharmony

The history of the dental occlusion, as related to TMDs, is long and complex within the dental profession. Managing occlusion is a major task within restorative dentistry and, not surprisingly perhaps, the focus on occlusion has often been at the boundary between clinical lore and scientific evidence. While deviations of the occlusion from the ideal—so-called occlusal disharmony—can be construed in many ways, operational features that clearly distinguish a "good" occlusion from a "bad" occlusion remain missing from the discussions; moreover, the persistent focus on occlusion and TMDs contrasts with the inadequate to poorly designed and executed research used to support that focus. A short history of these concepts will be followed by focusing on some of the major claims regarding the presumed importance of occlusion in relation to TMDs. That this section has been retained, if not expanded, over the past several editions of this book is telling in itself: dentistry is reluctant to abandon the evaluation and treatment of occlusion with regard to TMDs, perhaps to the point that occlusion becomes a cause célèbre.

The relationship of so-called occlusal disharmony and TMD became the center of attention within the profession after Costen reported that a group of patients with multiple complaints associated with the jaws and ears improved after the occlusal–vertical dimension of their dentures was altered.[61] Despite the lack of anatomic support for occlusal–vertical dimension as a mechanism,[62] the occlusal hypothesis was nevertheless expanded to include other occlusal parameters, each believed to be responsible in addition to loss of vertical dimension for causing a TMD,[63,64] yet without evidence. During the 1950s and 1960s, a muscular cause not directly related to occlusion was proposed; the mechanisms were generic for similar pains elsewhere in the body, thereby highlighting the strong plausibility of the model.[65–67] In contrast, because this particular model ignored occlusion as a cause of TMD, the model proved to be very controversial within dentistry, setting the stage for ongoing controversy for any model that did not include occlusion as a cause. In the late 1970s, advances in diagnostic imaging resulted in a better understanding of intracapsular dynamics of the TMJ, and the focus was renewed upon so-called abnormalities of structure, now in the TMJ, as the "cause of TMD" and clearly evident via imaging.[68,69] The lack of a clear understanding with regard to cause, the existence of multiple hypotheses, and strongly held beliefs by some clinicians have resulted in

a wide spectrum of views about what TMD constitutes, regardless of the absence of supporting evidence. This wide spectrum of views continues in the present, such that the transfer of science regarding TMDs to the clinical setting is often compromised, with inappropriate diagnosis and treatment as a consequence.

Clear and convincing evidence for so-called occlusal disharmony as a primary etiology of TMDs does not exist.[70] Research studying discrepancies between centric occlusion and maximal intercuspal position, nonworking side occlusal interferences, posterior crossbite, and Angle's occlusal classification has not established a strong association in patients with myofascial pain compared with controls.[45,71,72] Significant differences in occlusal characteristics are not found between patients with myofascial pain compared with control subjects.[73] Overjet and overbite do not have a strong relationship with joint clicking, crepitus, pain, or limited opening.[74,75] A number of studies have been performed to investigate a possible relationship between orthodontic malocclusions and treatment and the development of TMD, but the results do not support a causal relationship.[76–80]

A mainstay in the clinical lore regarding occlusion and TMDs is centric relation as an index for the position of the mandible relative to the maxilla. Centric relation is a position that has traditionally relied on guiding the condyles into a position to rotate around a stationary axis in the mandibular fossa, and it has served as both a highly idealized and a highly contentious anatomical point. The standard definition is "the maxillomandibular relationship, independent of tooth contact, in which the condyles articulate in the anterosuperior position against the posterior slopes of the articular eminences."[81] This position of condylar rotation about a stationary axis can be reproduced and transferred to an articulator, and while that is useful clinically for restorative dentistry, a biological basis for the manipulated position has not been identified. A mandibular position usefully defined in operational terms for purposes of restorative dentistry should not be confused with necessarily having diagnostic or biological value beyond the operational definition. Evidence for centric relation as a diagnostic test or proxy for TMDs does not exist. Adjusting the maximum intercuspal position to be coincident with centric occlusion (the occlusion that exists when the mandible is at centric relation) has been strongly recommended by some clinicians to treat TMDs, but the biological evidence for this as a standard treatment is absent.[82] In contrast, the available evidence indicates that the "stationary axis" is itself dynamic: for example, restoring a dentition for centric occlusion coincidence with maximum intercuspal position results in the development of a new centric occlusion over time,[83] implying that centric relation is a boundary of a zone used for normal movement. Moreover, such adjustments may actually increase risk for a TMD based on evidence suggesting that a gap in the maximal intercuspal position vs. centric occlusion is protective against TMD onset.[84] The biology associated with centric relation does not appear to support a causal linkage with TMDs.

A particularly contentious topic has been that premature occlusal contacts, such as faulty restorative dentistry, initiate sleep bruxism. This belief stems from research studies that are typically uncritically cited[85,86] but which were completely inadequate for any scientific conclusion. Premature occlusal contacts actually trigger the opposite in healthy individuals: a decrease in the activity of masticatory elevator muscles during sleep.[87] In contrast, the same premature occlusal contact in individuals with a TMD or a prior history of a TMD will cause increased activity of the masticatory elevator muscles during sleep.[88] Importantly, this increased muscle activity in those with a TMD is not evidence of causation. Rather, the impact of such premature occlusal contacts appears to depend on pre-existing trait anxiety and extent of oral parafunctional behaviors.[89]

To date, as summarized elsewhere,[70] TMDs exhibit an association with only a very few attributes of a static occlusion, and the magnitude of the association is relatively small and inconsistent across studies. These associations are based on cross-sectional study designs, not longitudinal designs, and collectively suggest that the specific occlusal features have a complex relationship to TMD pain. The available evidence indicates that that complex relationship, pointedly, does not include a direct causal role. Just as the evidence has not supported occlusal attributes as cause of TMD, the research literature has not supported any efficacy of occlusal treatment for a TMD.[90] Overall, studies examining occlusal characteristics and TMD symptoms have failed to identify a strong association.[91] Returning to the early work of Costen, the loss of occlusal vertical dimension has been (and perhaps continues to be) considered a cause of a TMD, but contemporary evidence for this remains lacking.[92] Finally, the focus on static occlusal features sidesteps the potentially far more important dynamic aspects of the dentition where more force and greater instability occur: during mastication, when the teeth do not actually contact.

Complicating static and dynamic occlusion is where the teeth should be when the teeth do not need to touch and the mandible does not need to function. When the mandible is not functionally active, it adopts a so-called rest position in which the condyle occupies a relatively neutral position in the glenoid fossa with the teeth separated. The rest position is considered to be associated with minimum muscular activity and with the articulating surfaces of the mandibular teeth a few millimeters from the occlusal contact position with the opposing teeth.[93] "Rest position" is, however, somewhat of a misnomer since a wide range of activity in the masticatory muscles is observed, under the presumed

condition of "rest," across individuals as well as within individuals across time; the masticatory muscles seldom exhibit a reliable level of lowest activity, even among those who have no signs or symptoms associated with a TMD. Consequently, the muscle activity as well as mandibular position vary for a number of reasons (for example, head posture, emotion, cognition, pain) and "rest position" is not an exact position.[94] Clinical diagnoses that require an interpretation of rest position must be considered very cautiously.

It may be premature to completely dismiss occlusal attributes for possible causal roles in TMD; a substantial limitation in a majority of studies of occlusion as a putative cause of TMD are that terms such as "disharmony" are used without an adequate operational definition, leading to research that is not reproducible. Inappropriate focus on largely minor occlusal features may have resulted in insufficient attention to the most important attribute of occlusion: stability.[95] Illustrating that perspective, a relationship between tooth loss and osteoarthrosis has been observed in patients with TMD but not in nonpatient populations.[96] In contrast, incisal relationships, condylar position, and joint sounds do not reliably differentiate symptomatic individuals and nonpatient populations.[97–99] Finally, perspectives regarding the importance of occlusion in TMDs typically ignore behavior: premature contacts in one dental segment coupled with balancing interferences on that same side could be due to unilateral guarding behavior in response to the TMD pain. Moreover, a shift in the apex point of the gothic arch can be initiated by masseter pain induced by saline injections, suggesting that pain might be the critical factor in producing the occlusal changes that are sometimes reported by patients with TMD.[100] And, finally, patient reports of changes in their occlusion (either accompanying other signs or symptoms of a TMD, or not), often interpreted by dentists as indicative of a problem in the occlusion that must be addressed through alteration of the occlusion, may represent occlusal dysesthesia.[101] Dysesthesia refers to alteration in sensory perception, which can be induced by a variety of mechanisms such as persistent pain or altered behavior. The occlusal sense—the feeling of the body state regarding how the teeth fit together and as mediated by periodontal proprioceptors and muscle spindles—can be altered such that even a stable occlusion may be perceived as unstable.

Muscle Hyperactivity

Masticatory muscle hyperactivity—muscle activity without functional purpose—has been proposed as a cause of myofascial pain, also using the diagnostic terms in this context *myospasm*, *muscle spasm*, and *reflex splinting*. The combination of muscle hyperactivity and the muscle pain disorder has been characterized as a "vicious cycle" of hyperactivity and pain mutually reinforcing each other.[102] Muscle hyperactivity is usefully separated into sleep bruxism and waking parafunction, corresponding to the respective states. The favored hypothesis for over 50 years was that sleep bruxism is caused by abnormalities of occlusion, but this was based on heavily flawed research mentioned above.[85,86] Currently, evidence strongly supports sleep bruxism as a parasomnia type of sleep disorder; specifically, sleep bruxism events are related to microarousals during sleep.[103,104] While microarousals are a normal part of sleep architecture in everyone, microarousals selectively trigger bruxism events in those individuals with the disorder, and do not do so in individuals without the disorder—for reasons as yet unknown. The evidence to date is circular, and it does not support microarousals as the cause of sleep bruxism; rather, individuals at risk for sleep bruxism may be differentially primed to respond to microarousals with bruxism events.

A variety of studies have linked sleep bruxism to pain.[105–111] The common explanation is that the pain is simply due to overuse of the muscle during sleep, as in postexercise pain. Clinical observations have indicated, however, that severe sleep bruxism, as measured by extensive tooth wear, can occur without symptoms. Moreover, empirical data demonstrate that not only pain but TMJ clicking and masticatory muscle tenderness are unrelated to severe tooth wear from sleep bruxism.[112] These contradictory findings lead to an important paradox: how could the most severe form of a disorder not produce pain while the less severe form presumably does? Polysomnography-based measurement of jaw muscle activity during sleep demonstrates that sleep bruxism may have, at best, a weak relationship to pain on waking the following morning.[113] In other words, individuals with TMD pain may simultaneously have evidence of sleep bruxism and report jaw pain on awakening, but the bruxism may not directly cause the pain.

Parafunction while awake has for more than 50 years also been regarded as a cause of TMD pain, but only recently has any substantial evidence emerged. Waking parafunction has classically been depicted as excessive tooth clenching, but waking parafunction appears to be a much more complex process in terms of a wide range of behaviors (e.g., bracing, pushing, guarding, pressing), a high frequency of occurrence, and generally lower forces than previously assumed. The duration of such behaviors necessary to cause pain appears to vary across individuals. As described previously, muscle activity at so-called rest does not differ between individuals with painful vs. nonpainful jaw-closing muscles,[114] suggesting that jaw behavior is very dynamic across the span of a day.[115] Waking behaviors, such as tooth clenching or muscle guarding, are remarkably concrete and reliable in how they manifest across persons with or without TMD.[116,117] Experimental evidence suggests that tooth clenching at a

relatively low but sustained level might be a source of pain in some individuals.[118] As primary evidence that parafunctional behaviors can cause pain, positive findings on muscle examination are more frequent in individuals who perform tooth-clenching activities.[119] In addition, among individuals who have developed a first lifetime episode of TMD pain, parafunctional behaviors are reported at a much higher rate prior to the development of the painful TMD compared to those who do not develop TMD, demonstrating the potential of these behaviors to contribute to the development of painful TMD.[120] Oral parafunctional behaviors exhibit a substantial association with chronic TMD pain, suggesting that the parafunctional behaviors have both contributed to the persistence of the TMD and become a result of the TMD pain.[121] Increasing frequency of such behaviors is also associated with presence of articular disc disorders;[122] the contribution of parafunction over time to potential worsening of disc displacements remains to be evaluated.

The Pain-Adaptation Model has been proposed as an alternative to the "vicious cycle" hypothesis regarding pain and muscle hyperactivity. The Pain-Adaptation Model is based on observations that EMG activity and force output of the muscle are lower in patients with musculoskeletal pain.[123] The reduction in muscle activity is thought to be protective to prevent further injury, and for acute pain, this model is both sensible and clinically useful. The Pain-Adaptation Model and the vicious cycle hypothesis are not incompatible, however; experimental evidence indicates that persistent parafunctional behaviors occurring at low levels of contractile activity are sufficient to cause pain.[124] Moreover, in chronic pain, the Pain-Adaptation Model fails to have the same relevance in that adaptation and goal-oriented behavior can over-ride the model-specified inhibition in behavior; for example, a person will chew tough textured foods regardless of the pain if the food is desired. In recognition of this clearly observed discrepancy between clinical presentations and the Pain-Adaptation Model, Peck and colleagues provided experimental evidence demonstrating the limits of the Pain-Adaptation Model in understanding pain and behavior.[125] Overall, the available evidence provides strong support for parafunctional behaviors having a strong role in the etiology of TMD as well as a strong role as a contributing factor for persistence of TMD.

Central Pain Mechanisms

In addition to local factors affecting muscle function, the results of a number of experimental studies of myofascial pain support the hypothesis that chronic pain is caused by altered central nervous system (CNS) processing.[126–130] However, these studies have not been able to distinguish whether the findings are a consequence of the pain rather than the cause of the pain. For example, altered CNS processing related to pain amplification occurs in response to having a pain disorder rather than contributing to the etiology of the disorder.[131] Central pain mechanisms are also proposed as the mechanism underlying the increased risk conferred by a pain disorder for developing another pain disorder.[132] As such, comorbidity with widespread musculoskeletal pain is likely to contribute toward the development of a chronic TMD. Individuals with fibromyalgia, a chronic widespread musculoskeletal pain disorder, have a significantly higher frequency of masticatory myofascial pain than the general population.[133,134] In a follow-up study on TMD patients, the group that self-reported the coexistence of fibromyalgia had a higher frequency of chronic TMD symptoms.[135] The presence of pain in other body sites in individuals with a TMD pain diagnosis is high [121,136] and may indicate that a musculoskeletal problem affecting the jaws is part of a more generalized pain disorder, itself a reflection of central mechanisms.

Psychological Distress

The psychological distress hypothesis proposes that TMD evolves as a consequence of pre-existing problems in overall functioning, usually due to the individual's stressful environment coupled with poor coping skills, which leads to distress in the form of depression, anxiety, or both. Two pathways by which the psychological distress leads to TMD have been proposed. The most common pathway in the TMD literature specifies that distress leads to oral parafunctional behaviors (as described above) that then result in muscle pain.[137–139] The second pathway, which is common in the general pain literature, specifies that psychological distress results in an overall increased risk for an individual to experience pain in response to some event (for example, a traumatic yawn). A challenge that is continually faced in the clinic when evaluating patients with chronic pain disorders is determining how much of the psychological distress is a cause or a consequence of chronic pain.[140] The weight of the evidence has suggested that the emotional distress is more likely a consequence than a cause of pain.[141] That evidence has been, however, largely cross-sectional at the time of entry into the clinic, and prior functioning is assessed retrospectively. In contrast, recent evidence from a large-scale prospective longitudinal study indicates that psychological distress, in the form of depression, anxiety, and problems with stress and coping, exerts a long-term effect on the individual with respect to increased risk for subsequent development of a painful TMD and, consistent with the prior cross-sectional evidence, chronic TMD is associated with greater extent of distress.[142,143]

Trauma

The role of trauma as a primary etiology for TMDs varies from self-evident (e.g., pain or mechanical TMJ problem, following

direct blow to the jaw and associated with regional swelling) to purely inferential (e.g., onset of jaw pain 6 months after a motor vehicle collision). While the literature points to some trauma events as having greater likelihood of being a sufficient cause of a TMD and other trauma events as not sufficient on their own to cause a TMD, conflicting conclusions emerge from other studies. The best evidence to date may come from two studies using the same methods and conducted in parallel. In a case-control study, individuals with chronic painful TMD reported a high number of trauma events, compared to individuals with no lifetime history of a TMD.[121] Further results from that study indicate that while reported injury, stemming from various injurious events, is a strong predictor of developing a painful TMD, most such instances of injury are without observable tissue damage and injury does not act alone.[144,145] For example, pain sensitivity, psychological distress, and oral parafunctional behaviors remain important contributors to TMD onset, even when injury has occurred. Regardless of whether trauma has a direct causal role for a TMD, traumatic response to any potential tissue-damaging event appears to be increased once painful TMD is present, and consequently trauma becomes a potent perpetuating factor when pain becomes chronic. Individuals with a TMD and a history of regional trauma may be less responsive to treatment and may consequently require more health care resources.[146,147] Collectively, the research suggests that unless a traumatic event has a self-evident relationship to symptom onset, a simple cause–effect relationship may not adequately describe the potential relationship between such events and TMD symptoms.

Integration of Etiologic Factors

The time period over which potentially etiologic events, from trauma to stress reactivity, occur as well as the latency between event and biological or behavioral consequences make assigning causation very difficult.[51] The lack of a clear single cause of TMD is notable in the majority of individuals, and in such individuals, TMD is increasingly thought to emerge in response to multiple risk determinants: no one factor by itself is sufficient to cause the disorder, whereas multiple factors increase the risk. A final initiating event may even be relatively minor, but if it occurs in conjunction with other already active determinants, then critical thresholds can be exceeded and symptoms emerge. In other words, multiple factors often come together contributing to the initiation, aggravation, and/or perpetuation of the disorder. Given the available evidence, the factors that have supporting evidence and at least some biological plausibility are, from local to systemic, summarized as follows:

- TMJ hypermobility.[148–150]
- Trauma (e.g., dental procedures, oral intubations for general anesthesia, yawning, hyperextension associated with cervical trauma).[145,147,151–156]
- Parafunctional behaviors (e.g., sleep bruxism, tooth clenching, jaw guarding, lip or cheek biting).[120–122,157–159]
- Sleep disturbance.[160,161]
- Comorbidity in the form of other rheumatic, musculoskeletal, or pain disorders. [162,163]
- Emotional distress.[142,143,164,165]
- Poor general health and an unhealthy lifestyle.[166,167]

The factors listed above vary in the strength of both evidence and association with TMD. Each factor can occur, for the most part, along continua defined by magnitude (i.e., weak to strong), frequency (seldom to continuous), and duration (short term to enduring). The actual threshold by which each factor exerts an influence on a given individual likely varies according to their susceptibility to each factor for its potential to cause problems for the organism. Plus, each TMD would appear to have its own profile of risk factors. For example, myofascial pain with arthralgia and myofascial pain alone were associated with trauma, clenching, third molar removal, somatization, and female gender.[168] Emerging research will likely provide much better estimates regarding the relative significance of these and other factors.

Classification

Due to the uncertainty about etiology, the present diagnostic classifications of TMD have been based only on signs and symptoms. Whether this descriptive approach is a particular strength, given the complexity of etiology, or whether this is a weakness, given the emerging data regarding types of pain[169] and pain processing models,[170] remains to be determined. Substantial evidence is now emerging regarding the myriad factors that predict the first lifetime episode of TMD,[171] and collectively the evidence indicates that TMD is a complex disease. A complex disease is one that does not follow simple classical etiologic pathways, whereby a single necessary and sufficient etiologic factor exists; instead, epigenetic factors, phenotypic factors, and environmental factors are dynamic and interact over time. Part of this interaction may also include feedback loops, whereby the activity of a particular factor will facilitate its emergence again; for example, stress experience due to poor coping tends to progress in a downward spiral. This type of complexity requires multidimensional assessment and, correspondingly, multiaxial classification. See Tables 10-1–10-5.

Current perspectives on taxonomy development point to the inadequacy, both scientific and clinical, of classification systems for complex disease developed according to traditional methods. For the future, we envision the merger of genetics, pain medicine, neuroscience, psychology, and bioinformatics as underlying the next major diagnostic system

Table 10-1 Taxonomic classification for temporomandibular disorders.

I. TEMPOROMANDIBULAR JOINT DISORDERS
1. Joint pain
A. Arthralgia
B. Arthritis
2. Joint disorders
A. Disc disorders
1. Disc displacement with reduction
2. Disc displacement with reduction with intermittent locking
3. Disc displacement without reduction with limited opening
4. Disc displacement without reduction without limited opening
B. Hypomobility disorders other than disc disorders
1. Adhesions/Adherence
2. Ankylosis
a. Fibrous
b. Osseous
C. Hypermobility disorder
1. Dislocations
a. Subluxation
b. Luxation
3. Joint diseases
A. Degenerative joint disease
1. Osteoarthrosis
2. Osteoarthritis
B. Systemic arthritides
C. Condylysis/Idiopathic condylar resorption
D. Osteochondritis dissecans
E. Ostronecrosis
F. Neoplasm
G. Synovial Chondromatosis
4. Fractures
5. Congenital/developmental disorders
A. Aplasia
B. Hypoplasia
C. Hyperplasia
II. MASTICATORY MUSCLE DISORDERS
1. Muscle pain
A. Myalgia
1. Local myalgia
2. Myofascial pain
3. Myofascial pain with referral
B. Tendonitis
C. Myositis
D. Spasm
2. Contracture
3. Hypertrophy
4. Neoplasm
5. Movement Disorders
A. Orofacial dyskinesia
B. Oromandibular dystonia
6. Masticatory muscle pain attributed to systemic/central pain disorders
A. Fibromyalgia or widespread pain
III. Headache
1. Headache attributed to TMD
IV. Associated structures
1. Coronoid hyperplasia

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for TMD.[172–176] In addition, we envision that diagnostic systems designed for each domain (jaw, head, back, etc.) will be integrated into one system based on a standard set of rules.[177] Yet, it is also likely that the traditional taxonomic approach based on signs and symptoms will continue to be used, despite the limitations inherent in that approach, because the need for identifying the disorder at the local tissue level will continue to have clinical utility. For example, the present validated system for the common TMDs[3] minimizes false positive diagnoses and thereby unnecessary treatment. And this will continue to be a major strength.

In the late 1980s and early 1990s, TMD classification was influenced by several independent developments. The first developments emphasized concise symptom- and sign-based classification systems that were developed for use by the practicing clinician.[178–180] The American Academy of Orofacial Pain (AAOP) published a more far-reaching general classification of disorders that was developed by a broad group of experts who applied available knowledge to the development of an acceptable and useful system for clinical practice,[181] and emphasized multiple diagnoses which reflected clinical reality.[182,183] This classification system was inclusive of all disorders a clinician might encounter but it was not highly reliable (due to its structure) and it was not assessed for validity. These developments, however, did not facilitate research, creating a large hole that was too often filled with poorly done etiologic and treatment studies. The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) was published as a system "offered to allow standardization and replication of research into the most common forms of muscle and joint-related TMD."[184] This system was based on several core principles with

Table 10-2 Diagnostic criteria for the most common pain-related temporomandibular disorders.

Myalgia (ICD-9 729.1)		
	Description	Pain of muscle origin that is affected by jaw movement, function, or parafunction, and replication of this pain occurs with provocation testing of the masticatory muscles.
Criteria	HISTORY	1) Pain[1] in the jaw, temple, in the ear, or in front of ear; AND 2) Pain modified with jaw movement, function or parafunction.
Criteria	**AND**	
Criteria	EXAM	1) Confirmation[2] of pain location(s) in the temporalis or masseter muscle(s); AND 2) Report of familiar pain[3] in the temporalis or masseter with <u>at least</u> 1 of the following provocation tests: a) Palpation of the temporalis or masseter muscle(s); OR b) Maximum unassisted or assisted opening.
Validity		Sensitivity 0.90; Specificity 0.99
Comments		The pain is not better accounted for by another pain diagnosis. Other masticatory muscles may be examined as dictated by clinical circumstances but the sensitivity and specificity for this diagnosis based on these findings has not been established.
Myofascial Pain with Referral (ICD-9 729.1)		
	Description	Pain of muscle origin as described for myalgia with referral of pain beyond the boundary of the masticatory muscle(s) being examined when using the myofascial examination protocol. Myofascial pain with referral is a subtype of myalgia.
Criteria	HISTORY	1) Pain[1] in the jaw, temple, in the ear, or in front of ear; AND 2) Pain modified with jaw movement, function or parafunction.
Criteria	**AND**	
Criteria	EXAM	1) Confirmation[2] of pain location(s) in the temporalis or masseter muscle(s); AND 2) Report of familiar pain[3] with palpation of the temporalis or masseter muscle(s); AND 3) Report of pain at a site beyond the boundary of the muscle(s) being palpated.
Validity		Sensitivity 0.86; Specificity 0.98
Comments		The pain is not better accounted for by another pain diagnosis. Other masticatory muscles may be examined as dictated by clinical circumstances but the sensitivity and specificity for this diagnosis based on these findings has not been established.
Arthralgia (ICD-9 524.62)		
	Description	Pain of joint origin that is affected by jaw movement, function, or parafunction, and replication of this pain occurs with provocation testing of the TMJ.
Criteria	HISTORY	1) Pain[1] in the jaw, temple, in the ear, or in front of ear; AND 2) Pain modified with jaw movement, function or parafunction.
Criteria	**AND**	
Criteria	EXAM	1) Confirmation[2] of pain location in the area of the TMJ(s); AND 2) Report of familiar pain[3] in the TMJ with <u>at least</u> 1 of the following provocation tests: a) Palpation of the lateral pole or around the lateral pole; OR b) Maximum unassisted or assisted opening, right or left lateral movements, or protrusive movements.
Validity		Sensitivity 0.89; Specificity 0.98
Comments		The pain is not better accounted for by another pain diagnosis.
Headache attributed to TMD (ICD-9 339[4])		
	Description	Headache in the temple area secondary to pain-related TMD* that is affected by jaw movement, function, or parafunction, and replication of this headache occurs with provocation testing of the masticatory system.
Criteria	HISTORY	1) Headache[1] of any type in the temple; AND 2) Headache modified with jaw movement, function or parafunction.
Criteria	**AND**	
Criteria	EXAM	1) Confirmation[2] of headache location in the area of the temporalis muscle(s); AND 2) Report of familiar headache[3] in the temple area with **at least** 1 of the following provocation tests: a) Palpation of the temporalis muscle(s); OR b) Maximum unassisted or assisted opening, right or left lateral movements, or protrusive movements.
Validity		Sensitivity 0.89; Specificity 0.87
Comments		The headache is not better accounted for by another headache diagnosis.
Footnote		*A diagnosis of painful TMD (e.g., myalgia, myofascial pain with referral, or TMJ arthralgia) is derived using valid diagnostic criteria.

[1] The time frame for assessing pain including headache is in "the last 30 days" since the stated sensitivity and specificity of these criteria were established using this time frame. Although the specific time frame can be dependent on the context in which the pain complaint is being assessed, the validity of this diagnosis based on different time frames has not been established.

[2] The examiner must identify with the patient all anatomical locations that they have experienced pain in the last 30 days. For a given diagnosis, the location of pain induced by the specified provocation test(s) must be in an anatomical structure consistent with that diagnosis.

[3] "Familiar pain" or "familiar headache" is based on patient report that the pain induced by the specified provocation test(s) has replicated the pain that the patient has experienced in the time frame of interest, which is usually the last 30 days. "Familiar pain" is pain that is similar or like the patient's pain complaint.

[4] The International Classification of Diseases 9th Edition (ICHD-9) has not established a specific code for *Headache attributed to TMD;* ICD-9 339 is for *"other headache syndromes."* If a primary headache is present (e.g., *tension type headache*) then the headache can be classified according to the primary headache type.

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Table 10-3 Diagnostic criteria for the most common intra-articular temporomandibular disorders.

Disc Displacement with Reduction (ICD-9 524.63)		
Description		An intracapsular biomechanical disorder involving the condyle-disc complex. In the closed mouth position the disc is in an anterior position relative to the condylar head and the disc reduces upon opening of the mouth. Medial and lateral displacement of the disc may also be present. Clicking, popping or snapping noises may occur with disc reduction. A history of prior locking in the closed position coupled with interference in mastication precludes this diagnosis.
Criteria	HISTORY	1) In the last 30 days[1] any TMJ noise(s) present with jaw movement or function;
	AND	**OR**
		2) Patient report of any noise present during the exam.
	EXAM	1) Clicking, popping and/or snapping noise detected during both opening and closing, with palpation during at least 1 of 3 repetitions of jaw opening and closing;
		OR
		2) Clicking, popping and/or snapping noise detected with palpation during at least 1 of 3 repetitions of opening or closing; AND
		3) Clicking, popping and/or snapping noise detected with palpation during at least 1 of 3 repetitions of right or left lateral movements, or protrusive movements.
Validity		Without imaging: sensitivity 0.34; specificity 0.92. Imaging is the reference standard for this diagnosis.
Imaging		When this diagnosis needs to be confirmed, then TMJ MRI criteria[2] are positive for <u>both</u> of the following:
		1) In the maximum intercuspal position, the posterior band of the disc is located anterior to the 11:30 position **and** the intermediate zone of the disc is anterior to the condylar head;
		AND
		2) On full opening, the intermediate zone of the disc is located between the condylar head and the articular eminence.
Disc Displacement with Reduction with Intermittent Locking (ICD-9 524.63)		
Description		An intracapsular biomechanical disorder involving the condyle-disc complex. In the closed mouth position the disc is in an anterior position relative to the condylar head, and the disc intermittently reduces with opening of the mouth. When the disc does not reduce with opening of the mouth, intermittent limited mandibular opening occurs. When limited opening occurs, a maneuver may be needed to unlock the TMJ. Medial and lateral displacement of the disc may also be present. Clicking, popping, or snapping noises may occur with disc reduction.
Criteria	HISTORY	1) In the last 30 days,[1] any TMJ noise(s) present with jaw movement or function; OR
	AND	2) Patient report of any noise present during the exam.
		AND
		3) In the last 30 days,[1] jaw locks with limited mouth opening, even for a moment, and then unlocks.
	EXAM	Same as specified for Disc Displacement with Reduction. Although not required, when this disorder is present clinically, examination is positive for inability to open to a normal amount, even momentarily, without the clinician or patient performing a specific manipulative maneuver.
Validity		Without imaging: sensitivity 0.38; specificity 0.98. Imaging is the reference standard for this diagnosis.
Imaging		When this diagnosis needs to be confirmed, then the imaging criteria[2] are the same as for disc displacement with reduction if intermittent locking is not present at the time of imaging. If locking occurs during imaging, then an imaging-based diagnosis of disc displacement without reduction will be rendered and clinical confirmation of reversion to intermittent locking is needed.
Disc Displacement without Reduction with Limited Opening (ICD-9 524.63)		
Description		An intracapsular biomechanical disorder involving the condyle-disc complex. In the closed mouth position the disc is in an anterior position relative to the condylar head, and the disc does not reduce with opening of the mouth. Medial and lateral displacement of the disc may also be present. This disorder is associated with persistent limited mandibular opening that does not resolve with the clinician or patient performing a specific manipulative maneuver. This is also referred to as "closed lock."
Criteria	HISTORY	1) Jaw lock or catch so that the mouth would not open all the way; AND
	AND	2) Limitation in jaw opening severe enough to limit jaw opening and interfere with ability to eat.
	EXAM	Maximum assisted opening (passive stretch) < 40mm including vertical incisal overlap.
Validity		Without imaging: sensitivity 0.80; specificity 0.97. Imaging is the reference standard for this diagnosis.

Imaging		When this diagnosis needs to be confirmed, then TMJ MRI criteria[2] are positive for both of the following: 1) In the maximum intercuspal position, the posterior band of the disc is located anterior to the 11:30 position **and** the intermediate zone of the disc is anterior to the condylar head, **AND** 2) On full opening, the intermediate zone of the disc is located anterior to the condylar head. Note: Maximum assisted opening of < 40mm is determined clinically.
Footnote		Presence of TMJ noise (e.g., click with full opening) does not exclude this diagnosis.
Disc Displacement without Reduction without Limited Opening (ICD-9 524.63)		
Description		An intracapsular biomechanical disorder involving the condyle-disc complex. In the closed mouth position the disc is in an anterior relative the condylar head and the disc does not reduce with opening of the mouth. Medial and lateral displacement of the disc may also be present. This disorder is NOT associated with limited mandibular opening.
Criteria	HISTORY	Same as specified for Disc Displacement without Reduction with Limited Opening.
	AND	
	EXAM	Maximum assisted opening (passive stretch) ≥ 40mm including vertical incisal overlap.
Validity		Without imaging: sensitivity 0.54; specificity 0.79. Imaging is the reference standard for this diagnosis.
Imaging		When this diagnosis needs to be confirmed, then TMJ MRI criteria[2] are the same as for disc displacement without reduction with limited opening. Note: Maximum assisted opening of ≥ 40mm is determined clinically.
Footnote		Presence of TMJ noise (e.g., click with full opening) does not exclude this diagnosis.
Degenerative Joint Disease (ICD-9 715.18)		
Description		A degenerative disorder involving the joint characterized by deterioration of articular tissue with concomitant osseous changes in the condyle and/or articular eminence.
Criteria	HISTORY	1) In the last 30 days[1] any TMJ noise(s) present with jaw movement or function;
	AND	**OR**
		2) Patient report of any noise present during the exam.
	EXAM	At least one of the following must be present: 1. Crepitus detected with palpation during opening, closing, lateral, or protrusive movements.
Validity		Without imaging: sensitivity 0.55; specificity 0.61. Imaging is the reference standard for this diagnosis.
Imaging		When this disorder is present, then TMJ CT criteria[2] are positive for **at least** one of the following: Subchondral cyst(s), erosion(s), generalized sclerosis or osteophyte(s). Note: Flattening and/or cortical sclerosis are considered indeterminant findings for DJD and may represent normal variation, aging, remodeling or a precursor to frank DJD.
Subluxation (ICD-9 830.1)		
Description		A hypermobility disorder involving the disc-condyle complex and the articular eminence: In the open mouth position, the disc-condyle complex is positioned anterior to the articular eminence and is unable to return to a normal closed mouth position without a specific manipulative maneuver. The duration of dislocation may be momentary or prolonged. When prolonged the patient may need the assistance of the clinician to reduce the dislocation and normalize jaw movement; this is referred to as luxation. This disorder is also referred to as "open lock."
12	HISTORY	1) In last 30 days,[1] jaw locking or catching in a wide open mouth position, even for a moment, so could not close from the wide open position; AND
	AND	
		2) Inability to close the mouth without a specific manipulative maneuver
	EXAM	Although no exam findings are required, when this disorder is present clinically, examination is positive for inability to return to a normal closed mouth position without the patient performing a specific manipulative maneuver.
Validity		Without imaging and based only on history: sensitivity 0.98; specificity 1.00.
Imaging		When this disorder is present, then imaging criteria are positive for the condyle positioned beyond the height of the articular eminence.

[1] The time frame for assessing selected biomechanical intra-articular disorders is in "the last 30 days" since the stated sensitivity and specificity of these criteria was established using this time frame. Although the specific time frame can be dependent on the context in which the pain complaint is being assessed, the validity of this diagnosis based on different time frames has not been established.

[2] Ahmad M, Hollender L, John M, Anderson Q, Kartha K, Ohrbach R, Truelove, E and Schiffman E. Research Diagnostic Criteria for Temporomandibular Disorders: Development of Image Analysis Criteria and Examiner Reliability for Image Analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:844–860.

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Table 10-4 Imaging-based diagnosis of soft-tissue and hard-tissue TMJ disorders.

Disorder	Criteria
Disc diagnosis for the TMJ, based on MRI *	
Normal	Disc location is normal on closed and open-mouth images.
Disc displacement with reduction	Disc location is displaced on closed-mouth images but normal on open-mouth images
Disc displacement without reduction	Disc location is displaced on both closed-mouth and open-mouth images.
Indeterminate	Disc location is not clearly normal or displaced in the closed-mouth view
Disc not visible	Neither signal intensity nor outlines make it possible to define a structure as the disc in the closed-mouth and open-mouth views. If the images are of adequate quality in visualizing other structures in the TMJ, then this finding is interpreted to indicate a deterioration of the disc, which is associated with advanced disc pathology.
Osseous diagnoses for the TMJ, based on CT **	
Normal	a) Normal relative size of the condylar head; and b) No subcortical sclerosis or articular surface flattening; and c) No deformation due to subcortical cyst, surface erosion, osteophyte, or generalized sclerosis.
Indeterminate for osteoarthritis	a) Normal relative size of the condylar head; and b) No deformation due to subcortical cyst, surface erosion, osteophyte, or generalized sclerosis; and c) Either of: i) Subcortical sclerosis; or ii) Articular surface flattening
Osteoarthritis	a) Deformation due to subcortical cyst, surface erosion, osteophyte, or generalized sclerosis

Source:
*Adapted from Table IV, Ahmad et al, OOOOE, 2009
** Adapted from Table II, Ahmad et al, OOOOE, 2009

Table 10-5 Selected TM disorders and supplemental characteristics.

Disorder	Characteristics
Deviation in form Note: Painless mechanical dysfunction or altered function due to irregularities or aberrations in the form of intracapsular soft and hard articular tissues. Does not require intervention.	• Complaint of faulty or compromised joint mechanics • Reproducible joint noise, usually at the same position during opening and closing • Radiographic evidence of structural bony abnormality or loss of normal shape
Disc displacement with reduction Note: Clinical significance is related to pain associated with the noise, to mechanical locking, or interference in mastication or other functional activities.	• Pain (when present) is directly associated with joint noise during movement • Clinical assessment is often unreliable due to poor stability of the noise • Mandibular deviation during opening or closing coinciding with a click
Disc displacement without reduction	• History of clicking that stopped when the locking began • Pain clearly localized to the TMJ precipitated by function, when acute • Marked limited mandibular opening when acute • Uncorrected deviation to the affected side on opening and marked limited laterotrusion to the contralateral side when acute • Localized pain precipitated by forced mouth opening • Ipsilateral hyperocclusion, when acute
Synovitis or capsulitis Note: Inflammation of the synovial lining or loading of capsular lining. Difficult to clearly differentiate from arthralgia.	• Localized pain at rest exacerbated by function, especially with superior and posterior joint loading • Limited range of motion secondary to pain • T2-weighted MRI may show joint fluid

Table 10-5 (Continued)

Disorder	Characteristics
Osteoarthrosis Note: Degenerative noninflammatory condition of the joint, characterized by structural changes of joint surfaces secondary to excessive strain on the remodeling mechanism. Distinguish from osteoarthritis, which is a secondary inflammatory condition. Both osteoarthrosis and osteoarthritis are subsumed within degenerative joint disease in the DC/TMD.	• Crepitus on examination • Absence of joint pain
Myofascial pain Note: Is a regional disorder, distinguishing it from fibromyalgia. When the pain is local to the area of stimulation, this disorder is termed myalgia in the DC/TMD in order to note the presence of hyperalgesia without spreading, referral, or autonomic reactions. The clinical significance of these additional characteristics is with differential diagnosis; the requirement for specific treatments when referral is present remains untested but anecdotally rich.	• Taut bands and trigger points are hallmark characteristics but exhibit only fair examiner reliability • Reduction in pain with local muscle anesthetic injection or vapocoolant spray, coupled with stretch of the muscle
Protective muscle splinting Note: Restricted or guarded mandibular movement due to co-contraction of muscles as a means of avoiding pain caused by movement of the parts. Should be distinguished from fear-avoidance behavior by ruling out local nociceptive source, either by history or by examination.	• Severe pain with function but not at rest • Marked limited range of motion (generally, pain-free opening and maximal unassisted opening will be similar), and opening is only minimally responsive to attempted passive stretch (maximal assisted opening) initially, and active resistance to further attempts at stretch can be noted
Contracture Note: Chronic resistance of a muscle to passive stretch as a result of fibrosis of the supporting tendon, ligaments, or muscle fibers themselves.	• Limited range of motion • Unyielding firmness on passive stretch • History of trauma or infection

Adapted from McNeill C.[127]
MRI = magnetic resonance imaging; TMJ = temporomandibular joint.

enduring value for the field.[185] The assessment of physical status (Axis I) was described in sufficient detail for standardized data collection, allowing reliable diagnoses and comparison of findings across investigators and clinicians. Because pain transcends a given organ system, the classification system also reflected psychological, behavioral, and social factors considered to be as important as an accurate description of the physical pathology. Consequently, the RDC/TMD classification contained a separate Axis II to assess psychosocial status and pain-related disability. The RDC/TMD was designed for research, and thereby permitted far more reliable diagnoses of the disorders the clinician encounters most often.

The RDC/TMD classification was subsequently assessed in a multicenter study for validation and the findings and subsequent publications improved upon the RDC/TMD while retaining the core features described above.[186] The publications included: Diagnostic Criteria for TMDs (DC/TMD);[3] an overall taxonomy and draft criteria for the less common TMDs;[187] and incorporation of both into the AAOP guidebook.[1,188] In summary, reliable and valid diagnoses of the common TMDs are readily available for clinical and research use. The DC/TMD allows, for each individual, multiple TMD diagnoses: several pain diagnoses and, for each joint, pain, disc displacement, degenerative joint disease, and subluxation diagnoses. The terms used are clearly defined, the clinical examination procedures are completely specified, and the criteria required to meet the diagnosis are specific. The pain diagnoses exhibit excellent sensitivity and specificity. In contrast, the joint disorders, with one exception, exhibit unacceptable sensitivity and specificity based only on clinical assessment. The one exception among the joint disorders is disc displacement without reduction, with limited opening, which does have acceptable sensitivity and specificity from clinical examination procedures.

In clinical practice, it has been generally believed that rigidly adhering to the criteria of a system such as the DC/TMD may not be possible due to the assumption that the common TMDs, for example, exhibit a wide spectrum of signs and symptoms. However, recent evidence indicates that each of the common TMD has reliable characteristics; for the very large majority of patients, the stated criteria clearly define the disorder. The consequence is that the clinician, using the described clinical assessment methods, can reliably and validly provide diagnoses for most individuals with TMD pain. Imaging will be required to establish a disc disorder diagnosis such as "disc displacement without reduction." The clinician should recommend diagnostic imaging as part of the

assessment when the prognosis or choice of treatment might benefit. The reader is referred to the publication by Schiffman and colleagues for a full description of the DC/TMD, to the publication by Peck and colleagues for diagnostic criteria for the less common TMD, to the text by DeLeeuw and Klasser for a comprehensive guidebook to evaluation, diagnosis, and treatment, and to the website of the International Network for Orofacial Pain and Related Disorders Methodologies (INfORM; http://rdc-tmdinternational.org) for clinical examination specifications, training videos, and all patient assessment instruments. Consequently, a system such as the DC/TMD appropriately guides the clinician towards better diagnosis. Yet, despite these developments toward a well-operationalized, reliable, and valid physical examination, it is underutilized and the psychosocial assessment domain is similarly underutilized.[189]

Where sleep bruxism belongs within a TMD classification system was a challenge for the RDC/TMD authors—who omitted it from the classification—and similarly it is not part of the DC/TMD. Is sleep bruxism a disorder, or is it a process?[190] Classification of sleep bruxism remains an ongoing question, as does whether sleep bruxism aggravates or contributes to the persistence of pain symptoms associated with TMD. While the cause of bruxism is not fully understood, the evidence strongly indicates that occlusal abnormalities are not the cause.[191,192] Occlusal appliances may protect the teeth from the effects of bruxism but cannot be expected to prevent or decrease the bruxism activity.[193] When bruxism is considered to be the cause or a factor of TMD symptoms, oral appliance therapy is often effective, but symptoms are likely to return when appliance therapy is withdrawn.[194] In one report, nocturnal aversive biofeedback and splint therapy caused a decrease in the frequency and duration of bruxism, but bruxism activity returned after treatment was withdrawn.[195] Occlusal splints worn during sleep have not been found to stop bruxism but do reduce the signs of bruxing.[196] While oral appliances remain the treatment with the best evidence for sleep bruxism,[197] it is notable that placebo intraoral appliances are equally effective for reducing myofascial pain.[198] The efficacy of the placebo-type oral appliance for bruxism critically questions the nature of the problem that the traditional oral appliance is assumed to address.

The critical question raised by placebo oral appliances is extended when medication treatments are considered. Reports of bruxism and symptoms of facial pain, earache, and headache associated with the use of selective serotonin reuptake inhibitors (SSRIs) have been published.[199] Symptoms of bruxing resolved when the dosage was decreased or when buspirone was added.[200] Buspirone has a postsynaptic dopaminergic effect and may act to partially restore suppressed dopamine levels associated with the use of SSRIs. Tan and Jankovic injected severe bruxers in the masseter muscles with botulinum toxin in an open-label prospective trial and reported significant improvement in symptoms and minimal adverse effects.[201] Botulinum toxin exerts a paralytic effect on the muscle by inhibiting the release of acetylcholine at the neuromuscular junction. The treatment effect lasted approximately 5 months and had to be repeated. The implications of this research, whereby the end organ response of the motor cortex signal is blocked, remain for future investigators.

ASSESSMENT

The most valuable aspect of the diagnostic assessment is a thorough history;[202] pain disorder diagnoses rely predominantly on the history, and the diagnosis of some pain disorders, such as headache, relies exclusively on the history.[203] For some disorders such as headache, the history serves to rule out other forms of pathology; for TMD, the examination is confirmatory for a pain diagnosis but remains only suggestive for most of the joint disorders. An examination for a particular disorder (e.g., the comprehensive examination of TMD, as described),[204] must be supplemented by examination procedures as indicated for a differential diagnosis; for example, ruling out odontogenic causes of regional masticatory system pain. In contrast to the situation 30 years ago when TMD diagnostic tests were not validated or standardized,[180] the clinical tests most needed for the assessment of a person with a TMD are now standardized, reliable, and valid.[3,205] In contrast, diagnostic tests such as ultrasonography of joint sounds, thermography, jaw tracking, and EMG, all of which exhibit high measurement reliability and precision, do not offer the assurance of a more accurate diagnosis or better treatment outcomes.[206] These devices were reviewed for their diagnostic value in assessing patients with temporomandibular complaints, and were judged 30 years ago to not have the necessary sensitivity and specificity for a valid diagnosis.[202] No additional supporting evidence has emerged over the past several decades. Claims that they are adjunctive tests must nevertheless be accompanied by the same evidence as required for any diagnostic test; if an adjunctive test is to be useful, incremental validity must be demonstrated. Incremental validity refers to the ability of an additional test to provide unique information that improves the sensitivity or specificity of the information obtained prior to the additional test. For example, analysis of TMJ synovial fluid is an active area of research but has not yet become a standard procedure in diagnosis or the selection of treatment. These tests require sophisticated instrumentation that would increase health care costs to the patient that, for the present, are not justified.

Consequently, history, clinical examination, and imaging when indicated remain the recommended diagnostic approach for most patients.[4,179] Diagnostic imaging is of value in selected conditions but not as a routine part of a standard assessment. Diagnostic imaging can increase accuracy in the detection of internal derangements[207] and abnormalities of articular bone.[208] The clinical meaningfulness of such tests, however, must be determined prior to ordering the test; a special test should be preceded by a clinical hypothesis (differential diagnosis) that the test will be able to answer, and the clinical hypothesis should be related to a particular course of action. For example, if treatment for what appears to be a painful recurrent mechanical joint problem will proceed in one direction if the problem is a disc displacement, but in another direction if the disc is normal, then imaging would be well-justified. If, on the other hand, both treatments for this stated example would be pursued, each for 4–6 weeks and with no or minimal risk of adverse effects, then the treatment trial without imaging may be more prudent, thereby not unnecessarily expending health care resources and not adding imaging information that may only confuse rather than clarify. A painful clicking joint should be treated, regardless of whether the problem is due to an internal derangement or not.[209] If the choice of treatment depends on a more accurate diagnosis, then imaging would be indicated.

Similarly, other tests should be ordered when the differential diagnosis warrants further diagnostic exploration. Examples follow. Facial pain similar to the pain of a painful TMD may be associated with serious undetected disease. Muscle or joint pain may be a secondary feature of another disease or may mimic a TMD. A diagnosis of a more serious condition may be missed or delayed.[210,211] Severe throbbing temporal pain associated with a palpable nodular temporal artery, increasingly severe headache associated with nausea and vomiting, and documented altered sensation or hearing loss are all indications of serious disease requiring timely diagnosis and management. In short, TMD diagnosis (and management) requires ongoing use of clinical decision-making skills.

History

The most common symptom related to TMD is pain, and it is the overwhelming reason people seek care. Pain may be present at rest, may be continuous or intermittent, and characteristically increases with jaw function such as chewing or opening wide. Other chief complaints in relation to seeking care for a TMD include restricted jaw movement, painful or loud TMJ clicking or crepitus, and jaw locking.

Pain severity or intensity is a subjective measure provided by the patient and can be rated in several ways.[212] A rating scale can be either numeric or verbal. A numeric scale asks the patient to rate pain by identifying a number, typically between 0 and 10, that best reflects pain intensity. Verbal descriptors such as no pain, mild pain, moderate pain, and severe pain can also provide an equally valid assessment. If an estimate with greater precision is needed, a visual analogue scale (VAS) has high sensitivity to change and better independence when using repeated measures. A VAS uses a 10-cm line anchored on the left side with the descriptor of "no pain" and on the right an extreme descriptor such as "the worst pain ever experienced." The patient is asked to mark his or her pain intensity by placing a mark on the line, and the score is obtained by measuring from the left end to the mark.

Because pain intensity associated with TMDs typically varies, including periods of no pain, assessing pain intensity only at one time point—for example, at the clinic consultation—can be misleading. Any of the pain intensity rating scales can be used to assess differing aspects of pain, such as current, minimum and maximum in the past, or average pain ratings. Consideration of time period is important: too short, and meaningful variability may be lost; too long, and memory and relevance become potential problems. For the temporal reference frame regarding whether pain has been present or absent, the DC/TMD (Diagnostic Criteria for Temporomandibular Disorders)[3] explicitly uses the "last 30 days" for two reasons: memory for prior pain is better with shorter time periods, and, in general, the last 30 days appears to be sufficient for an active chief complaint of pain. For assessing pain intensity, the DC/TMD utilizes the pain measurement scales from the Graded Chronic Pain Scale,[213] in order to determine a characteristic pain index, based on current and, over the prior 30 days, average and worst pain.

As defined by the DC/TMD, regional masticatory system pain should be influenced by mandibular function, or an alternative diagnosis should be suspected. Table 10-2 indicates that pain aggravated by function is a criterion for a diagnosis of either myalgia or arthralgia. Mandibular functions shown to reliably increase or trigger myofascial pain include chewing hard or tough food, opening the mouth, or moving the jaw. Table 10-6 lists questions that are useful parts of the history for assessing mandibular function.

A pain drawing that contains the full body is helpful in defining the extent of pain; the recording of other body regions helps identify patients who have multiple sites of pain, which suggests a more systemic or generalized disorder. A pain drawing completed at initial evaluation may also be used to assess treatment progress of the TMD. Following the initial evaluation, a pain diary can be a useful tool for identifying events or times of increased and decreased pain; it may also serve to identify behaviors or situations that are contributing to the persistence of symptoms.[214]

Table 10-6 Assessment of TMD history.*

Where is the pain located? Is there pain in any other areas of the body?
When did the pain first begin? What has been the pattern over time; have there been notable periods of remission, or notable periods of exacerbation, and what were the circumstances?
How often do episodes (or, if pain is continuous: flareups) occur, duration, temporal pattern to the bouts (time of day, day of week), and how managed?
When is pain at its worst (morning [on awakening] or as day progresses [toward evening])?
What aggravates the pain (e.g., when using the jaw such as opening wide, yawning, chewing, speaking, or swallowing; stress or deadlines; postural positions)?
What alleviates the pain (e.g., rest, analgesic, holding the jaw rigid in specific positions)?
[If other pains such as headaches, earaches, neckache, or cheek pain are present] When did the other pain(s) begin, did they worsen when the jaw pain worsened, did they respond to treatment for the jaw pain?
Is there pain or thermal sensitivity in the teeth? Does biting on any teeth cause pain?
Do jaw joint noises (clicking, popping, grinding, or crepitus) occur when moving the jaw or when chewing?
Does the jaw ever hesitate, get stuck, or lock when trying to open or when trying to close from a wide open position?
Does jaw motion feel restricted?
Has the jaw ever been injured?
Has there been an abrupt change in the way the teeth meet or fit together? Does the bite feel "off" or uncomfortable?
What treatments have been provided? What was the outcome? What was the compliance with treatment requirements?

* Miscellaneous symptoms sometimes reported in association with TMD-related include: dizziness; nausea; fullness or ringing in the ears; diminished hearing; facial swelling; redness of the eyes; nasal congestion; altered sensation such as numbness, tingling, or burning; altered vision; and muscle twitching.

Table 10-7 Problem list of domains and specific factors contributing to persistence and symptom amplification in temporomandibular disorders.

Lifestyle	Emotional Factors	Cognitive Factors	Biologic Factors	Social Factors
Diet	Prolonged anger	Negative self-image	Other illnesses	Work stresses
Sleep	Anxiety	Unrealistic expectations	Past trauma	Unemployment
Alcohol	Excessive worry	Inadequate coping	Past jaw surgery	Family stresses
Smoking	Depression			Litigation
Overwork				Financial difficulty

Source: Adapted from Fricton J.[163]

A range of other symptoms sometimes reported in association with a TMD include dizziness, ear symptoms of fullness, ringing, or earache. Altered occlusion and jaw misalignment are also commonly reported.[215] Some patients, especially those with stress related disorders, report additional symptoms such as swelling and numbness, which are functional in nature. Functional symptoms are reported physical abnormalities which are not detected on a careful clinical examination.

Behavioral Assessment

Assessment for psychological distress and pain-related disability is frequently an important component of a TMD evaluation. Some TMDs evolve into a chronic pain disorder, resulting in psychological distress, disruption of interpersonal relationships, and an inability to perform daily activities, including work. Psychosocial factors are considered more important than physical factors in predicting treatment outcome.[216] The lack of a direct relationship between physical pathology and intensity of pain to subsequent disability emphasizes the need to assess the psychological and behavioral effects of the disorder in order to better understand: (1) the reported pain and not assume that as-yet undetected physical pathology is responsible; (2) anticipated barriers to successful treatment; and (3) the potential for relapse.

Table 10-7 lists multiple potential contributing factors, organized by domain, to TMD pain often reported in the pain research literature. No one health care professional can be expected to manage the physical pathology of the temporomandibular structures along with all of the various lifestyle, emotional, cognitive, and social issues that may affect the individual with chronic pain. Chronic TMDs with a significant emotional component are best managed in a multidisciplinary setting.

Cluster models have provided replicable insights into the different constellations of factors important for chronic pain. Rudy et al. classified TMD patients based on psychosocial and behavioral parameters into three unique subgroups: dysfunctional, interpersonally distressed, and adaptive copers.[217] Patients with painful TMD exhibited psychosocial and behavioral profiles similar to those of patients with back pain or with headache.[6] Similarly, Bair et al. also classified individuals with a painful TMD into three unique subgroups: adaptive, pain sensitive, and dysfunctional categories,[218] overall very similar to those identified by Rudy and colleagues. These findings highlight the substantial overlap in important characteristics exhibited by patients with a variety of chronic pain disorders. Clinical evaluation of patients with TMD complaints which do not include consideration of emotional factors often result in incorrect diagnosis, a persistent belief on the part of the patient that a cure is imminent, and unsuccessful treatment.

It is difficult to determine the presence of active oral parafunction, such as bruxism. Direct interview will produce a high rate of false negatives due to the unconscious nature of the behavior. Patients are often unaware of tooth clenching or other behaviors associated with jaw hyperactivity during the waking hours. There are several methods that can improve this assessment. Use of a checklist that describes the common types of parafunctional behaviors appears to trigger intentional access to memory via the patient deciding to "test" each listed behavior in order to determine whether the behavior feels familiar (i.e., I must do this one) or not familiar (i.e., I probably don't do that one). Field monitoring of daytime jaw activity, reports by friends and coworkers of observed behaviors (e.g., clenching with associated observable masseter contraction), and reports by a bedroom partner of tooth-grinding noises during sleep are helpful. Finally, teaching a therapeutic jaw relaxation posture will often uncover the otherwise denied or unknown behaviors via recognition, typically by both patient and clinician, that the target therapeutic behavior is very challenging.

Clinical characteristics that are indicators of the need for expert psychological evaluation of a person with TMD include the following:[219]

1) The persistence of pain beyond the expected healing time and no clear physical explanation is identified.
2) Inconsistent or poor response to usual treatments,
3) Significant psychological distress, as revealed via self-reported instruments and confirmed through clinical interview,
4) Disability greatly exceeds what is expected on the basis of the clinical findings.
5) Excessive or inappropriate use of health care services, encompassing tests and treatments, including prolonged use or reliance on opioids, sedatives, minor tranquilizers antianxiety medications, or alcohol for pain control.

Physical Examination

There is no single pathognomonic physical finding that can establish a TMD diagnosis. Historically, and as described previously for the AAOP Guidelines, a set of possible physical findings was listed for each type of TMD, but in the absence of clear data regarding what constituted a given problem, the diagnostic rubric was based on the presence of any of the findings. By extension, the more such findings occur, either the more severe the disorder or the more certain the diagnosis. For the common TMDs, as initiated by the RDC/TMD and now validly described in the DC/TMD,[3] each disorder is defined by, or constituted by, specific characteristics, and all of them must be present in order for the putative diagnosis to correctly identify the problem. Table 10-8 provides a general overview of the DC/TMD examination procedures. For the uncommon TMDs,[187] each disorder is less strongly defined by the stated characteristics, simply because there are, at present, little data to empirically characterize each of those disorders. Distinguishing clinical decision-making when we have sufficient data versus when we do not is a critical function of being an expert: knowing when—and when not to—use the rules.[220,221] In recognizing that the DC/TMD is not 100% accurate, the clinician must consequently know when exceptions to the rules are optimally invoked. Taking a history prior to the examination has a seminal role: serving as sufficient information by which the clinician has developed clinical hypotheses (i.e., differential diagnoses) and then knows what to look for in the examination. Unexpected findings should be appropriately followed up. A standardized examination routine (as defined by the DC/TMD and available as a full set of specifications[204] from INfORM) and supplemented by a video for examiner training[222] simplifies the task of the examiner: it provides a reference frame emerging from consistent examinations and better identifies unexpected findings. In general, the clinical features that distinguish patients from controls are decreased passive mouth opening,[223] and masticatory muscle pain provoked by maximal mouth opening and palpation.[224] Among all individuals with a TMD, masticatory muscle tenderness on palpation (see Figure 10-10) is the most consistent examination feature.[182] In contrast, the literature has described an uncorrected deviation on maximum mouth opening as characteristic of acute disc displacements without reduction.[39] While that uncorrected deviation is perhaps common in the individual with an acute joint, such deviation is less reliable than assumed; such deviations in chronic conditions are far more variable as a finding. Moreover, uncorrected deviations require a differential diagnosis between disc displacement,

Table 10-8 Physical examination of the masticatory system for TMD.

Examination Component	Observations
Inspection	Facial asymmetry, swelling, and masseter and temporal muscle hypertrophy Opening pattern (corrected and uncorrected deviations, uncoordinated movements, limitations)
General palpation	Parotid and submandibular areas Lymph nodes
Mandibular range of motion (ROM)	Vertical jaw movements: pain-free opening, maximal opening with pain, and maximal assisted opening Horizontal jaw movements: lateral and protrusive movements Pain provocation, location, and replication are assessed with each movement
TMJ noises	Any noise produced by vertical or horizontal movements, as reported by the patient and as identified as to type by the examiner (e.g., click vs. crepitus), any pain and replication with noise, and any locking
Palpation for pain	Masticatory muscles Temporomandibular joints
Additional provocation tests as indicated	Static pain test (no mandibular movement to pressure) Dynamic pain test (active mandibular movement against resistance) Pain in the joints or muscles with tooth clenching or unilateral biting Reproduction of symptoms with chewing (wax, sugarless gum)
Other systems	Cervical ROM Palpation for pain of neck muscles and accessory muscles of mastication Neurologic screening, sensory testing
Intraoral examination	Signs of parafunction: cheek or lip biting, accentuated linea alba, occlusal wear Dental pathology: tooth mobility, percussion, thermal testing, fractures of enamel and restorations General soft tissue: scalloped tongue borders, parotid gland patency

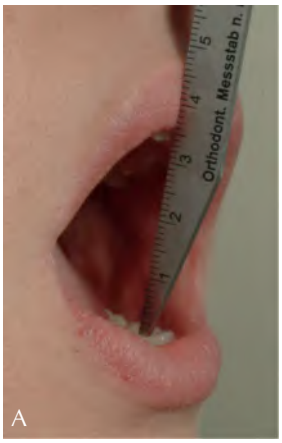
unilateral contractures, and guarding behavior. Components of the physical examination that are discussed in this section are summarized in Table 10-8.

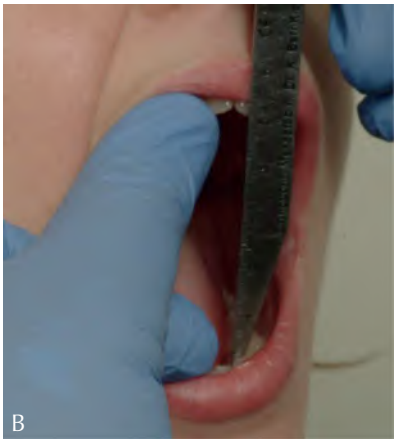
Mandibular Range of Motion

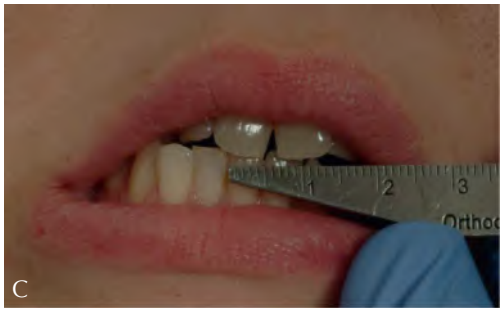
Mandibular range of motion (ROM) comprises three procedures in the vertical plane and three procedures in the horizontal plane. Measurements of vertical ROM are generally far more useful clinically, compared to those of the horizontal ROM. The three vertical ROM procedures include: maximal opening without pain, as wide as possible with pain, and after opening with clinician assistance; each of these is operationalized accordingly. These measures are termed in the DC/TMD pain-free opening, maximal unassisted opening, and maximal assisted opening, respectively. Vertical measurements are made with a ruler between opposing maxillary and mandibular incisal edges; the measurement can be corrected by the extent of vertical overlap of the teeth, if a measure of full mobility is desired. Mouth opening with assistance is accomplished by applying mild to moderate pressure against the upper and lower incisors with the thumb and index finger. All three of these measures exhibit excellent reliability (ICC > 0.90) among trained examiners, and therefore are excellent measures for monitoring status of the disorder over time.

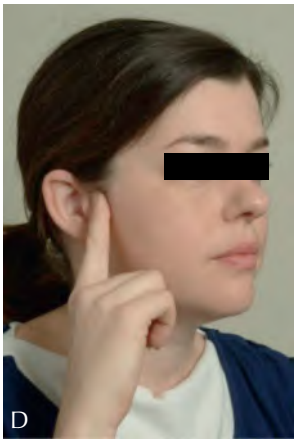
The three horizontal ROM procedures include: right and left lateral, and protrusive movements of the mandible, and all are executed "as far as possible, even if painful" while the teeth are slightly separated. Lateral movement measurements

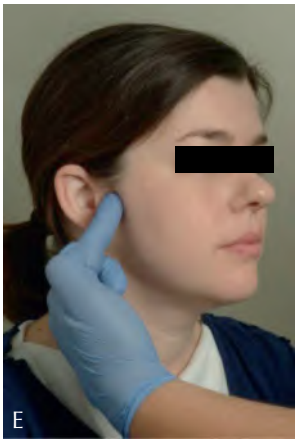
Figure 10-10 The core components of the clinical examination. (a) Measuring pain-free opening and maximal unassisted (active) opening. (b) Measuring maximal assisted (passive) opening. (c) Measuring right lateral movement of the mandible; this is repeated for movement of the mandible to the left, and then in protrusive. (d) Patient points to location of pain, which is asked after each of maximal unassisted and maximal assisted opening, right and left lateral movement, and protrusive. (e) Examiner confirms structure that the patient had pointed to as painful from the range of motion procedure. (f) Position of hands for palpation of single TMJ during range of motion. (g) Position of hands for simultaneous bilateral palpation of the TMJ during range of motion. (h) Location of palpation sites for palpation for pain of the temporalis and masseter muscles. (i) Visualization of lateral pole for palpation for pain of the lateral pole; finger is placed directly on the pole. (j) Visualization of starting finger position (green dot) for circumpolar palpation for pain of the TMJ; the finger rotates around the condyle, as shown by the black arrow. *Source:* Illustrations and photos are adapted from Ohrbach et al., *Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) Clinical Examination Protocol.*[204] See *Protocol* for full set of illustrations and instructions for the clinical examination.

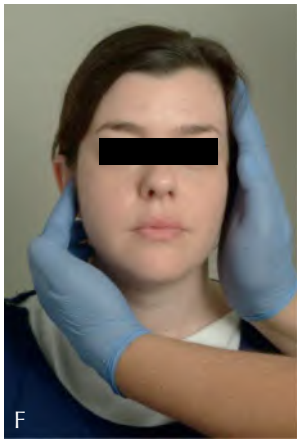


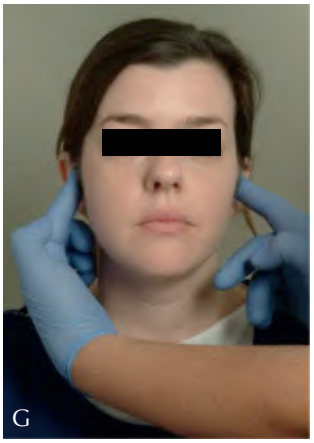


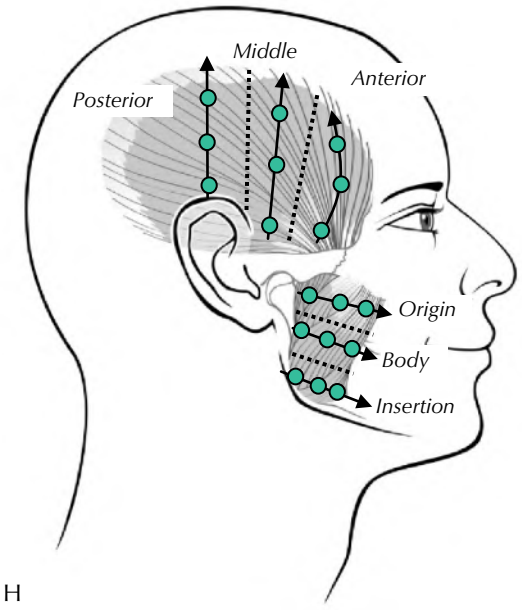


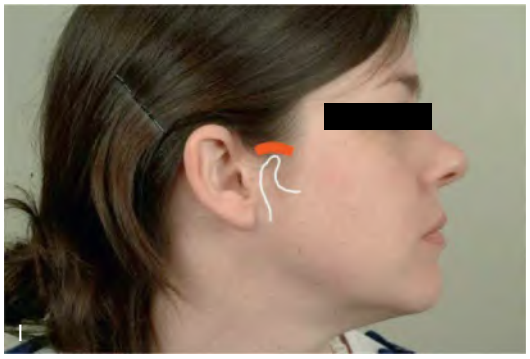


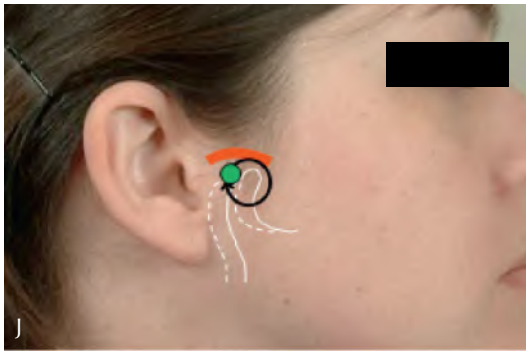












are made with the ruler measuring the displacement of the lower midline from the maxillary midline and adding or subtracting the lower-midline discrepancy. Protrusive movement measurement is made by adding the distance the lower incisors travel beyond the upper incisors to the horizontal distance between the upper and lower central incisors during full closure. All three of these measures exhibit acceptable reliability (ICC > 0.80) among trained examiners; these measures are less useful clinically.

Normal maximum mouth opening is ≥ 40 mm. In a study of 1160 adults, the mean maximum mouth opening was 52.8 mm (with a range of 38.7 to 67.2 mm) for men and 48.3 mm (with a range of 36.7 to 60.4 mm) for women.[225] Normal lateral and protrusive movements are ≥ 7 mm.[226–228] Measures of the mandibular range of movement are similarly performed in children. The mean maximum mouth opening recorded in 75 boys and 75 girls aged 6 years was 44.8 mm.[229] Similar values (a mean maximum opening of 43.9 mm, with a range of 32 to 64 mm) were observed in 189 individuals with a mean age of 10 years.[230] The means of left, right, and protrusive maximal movements were each approximately 8 mm.

ROM assessments have two types of diagnostic significance. The first is that following each of the tests (with the exclusion of pain-free opening), the patient is asked if the movement caused pain, and if so, to point to the area of pain and to indicate whether that pain replicated pain of complaint (see section Palpation for pain for further explanation regarding pain replication). The second is by using maximal assisted opening for distinguishing within the disorder of disc displacement without reduction the subtypes of with vs. without limitation. More generally, observed findings from the three vertical measures, and sometimes the three horizontal measures, are evaluated in relation to the history and other clinical findings: are the ROM measures expected or unexpected?

There are several non criterion-based uses of the ROM measures, particularly when comparing findings across all three procedures. Passive stretching (mouth opening with assistance) is a technique that may assist in differentiating limitation due to a muscle or joint problem, but clinical judgment is needed to interpret. In performing maximal assisted opening, the examiner can evaluate the quality of resistance at the end of the movement. Muscle restrictions are associated with a soft end-feel and should result in an increase > 5 mm beyond the maximal unassisted opening. Joint disorders such as acute nonreducing disc displacements are described as having a hard end-feel and characteristically limit assisted opening to < 5 mm. However, limited movement in response to attempted assisted opening can be due to two other causes: muscle contracture and guarding behavior by the patient. The latter can be especially meaningful when considering other biobehavioral factors, such as fear avoidance or kinesophobia,[231,232] for the direction of treatment. It is difficult to operationalize guarding behavior for reliable assessment.

Noises

Palpation of the TMJs is first performed to detect irregularities during condylar movement, described as clicking or crepitus. The lateral pole of the condyle is most accessible for palpation during mandibular movements. In addition to joint noise, there may be palpable differences in the form of the condyle comparing right with left. A condyle that does not translate may not be palpable during mouth opening and closing. This may be a finding associated with an ADD without reduction. A click that occurs on opening and closing and is eliminated by bringing the mandible into a protrusive position before opening is most often associated with ADD with reduction, but this maneuver for eliminating reciprocal clicks does not assure a diagnosis of ADD with reduction.[205]

Palpation for Pain

The most widely used clinical test for the assessment of a TMD is applying pressure to muscles and joints in order to determine if pain is elicited by the stimulus, known as palpation pain. While this procedure is deemed fully valid and appropriate for the extraoral muscles, intraoral palpation of the lateral pterygoid muscle has been challenged because of its location and inaccessibility (Figure 10-10).[233] In addition to poor reliability associated with its examination, the examination procedure is likely to cause discomfort in individuals without a TMD, diminishing the value of lateral pterygoid palpation as a diagnostic test.[234] The fibers of the deep masseter muscle are intimately related to the lateral wall of the joint capsule, which may explain the frequent localization by patients of the pain complaint to the preauricular area broadly. This anatomic characteristic makes differentiating muscle and joint pain in this area difficult.[235,236]

While pain is reported in response to ROM procedures among individuals with a TMD, pain is elicited much more frequently from palpation of the masticatory muscles and TMJs. Because palpation is a discrete stimulus, the response can be separated into reported pain local to the area of stimulation, pain spreading beyond the area of stimulation, and pain perceived in a different area (i.e., referred pain to another structure). These categories of pain response are particularly relevant for muscle tissue, but spreading and referral also occur, albeit less frequently, in response to palpation of the TMJs. A critical aspect of the DC/TMD examination is to inquire if provoked pain (whether from ROM or palpation procedures) is "familiar" to the person's usual pain (i.e., the examination procedure has provoked replication of the pain of complaint); this specific finding is part

of the criteria for the pain-related diagnoses. Another level of pain replication from palpation (but not ROM) is whether spreading or referral response is also familiar. While familiar spreading or referral are not, at this time, part of the criterion for the respective subtypes of myalgia, inquiring of the patient, with respect to whether any elicited referral patterns typically occur, during the palpation examination, is recommended. Differential diagnosis (e.g., TMD vs. odontogenic pain) sometimes depends critically on elicitation of referral response, its replication of the pain of the complaint, and the specificity in identifying the target tissue of the referral.

Many methods for palpation are advocated, and parameters that affect palpation, as a procedure, include amount of loading to the tissue, surface area of the loading, duration of loading, and where the loading is applied. The DC/TMD guidelines recommend 1.0 kg of loading for the muscles and 0.5 kg for lateral pole loading and 1.0 kg circumpolar loading of each TMJ, as based on population and clinical samples,[184,205] and an extensive range of research has generally supported these parameters. In recognition that fingertips used for palpation vary considerably in surface area, the indicated loadings will ultimately vary in terms of pressure to the peripheral receptors in the patient's tissue, and thereby introduce error in the palpation procedures. Hence, the DC/TMD specified that loading should be "at least" to the stated criterion. The alternative, for better standardization, is to use a simple algometer that will provide consistent pressure (loading/square area); one example is the Palpeter which is easy to use and has excellent reliability.[237] There appears to be sufficient empirical support for the stated magnitudes of palpation in terms of maximizing true positives and negatives, and minimizing false positives and negatives. During loading, the muscles should be in a noncontracted state. As further explained below, muscles may be placed on a stretch prior to palpation.

As an alternative to standardized loading, some clinicians have recommended that palpation loading be normalized to the individual's pain threshold: establish a baseline (to serve as a general guide or reference) by squeezing a muscle between the index finger and thumb or by loading the center of the forehead or thumbnail to gauge the minimum extent that becomes painful. While perhaps intuitively sensible, this approach has two problems: circularity, through the assumption that the individually tailored threshold for painful loading is "normal" for that person (and thereby sidestepping the considerable problem of widespread body tenderness as either a comorbid condition or simply as a reflection of central sensitization);[238] and likely poor reliability in applying the individually-tailored loading (which will vary from patient to patient) during the examination.

In contrast to palpation loading, duration of palpation is more nebulous in terms of empirical support. Patients report that fast palpation (e.g., loading of the tissue for less than 1 second) is too quick to feel confident about the response (e.g., painful yes or no?), whereas a stimulus that is at least 2 seconds in duration (including ramp up and down) appears to be sufficient to respond to. Referred pain phenomena, in contrast, seldom occur in relation to a stimulus as short as 2 seconds; the minimum duration to elicit referral is unknown, and a stimulus at least 10 seconds in duration has been recommended.[239] The DC/TMD attempts to provide a starting point for further research by requiring the stimulus to be at least 5 seconds in duration if referral is of interest; this stimulus duration is sufficient for at least a reliable diagnosis of referred pain. Clinically, if referral phenomena are suspected and are important for, say, differential diagnosis, then extending the palpation duration to 10 (or more) seconds would be justified, as based on reported observations; in addition, as Travell and Simons indicate, placing the muscle on a stretch prior to the palpation can reportedly facilitate elicitation of referral.[239] Whether increasing the magnitude of the loading is as important as the duration of the loading (in order to trigger temporal summation) is unknown, but anecdotal evidence points to increasing the duration of the loading for elicitation of referred pain. The necessary stimulus duration for elicitation of spreading phenomena is unknown, but because the mechanism is likely similar to that underlying referral, the same 5 seconds duration is recommended at this time.

The location of palpation is another parameter with much clinical lore. For simple myalgia, it seems that a sampling approach (e.g., divide the temporalis and masseter muscles into three zones each, and distribute three palpation sites across each zone) to the underlying tissue is sufficient. Critically, this method is reliable.[240] For eliciting referral phenomena, in contrast, the finding of "bands" and "trigger point nodules" is advocated, yet this method is only marginally reliable and then only with extensive training.[241] One problem affecting reliability in the examination of trigger points is that their location is not stable across relatively short periods of time.[242] Abnormalities such as trigger points and taut bands in muscle have not been sufficiently characterized in the masticatory muscles to enable the clinician to reliably distinguish these sites anatomically from normal muscle. If there is a particular clinical question (e.g., differential diagnosis) that needs to be answered with regard to presence of referred pain, then the most reliable method of detection is probably to sample the muscle in a systematic manner: divide the muscle into enough zones and each zone into enough palpation sites, such that the areas of stimulation via the fingertip are sufficiently small. If subtyping myalgia into local myalgia, spreading, or referral is important

primarily for adequate capture of the stated symptom descriptions, then the standard sampling method of the DC/TMD will likely be sufficient: palpate temporalis and masseter muscles at 1 kg loading, for 5 seconds at each of 9 palpation sites within each muscle.

Related to where to palpate each muscle is which muscle to palpate. The muscles of mastication include not only the temporalis and masseter, as the muscles most commonly associated with location of pain complaints, but also additional muscles of the lateral and medial pterygoids, the hyoids, and digastrics on each side. Yet, in terms of incremental validity, little is often gained by palpating these additional muscles versus the information gained from initially examining the temporalis and masseter muscles. The lateral pterygoid is in a position that does not allow access for adequate palpation examination, even though there are examination protocols and descriptions for palpating this muscle.[243] Hence, the DC/TMD requires palpation of temporalis and masseter, and palpation of the other muscles is optional and should be determined by the nature of the chief complaint.

The location in which to palpate the TMJ for pain, and its interpretation, has a range of perspectives. Traditionally, palpating the lateral pole and through the ear canal was believed to be sufficient to provoke pain associated with the capsular ligament. However, the Validation Project determined that lateral pole palpation alone was insufficient, and that the false negative rate of arthralgia diagnosis was too high. Consequently, a circumpolar dynamic palpation, with loading at a minimum of 1.0 kg, was recommended; the full circle around the lateral pole should take approximately 5 secs. The clinical literature states that pain elicited in one part of the joint is indicative of a posterior capsulitis, while pain from another part of the joint is indicative of a synovitis, etc.; while such differentiations may be possible in principle, the available empirical data only identify arthralgia as a reliable diagnosis.

The severity of the pain provoked from palpation can be assessed (e.g., using a 4-point verbal scale of none, mild, moderate, or severe; or by using a 0–10 numeric rating scale) but this type of discriminatory response has not, in the research literature, been shown to be more useful than the simple binary report of pain yes versus no with respect to disorder classification or overall severity of the condition. For monitoring pain sensitivity of a single muscle, the severity ratings could help. The report of pain is followed by the question of whether the provoked pain is familiar—whether it replicates the pain of complaint. Because pain sensitivity varies across individuals, some patients even after treatment may well report that palpation still induces pain, but if the patient no longer has pain, then the pain replication question will be negative, which would be essential for assessing treatment progress.

Provocation Tests

Provocation tests are designed to elicit the pain complaint. Assessing jaw ROM and palpation for pain are types of provocation tests. Since pain is often aggravated by jaw use according to the patient's history, an appropriate clinical test would assess function; a positive response adds support for a TMD diagnosis even though functional tests such as clenching the teeth (i.e., involving sustained muscle contraction) did not provide additional information that improved sensitivity and specificity for a TMD compared to a nonpain control.[205] In contrast, functional tests improved diagnostic validity of a painful TMD versus a comparison pain condition of odontogenic pain.[244] Consequently, including functional testing when the history or findings from the standardized clinical examination yield an ambiguous diagnostic outcome is very sensible and represents good practice. Four types of functional tests have been recommended and continue to be sensible at least in terms of face validity. These tests include static muscle contraction test, and dynamic muscle contraction test, bilateral loading via clench, and unilateral loading via clench.

The static pain test involves having the mandible slightly open and remaining in one position while the patient resists the slowly increasing manual force applied by the examiner in each of right lateral, left lateral, upward, and downward directions. If the mandible remains in a static position during the test, the muscles will be subjected to activation, and any pain should be specific to muscle. In the dynamic test, the mandible slowly moves against resistance, in each of the same directions as for the static test; any provoked pain should be specific to the joint. As for the static test, however, the specificity of response in muscle versus joint does not seem to accord with the putative principle. Nevertheless, dynamic and static tests exhibited excellent specificity: 84% of dental pain cases were negative for these tests.[244] Neither of the static or dynamic tests added incremental validity to the provocation tests of ROM and palpation procedures for a myalgia diagnosis.[205]

Clenching the teeth, biting on a unilateral separator between the teeth, or chewing wax or gum is expected to load the joints and muscles. According to one study, approximately 50% of TMD patients who chewed half of a leaf of 28-gauge casting wax for 3 minutes reported increased pain, but 30% reported decreased pain and 20% reported no change.[245] This is not surprising, given the report by many patients who participate in examiner reliability studies that despite the considerable provocation of painful muscles by palpation across four examiners, the repeated maximal opening and other jaw movements become therapeutic for some of the subjects. In the clinic, some patients will clearly report that chewing gum improves their pain (and they are seeking consultation primarily to rule out a more complex

disorder, and if so, with the plan to use gum more frequently). Biting on unilateral cotton roll or tongue blade has been recommended for many years as an important diagnostic test; however, the ability of this test to discriminate between muscle and joint pain is poor.[246] In summary, many adjunctive tests are available, but in the end their diagnostic utility must be rigorously assessed in order to determine if the test is useful, and in what circumstance.

Assessment of Consequences or Correlates of Parafunctional Behaviors

Each of tooth wear, soft tissue changes (evidence of lip or cheek chewing, an accentuated occlusal line, and scalloped tongue borders), and hypertrophic jaw-closing muscles has been suggested as an objective means of assessing for parafunctional behaviors (or muscle hyperactivity). The face validity, with regard to pathophysiology or cause-effect with parafunction, varies across these different types of findings, with tooth wear and muscle hypertrophy seemingly high and scalloped tongue borders seemingly lower. However, the interexaminer reliability of assessing tooth wear is fair at best,[247] and the other assessments also exhibit poor reliability, thereby decreasing the clinical utility of these procedures.

Cervical Region: ROM and Palpation of Muscles

Patients with TMDs often have musculoskeletal problems in other regions, particularly the neck.[248,249] The upper cervical somatosensory nerves send branches that synapse in the spinal trigeminal nucleus, which is one proposed mechanism to explain referral of pain from the neck to the orofacial region. The sternocleidomastoid and trapezius muscles are often part of cervical muscle disorders and may refer pain to the face and head. The cervical area and the masticatory area, therefore, share several linkages: mechanical, motor control, and afferent input.

Consequently, the cervical region warrants at least a screening examination. Mobility is assessed during flexion, extension, rotation, and side-bend of the neck. Using an observational method, the head should, in general, flex to the extent that the chin can touch the sternum, extend until the face is parallel to the ceiling, rotate 90° to either direction, and side-bend 45° to either direction. Methods, including ruler or goniometry, can be used for quantitative assessment, but utility of higher precision should be considered if the goal is screening. For palpation, the trapezius, levator scapula, and suboccipital muscle groups seem adequate for screening; other cervical muscle groups of SCM, splenius capitus, and semispinalis capitus can be included. The inclusion of examination and treatment of the cervical area, in relation to a TMD, is strongly advocated in the clinical literature, but there is little data at this time to draw on for evidence-based guidance. One substantially limiting factor is that research has been largely nonreplicable due to no universally held evaluation and diagnostic standard for the common forms of cervical pain (e.g., a hypothetical RDC/Cervical). A potential standard appears to be emerging for basic cervical diagnostic classification from the perspective of chronic pain.[250] One cervical parameter that seems to have sufficient agreement regarding assessment method is forward head posture; there is, however, no reliable relationship between static head posture and TMD.[251] Some type of RDC for cervical musculoskeletal pain problems is urgently needed in order to gain a better basic classification, from which science can move forward and clinical evaluation and treatment can have a better basis.

Diagnostic Imaging

The TMJs can be imaged using primarily noninvasive modalities; however, relatively invasive modalities are also used.[252] Noninvasive imaging includes conventional radiography (e.g., panoramic radiographs and transcranial radiographs), tomography (TMJ open and close), ultrasonography, computed tomography (CT), cone beam CT (CBCT), and magnetic resonance imaging (MRI). Relatively invasive imaging methods include arthrography, bone scintigraphy, and radioisotope scanning.

Imaging should be part of the assessment whenever any of the following characteristics are present: history or clinical findings suggesting a progressive pathologic condition of the TMJs; recent injury with progressive or worsening symptoms; sensory or motor abnormality; severe restriction in mandibular motion; nonresponse to usual treatment for a joint condition; differential diagnosis dictating change in treatment direction; or acute alterations of the occlusion. The most frequent abnormalities that are imaged in TMD patients are disc displacements and degenerative changes of the articular bones, both of which require imaging for a confirmed diagnosis.[3]

For the majority of TMDs, however, the information from diagnostic imaging has not proven to be important for directing treatment, predicting treatment outcome, and determining long-term prognosis. For example, a study was carried out comparing CBCT findings of bony changes in TMJ for symptomatic and asymptomatic patients with TMD. Bony changes were notably similar in both symptomatic (90%) and asymptomatic (86.7%) patients.[253] Consequently, imaging should be ordered only when a clinical hypothesis can be answered by incorporating such information. For example, imaging for confirming a diagnosis of disc displacement should be requested only if diagnostic confirmation will affect treatment direction or outcome.

Conventional and tomography plain film radiographs are largely used to evaluate normal anatomy (Figure 10-11A) and osseous changes in condyles (Figure 10-12), including advanced degenerative changes and asymmetry. A large variation exists in closed mandible condylar position as observed in plain-film radiographic and tomographic studies, making the closed condyle–fossa relationship of little value in the diagnosis or treatment of TMD.[254] No differences were found in joint-space narrowing in the centric occlusion position in symptomatic and asymptomatic patients by transcranial plain-film radiography and tomography.[255,256] Consequently, using plain films (such as transcranial radiography) to determine condylar position or using the condylar position on these films to infer disc position is not recommended.[256,257] Panoramic radiographs have limitations due to the presence of skull base and zygomatic arch superimpositions on captured images.

More emphasis is being placed on the use of three-dimensional and high-resolution imaging in the diagnosis of

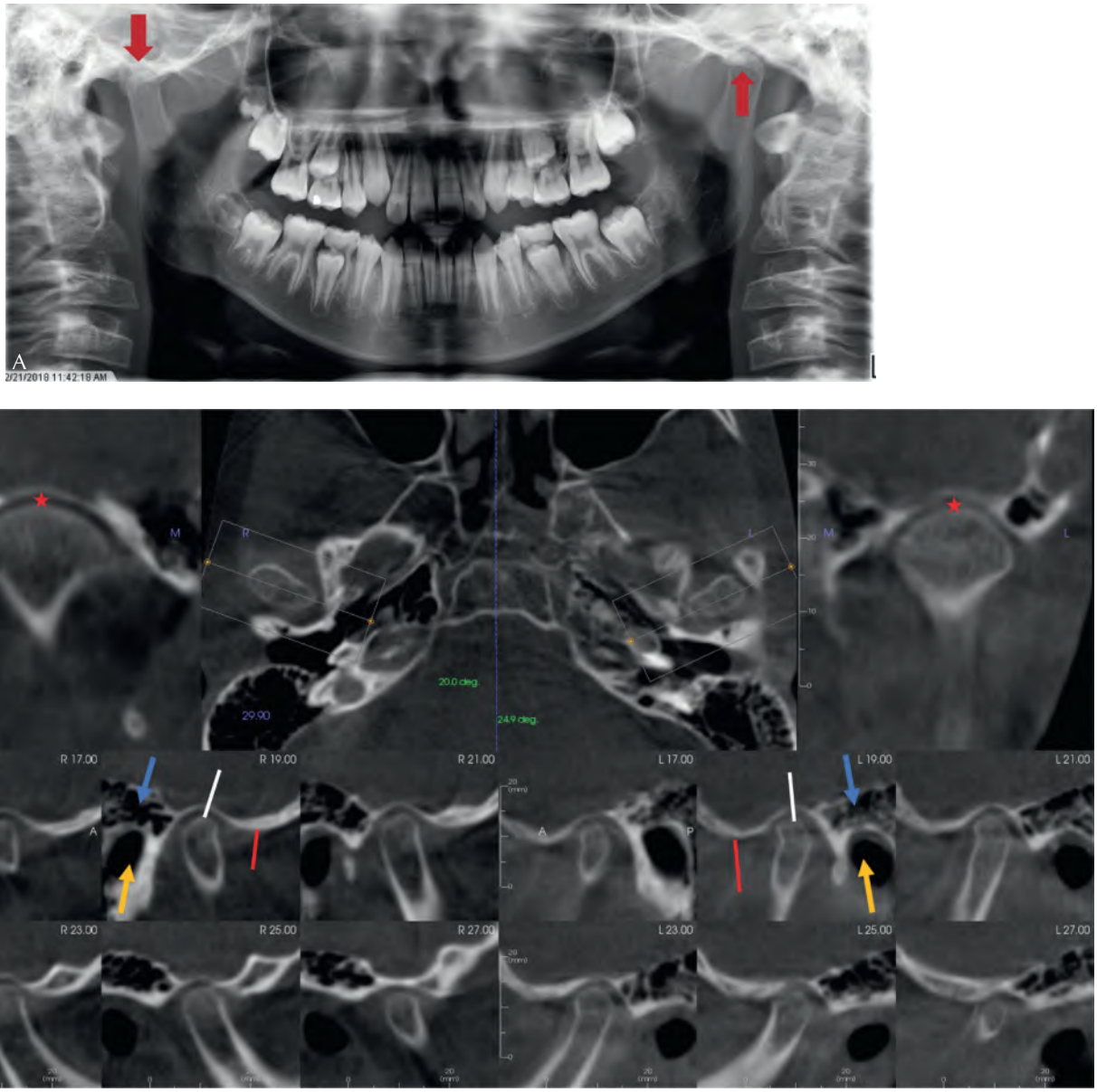


Figure 10-11 (A) Panoramic radiograph of a 12-year-old male patient showing the smoothly contoured normal anatomy of the right and left condyles. Note the superimposition of the zygomatic process on the articular eminence bilaterally (red arrows). (B) CBCT multiplanar representation of the temporomandibular joint of the same patient in Figure 10-11A showing the thin cortical outline of the condyles (white line) and articular eminences (red line). Note the mastoid air cells (blue arrow) and external auditory meatus (yellow arrow). The right and left articular spaces (red star) are within the limits of normal. *Source:* Courtesy Dr. Adeyinka Dayo. Oral radiology Penn Dental Medicine.

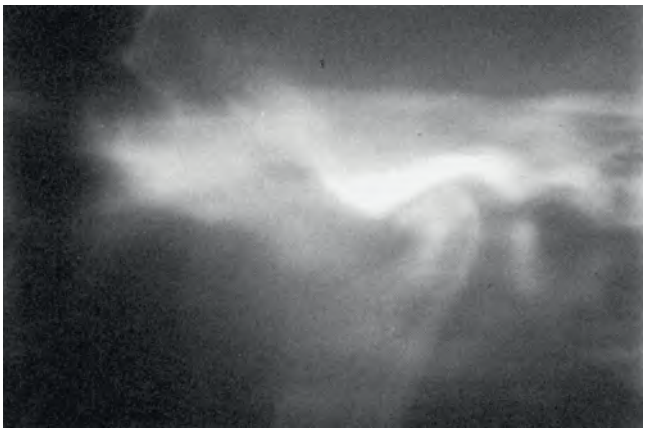


Figure 10-12 Temporomandibular joint tomogram displaying flattening of the condylar head in degenerative joint disease.

temporomandibular disorders, as there is better visualization of anatomic landmarks and no superimposition. Computed tomography—both multidetector computed tomography (MDCT) and cone-beam computed tomography (CBCT)—is the imaging method of choice (Figures 10-11B, 10-13A and 10-13B). CT provides detail for bony abnormalities and is an appropriate study when considering ankylosis, fractures, tumors of bone, and DJD (Figure 10-14). CBCT has an advantage of comparable low cost and low dose of radiation exposure.[258,259]

MRI remains the reference standard for TMJ soft tissue imaging, including articular disc and TMJ ligaments, and for muscles of mastication.[260] MRI effectively documents alterations in articular disc form and position in closed and open mouth positions. The value of MRI for TMJ soft tissue requires careful interpretation. MRI studies in asymptomatic volunteers have shown disc position abnormalities in approximately one-third of subjects,[261] and consequently abnormal disc position alone should not be considered a disorder. With the use of T2-weighted MR, a correlation between joint pain and joint effusion has been suggested, but the results are conflicting.[262–264] TMJ effusion is associated with an elevated concentration of synovial fluid proteins, including proinflammatory cytokines, but the ability to confirm the presence or absence of synovitis in the joint has not been established.[265] It is still not possible to predict the presence of pain based on MRI findings. Individual features on MRI of internal derangement, osteoarthrosis, effusion, and bone marrow edema are not predictive of TMJ pain, but when these features occur together, an increased risk of TMJ pain has been observed.[266]

Arthrography involves the fluoroscopic guided injection of contrast dye into the TMJ, followed by CT imaging. While this imaging modality provides perhaps the most dynamic depiction of joint and disc mechanics, the modality is not popular due to its invasive nature and risk of allergic reaction to contrast dye.

Radioisotope scanning for detecting increase in metabolic activity has been used to detect condylar hyperplasia. Bone scanning is a sensitive indicator of metabolic bone activity and will show similar activity in a joint that is undergoing physiologic remodeling as well. Scintigraphy is a sensitive test but is not specific for TMJ disease. Bone scintigraphy in combination with other imaging and clinical findings (including findings on periodic examinations) is usually effective in diagnosing continued condylar change due to hyperplasia.

Diagnostic Local Anesthetic Nerve Blocks

Injections of anesthetics into the TMJ or selected masticatory muscles may help confirm a differential diagnosis. Immediate elimination of or a significant decrease in pain and improved jaw motion should be considered a positive test result. In situations in which a joint procedure (such as surgical intervention) is being considered, local anesthetic injection of the joint may confirm the joint as the source of nociception. Injecting trigger points or tender areas of muscle should eliminate pain localized to that site and should also eliminate referred pain associated with the injected trigger point.[239] These tests, like all others, require interpretation in the context of all the diagnostic information since a positive result does not ensure a specific diagnosis. Injecting medication such as corticosteroids may be part of therapy.

Injection Sites

Kopp has described a technique for TMJ injection.[267] The site of injection should be anterior to the tragus to minimize the risk of intravascular injection of the external carotid artery or the accompanying vein. Because the auriculotemporal nerve enters the capsule from the medial aspect, injections (normally given from the lateral aspect) may not completely anesthetize the joint.[268] Fernandes and colleagues found the auriculotemporal nerve to be 10 to 13 mm inferior to the superior surface of the condyle and 1 to 2 mm posterior to the neck of the condyle.[269]

Occlusion

The purpose of evaluating the occlusion is to identify clear loss of normal stability as a result of acute occlusal change, which occurs as a consequence of a TMD. Occlusal changes of interest include the sudden onset, typically unilateral, of posterior open bite (associated with atypical disc displacement or synovial chondromatosis) or the gradual onset of bilateral anterior open bite (associated with progressive condylar erosion occurring, for example, in aggressive

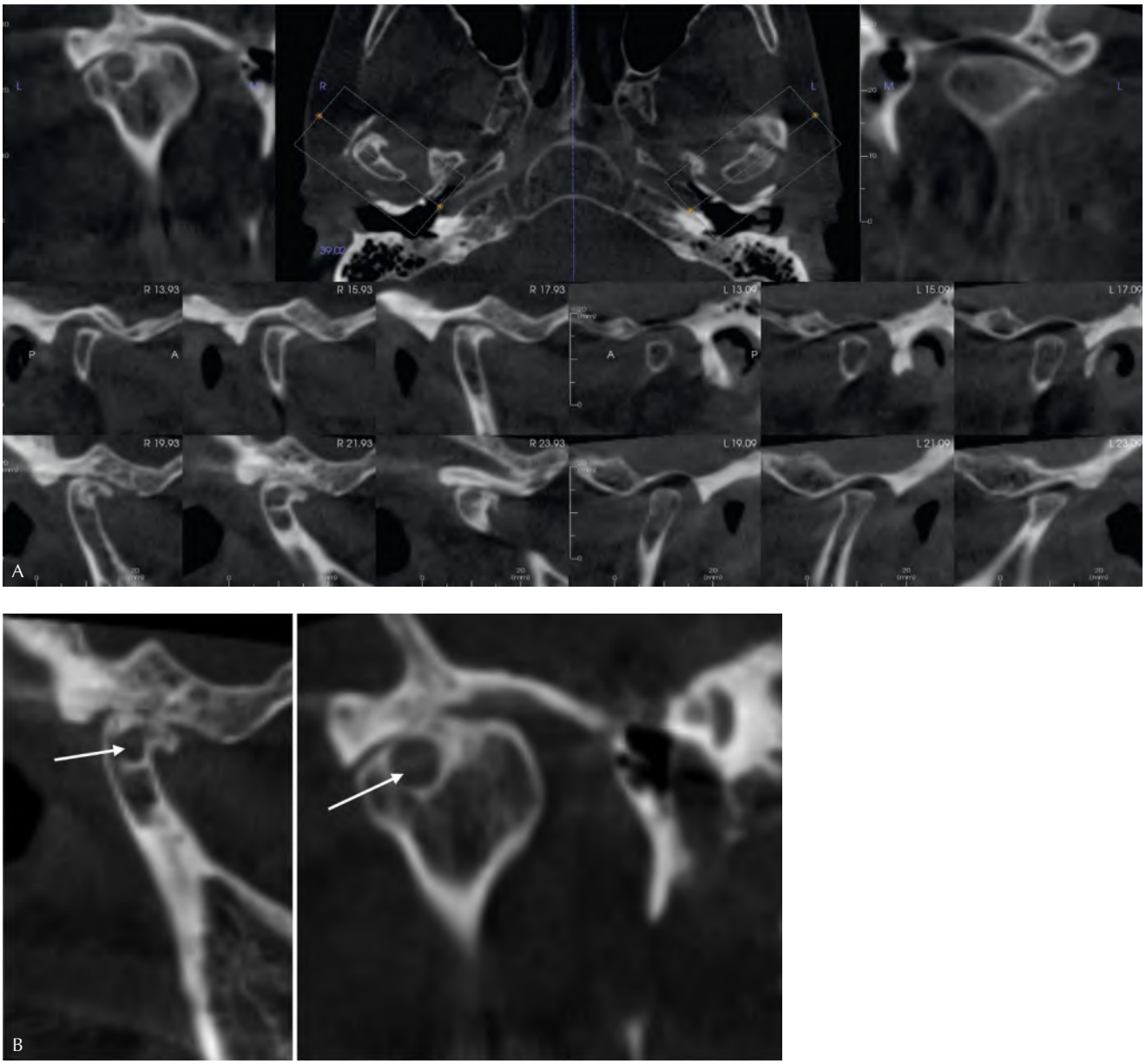


Figure 10-13 (A) CBCT multiplanar representation of the temporomandibular joint of a 68-year-old female with 2 mm slice interval of the sagittal view. There is subchondral sclerosis and flattening of the right condyle with osteophyte formation on the anterior pole of the right condylar head. Note the large subchondral cyst within the right condyle. The right articular eminence and glenoid fossa exhibit subchondral sclerosis and flattening with thinning of the right articular space. The radiographic features are consistent with moderate degenerative joint disease of the right temporomandibular joint. *Source:* Courtesy Dr. Adeyinka Dayo. Oral radiology Penn Dental Medicine. (B) Cone beam CT. (Left) parasagittal view of the right TMJ and (Right) coronal view in the same patient.

degenerative joint disease of the TMJs). The loss of normal stability is first suspected during the patient history, in which the patient will describe a sudden inability to firmly place the posterior teeth together in the usual way, or a gradual loss of ability to incise food. The patient description is the primary determinant for evaluating the occlusion for loss of stability with respect to what is normal for that individual. The intercuspal position is achieved when maximum intercuspation of opposing teeth occurs.[270] From this position, the occlusion is evaluated grossly for acute change versus being a functional occlusion. A functional occlusion does not have to be ideal; rather, a functional occlusion exhibits stability. The patient's perception of a minor change in maximal occlusal contract, such as often occurs in response to a masticatory muscle disorder, must be distinguished from the patient report of (typically intermittent) inability to fully

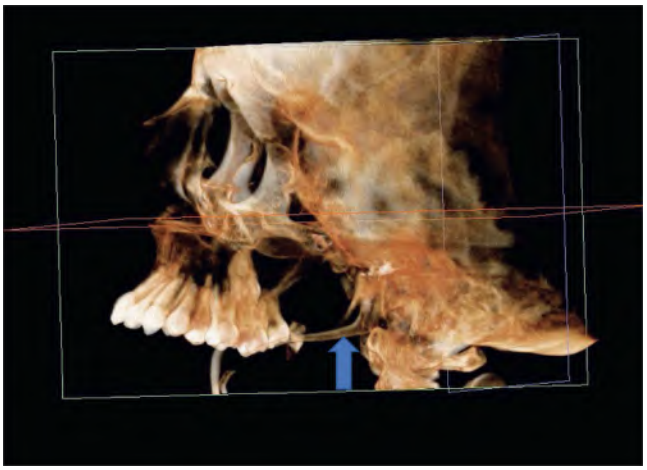


Figure 10-14 Sagittal view (CBCT) of a patient with First arch syndrome (Treacher Collins and Pierre Robin syndrome) and aplasia of the mandible. Arrow points to attempted fibular graft to replace the missing mandible.

close the posterior teeth or the gradually increasing space between anterior teeth and loss of incision. Detailed analysis of the patterns of occlusal contact during full closure, excursive movements, or with the mandible in some manipulated so-called reference position has neither etiologic nor diagnostic value. Recall that a very large volume of research has as yet failed to find associations between those occlusal attributes and a TMD. For example, a reduced number of contacting teeth in the intercuspal position and loss of posterior teeth have been hypothesized to be risk factors for the subsequent development of a TMD,[271] but at present no longitudinal evidence exists for this hypothesized relationship. The clinician must think dynamically about time and longitudinal change when considering the impact of a TMD on the occlusion.

MANAGEMENT: GENERAL GUIDELINES

Prediction of Chronicity

Whereas a majority of individuals with a TMD respond, at least in part, to nonsurgical management that can be provided or coordinated by a dentist, a substantial number of individuals with TMD evolve into a chronic musculoskeletal pain disorder that results in significant disability. Patient histories suggest that most individuals with acute TMD do not immediately seek care; instead, they wait for weeks or perhaps months in order for it to resolve on its own, much as one might with a flu, the common cold, or a joint sprain. Consequently, in clinical settings, most patients with a TMD have most likely already either begun the transition to having chronic pain, or already have chronic pain, increasing the importance of utilizing comprehensive assessment and treatment models routinely for all patients with a presumed TMD.

Chronic pain has been traditionally defined in three different ways: pain that persists beyond the time of usual healing; pain that does not respond to usual treatment; or pain that extends beyond a certain period. The first two definitions of chronic pain are very sensible and useful for patient discussions regarding treatment recommendations. However, both of those definitions include ambiguous reference points: what is the usual period for healing of this problem in this person, and how can the adequacy of treatment provided to date be judged for sufficiency? Consequently, the dominant definition for chronic pain revolves around time since onset and for many decades, a period of 6 months was selected,[272] but more recently the definition has been refined to "pain that occurs on at least half of the days for 6 months or more."[273] The rationales for using time include the commonly recognized behavioral or social changes that accompany persisting pain and which have their own latency period; and time is easy to measure.

Perhaps more important than chronicity is the impact of the pain. Some changes, such as worry, appear early, while financial and work-related problems tend to occur later. Whether depression is a cause of chronic pain or a consequence has been rigorously debated for many years; current evidence from the OPPERA project indicate that it is probably both: depression appears to be a significant risk factor for developing chronicity, and once pain becomes chronic, the CNS burden of ongoing pain leads to alterations at multiple levels in the CNS, and the state of depression is one manifestation, in terms of behavior and mood, of the CNS changes. Plus persisting depression only further exacerbates persistent pain; two obvious direct mechanisms for how depression worsens pain include dampening of descending modulatory systems and the impact on motivation and intentional behavior necessary for adherence to any treatment that involves the development and use of self-regulatory skills. This type of recursive involvement of a factor, such as depression, readily illustrates the complex disease character of TMD. Individuals vary, of course, in the degree of impact by which chronic pain affects their functioning, and it is very useful to distinguish those who have less severe chronic pain from those who experience substantial disruption.[274] High-impact chronic pain is persistent pain with "substantial restriction of participation in work, social, and self-care activities for 6 months or more."[275] Among those with chronic painful TMD, 33% have high-impact pain, which is comparable to 35% among those with headache.[136] Similar to other chronic pain disorders, with high-impact chronic painful TMD comes substantial psychological distress, disruption of normal daily activities, and ongoing pursuit of health care resources.

Predicting which individual is likely to become chronic is important in order to provide alternative or additional interventions earlier in the scope of treatment. Early treatment that addresses biobehavioral factors appears to decrease the likelihood of acute pain becoming chronic.[276] Among the potential risk factors for the transition from acute to chronic which may be assessed, as based on the DC/TMD framework, the primary predictor of the transition from acute pain to chronic pain is pain: reported pain intensity (as measured by the Graded Chronic Pain Scale) and pain-free opening of the jaw, pain with movement of the jaw, and pain from palpation of the muscles and TMJ, as assessed by the clinical examination.[46] Similarly, a combination of high pain intensity (as measured by the Graded Chronic Pain Scale) and a myofascial pain diagnosis was predictive of persisting TMD symptoms.[276] From a clinical perspective, any patient who comes for a consultation should be considered for chronicity. Overall, chronicity is a function of multiple factors, and focusing primarily on seemingly obvious ones, such as trauma (with a presumed biological impact), to the exclusion of other, more abstract ones, such as depression, anxiety, or pain-related disability, is to contribute to the patient's pain chronicity.

Principles of Treatment

The most important feature of TMD is, in general, pain; and consequently pain is the most important patient reported outcome (PRO) with regard to whether a treatment was helpful. Other common and important features that can serve as a target for a PRO include inability to eat hard-to-chew foods, restricted range of mandibular movement, and mechanical joint problems that interfere with function. Chronic TMD pain (like all chronic pain) results in psychological, behavioral, and social disturbances, and while these characteristics may be a dominant part of the overall symptom presentation, they seem to be less often regarded as important by the patient with TMD or by the provider. However, patient education into how biobehavioral factors are linked to their pain can make such variables more relevant as indicators for specific treatment types as well as important PRO measures.[277,278]

Treatment goals for TMDs can be divided into two levels, both of which are equally relevant. The first level includes: control pain, improve mandibular motion, and restore function as close to normal as possible. The second level concerns: impact to the person by the pain, methods to restore general functioning, and strategies for relapse prevention. The relative importance and timing of implementing each level is determined by many patient-specific factors as well as available health care expertise. Explanatory models[279] held by each of patient and clinician will affect how treatments oriented to each of the two levels will proceed; when pain is the dominant symptom (as it typically is at the first consultation), addressing the pain directly is generally the first priority, and success in reducing or better controlling the pain helps patients incorporate other treatment recommendations that may exist outside their explanatory model of illness. Unless an obvious and clearly causal source of nociception is identified for the TMD pain which warrants invasive therapy (e.g., chronic pulpitis presenting as myalgia), initial treatment should focus on noninvasive therapies which also have desirable nonspecific effects and which readily permit the integration of therapies across the two levels described here.

Clinical case studies and a variety of randomized controlled trials suggest that the majority of individuals with TMD respond to conservative noninvasive therapy, making the use of invasive procedures unwarranted as initial therapy. No one treatment has emerged as superior, although many of the treatments studied have shown beneficial effect.[280] The symptoms of painful TMDs tend to be intermittent, fluctuate over time, and are often self-limiting.[281–283] A 5-year follow-up indicated that TMD patients could be allocated roughly into thirds: remission, recurring symptoms, or persisting symptoms.[284] The process of deciding whether to treat and how aggressively to treat should take into account the course of symptoms. Patients who are improving at the time of assessment may require a minimum of care and follow-up compared with the individual whose symptoms are becoming progressively more severe and disabling.

The variations in types of treatment recommended by dentists have been explained by the gap between published information in the medical and dental literature and individual dentist's beliefs and attitudes.[285,286] Yet, because the different types of TMD treatment appear to have more or less equivalent efficacy, the treatment effect may be nonspecific and related more to the therapeutic relationship established between therapist and patient than to the specific attributes of the treatment.[287] These factors further support the use noninvasive reversible therapies for managing TMD.

Management, not cure, is the guiding principle for selecting and deciding when, if at all, to escalate treatment of TMD. Widely known and generally accepted clinical observations are highly informative. Patients with irreversible anatomic abnormalities, such as disc disorders, are nevertheless able to regain pain-free jaw function.[288,289] Decreased pain and improved physical findings are not directly related.[216,290] The presence of joint noises and deviations from the ideal in occlusion, in maxillomandibular relationships, and in the morphology of bony structures such as the condyle are relatively common in the general population. Evidence supporting prophylactic treatment of these anatomic abnormalities when no pain, impairment of function, or disability exists is lacking. Rather, treatment should be

based on the severity of pain and disability and should be directed toward those factors that are considered important in initiating, aggravating, or perpetuating the disorder.

Episodes of pain and dysfunction may recur even after successful symptom control. Reinjury or factors that contributed to earlier episodes of symptoms may be responsible. Recurrence should not be considered a treatment failure, and therefore regarded as justification to escalate treatment; rather it is more prudent to first consider the initiation of previous treatment that was successful. Myogenous disorders appear to relapse more often and therefore require retreatment more frequently than do articular disorders.[291]

For the smaller group of patients in whom TMD progresses to a chronic pain disorder, treatment becomes more complex. These patients may still benefit from local therapies; however, it is essential for the provider to more carefully consider the need for more comprehensive management in order to address the emotional and behavioral disabilities that result from chronic pain. Drug therapy of chronic pain is becoming increasingly complex, requiring knowledge and experience that are not common in general dental practice. These patients are often at risk for unnecessary investigations or treatments that may be harmful (such as longer term opiate use) that may further complicate their problems.[292–294] Persistence of pain does not necessarily indicate progressive disease; one task for the clinician is to monitor for possible disease progression (and thereby reassure the patient), while simultaneously holding the reins on a management treatment model that focuses on successful adherence to self-management treatments and improving function.

A National Institutes of Health conference on TMD therapy, while now somewhat dated, produced the following conclusions which remain worth considering: [295]

1) Significant problems exist with present diagnostic classifications because these classifications are based on signs and symptoms rather than etiology.
2) No consensus has been developed regarding which TMD problems should be treated and when and how they should be treated.
3) The preponderance of the data does not support the superiority of any method for initial management, and the superiority of such methods to placebo controls or to no treatment controls remains undetermined.
4) Because most individuals will experience the improvement or relief of symptoms with conservative treatment, the vast majority of TMD patients should be initially managed with noninvasive and reversible therapies.
5) The efficacy of most treatment approaches for TMD is unknown because most have not been adequately evaluated in long-term studies and because virtually none have been studied in randomized controlled group trials.
6) Therapies that permanently alter the patient's occlusion cannot be recommended on the basis of current data.
7) Surgical intervention should be considered for the small percentage of patients with persistent and significant pain and dysfunction who show evidence of pathology or evidence that an internal derangement of the TMJ is the source of their pain and dysfunction and for whom more conservative treatment has failed.
8) Relaxation and cognitive–behavioral therapies (CBTs) are effective approaches to managing chronic pain.

Referral to a Pain Specialist

Many patients with TMD respond to usual treatments oriented towards symptom reduction, improvement of jaw mobility, and restoration of normal jaw function. Such treatment is appropriately managed by dental professionals. More severe myofascial pain or presence of comorbid cervical problems warrants the inclusion of physiotherapists or physiatrists. Presence of other comorbid pain disorders warrants the inclusion of providers specialized in pain management. For patients who have depression, anxiety, comorbid pain disorders, multiple nonspecific physical symptoms, or pain-related disability, psychologists or psychiatrists are helpful. Other health care professionals become important for conditions such as neuropathic pain or nonresponsive headache (neurologist), or for multiple joint pains (rheumatologist). Some patients may be more appropriately managed by a pain specialist within a setting of a multidisciplinary pain clinic. This may be indicated when: (1) the disability greatly exceeds what is expected on the basis of physical findings; (2) the patient makes excessive demands for tests and treatments that are not indicated based on existing evaluations and no subsequent symptom change; (3) the patient displays significant psychological distress (e.g., depression); (4) the patient displays aberrant behavior, such as continual nonadherence to treatment; or (5) the patient is unable to sufficiently control significant contributing environmental factors, such as family reaction to the patient's illness or persistent problems in illness behavior.

SPECIFIC DISORDERS AND THEIR MANAGEMENT

The majority of patients likely to present in a dental practice with a complaint of temporomandibular pain and dysfunction can be broadly categorized into muscle disorders, articular disc disorders, and disorders affecting the articular bones. The most common muscle disorder is myalgia (as per the DC/TMD; also commonly referred to as myofascial pain that remains localized to the hyperalgesic tissue upon

provocation). This pain is not associated with an identifiable anatomic muscle abnormality.

Intracapsular disorders affecting the TMJ are divided into two broad categories: articular disc disorders and degenerative joint disease. Either may be present without causing symptoms or impairment. It is important for the clinician treating patients with a TMD to distinguish clinically significant disorders that require therapy from incidental findings in a patient with facial pain from other causes. TMJ abnormalities are often discovered on routine examination and may not require treatment. The need for treatment is largely based on the level of pain and dysfunction and the progression of symptoms. The discovery of an anatomic abnormality such as a longstanding joint noise that is otherwise asymptomatic and consistent with a disc displacement is usually not treated given what is presently known about the longitudinal course of such disorders as well as the presently available treatments.

Myalgia and Myofascial Pain of the Masticatory Muscles

Description

The diagnostic terms *myalgia* and *myofascial pain* are used for muscle pain disorders that are characterized primarily by pain, limitation, and absence of progressive disease. The DC/TMD considers myalgia as the general disorder for muscle pain, and local myalgia and myofascial pain are subtypes of myalgia. Local myalgia refers to pain that remains local to the provoked muscle, and it contrasts with *myofascial pain* which can be associated with either spreading or radiating of the pain within the muscle or referral to a different structure when the muscle is stimulated during palpation.[3,187] Understanding the pathophysiology associated with muscle pain is still a challenge for further research. Since treatment cannot yet be designed to address a particular cause, multiple therapies for controlling symptoms and restoring range of movement and jaw function are usually combined in a management plan.[188] The general belief is that these therapies are more effective when used together than when used alone. Given the complex disease character of TMD, the multimodal approaches to treatment currently used for any pain condition may still be the primary form of treatment for TMD even when etiology is better understood.

Most of the research on the natural course of this disorder suggests that for most individuals, symptoms are intermittent and usually do not progress to chronic pain and disability. A comprehensive history and examination should be provided, leading to a differential diagnosis; management of these patients then logically follows. The principles of treatment provided here are based on a generally favorable prognosis and an appreciation that only a small number of clinically controlled trials exist indicating the superiority, predictability, and safety of the respective treatments. The literature suggests that many treatments have some beneficial effect; moreover, the literature suggests that the treatment effect may be nonspecific and not directly related to the particular treatment. Surgery for a chronic muscle pain disorder has no value. The principle of "do no harm" has particular salience for these disorders: aggressive treatments should be avoided, and adaptive biological responses should be supported.

Priority should be given to treatments that have the following characteristics: relatively accessible, acceptable cost, safe, and reversible. Treatments with these characteristics can be divided into two types. The first is based on self-management and includes education and acquisition of self-care skills. The second is based on provision of specialist treatments such as physical therapy, intraoral appliances, pharmacotherapy, and relaxation techniques (Table 10-9). Evidence suggests that combining treatments produces a better outcome.[296] Despite evidence clearly to the contrary, occlusal therapy continues to be recommended by some clinicians as an initial treatment or as a requirement to prevent recurrent symptoms. It bears repeating that research does not support occlusal abnormalities as a significant etiologic factor and the research does not support the use of occlusal treatment (e.g., occlusal adjustment) for TMDs.[297–299] The evaluation of occlusion and correction of occlusal abnormalities are not part of standard treatment for TMDs.

Self-Management

Self-management consists of patient education and a range of skills or activities that are synergistic in their effectiveness. The core activities include self-exercise, use of thermal modalities, avoidance of strain or overuse while chewing or yawning, reestablishing normal chewing patterns, self-massage, and parafunctional behavior control.[300] While the evidence is strong for efficacy of self-management in other diseases (e.g., arthritis),[301] the evidence is weak at present for these approaches for TMDs; yet, the principle of do no harm and the absence of progression of the painful TMDs points to the importance of using these approaches. Because the available evidence has consistently indicated that across pain conditions, psychosocial factors have been better predictors of treatment outcome compared to physical findings, diagnosis, or how much treatment was pursued,[302] treatments better aligned with the implications of psychosocial factors are more justified.

The key principles underlying self-management are as follows:[303–306]

- the activities do not require professional intervention (other than teaching and monitoring) but are entirely self-directed;

Table 10-9 Major treatment components for myofascial pain.

Treatment Component	Description
Self-management	Explanation regarding diagnosis, treatment, prognosis, and patient's and doctor's roles in therapy Information, skills training, and adherence monitoring for patient to be competent with self-exercise, thermal modalities, self-massage, diet and nutrition, bilateral chewing, yawn control, and parafunctional behavior control
Physiotherapy	Education regarding biomechanics of jaw, neck, and head posture and integrated movement patterns Passive modalities (heat and cold therapy, ultrasound, laser, and TENS) for pain Passive stretching and range of motion exercises Posture therapy sufficient to regain a neutral zone General exercise and conditioning program
Intraoral appliances	Cover all the teeth on the arch the appliance is seated on Adjust to achieve simultaneous contact against opposing teeth Adjust to a stable comfortable mandibular posture Does not alter mandibular position Use during sleep and rely on behavioral methods for waking hours
Pharmacotherapy	NSAIDs, acetaminophen, muscle relaxants, antianxiety agents, tricyclic antidepressants
Relaxation techniques & behavioral therapy	Relaxation therapy Hypnosis Biofeedback Cognitive–behavioral therapy

NSAIDs = nonsteroidal anti-inflammatory drugs; TENS = transcutaneous electrical nerve stimulation.

- acquiring skills and implementing them strategically takes time;
- adherence is essential but everyone adopts adherence at their own pace;
- therapeutic effects are cumulative over weeks to months, and adherence despite limited initial therapeutic benefit is often a challenge and benefits from provider assistance;
- symptom flareups are common but do not indicate either progression of a disorder or the need to escalate treatment;
- integration of skills with lifestyle and symptom patterns is the desired endpoint in skills acquisition; and
- control and knowing that one can manage flareups is empowering, and self-management skills acquired for a TMD have heuristic value for further self-development.

Education and Information

A source of great anxiety for patients with complaints of pain and limitation in the jaw is the possibility that their condition is progressive and degenerative and will thereby lead to greater pain and disability in the future. Patients may have sought prior consultations from other physicians and dentists who were not able to establish a diagnosis or explain the nature of the problem. This often leads to fears of a more catastrophic problem, such as a brain tumor or other life-threatening disease. Explaining the nature of pain, its distinction from nociception as an indicator of tissue damage, and the varied nature of the symptoms across time and linked to function and behavior has multiple important effects. Understanding one's disorder is the basis for the self-care activities that patients must perform for immediate symptom control as well as for longer-term rehabilitation and maintenance. Being better informed generally reduces anxiety, and that in turn decreases pain amplification and disability. Successful patient education requires enough time in an unhurried environment for the clinician to provide the necessary information and to allow the patient to express any concerns and ask questions. This interaction is the basis for the therapeutic relationship. Education and information provide the patient with an understanding of the condition and the ability to perform activities and make choices that have a direct effect on the symptoms. The patient has to participate in developing strategies to avoid stresses that aggravate symptoms or interfere with the ability to manage therapy.

Self-exercise Therapies

The most common self-exercise is simple stretching of the masticatory elevator muscles; face validity for this exercise is very high, given the pain accompanying restriction in opening the mouth as perhaps the most frequent symptom of the common TMDs. Muscle stretching, for most patients, should be performed 2–3 times each day; about 10 repetitions, each held for about 5 seconds, seem sufficient. Stretching should be performed within the limits of pain threshold; that is, in a comfort zone; excessive stretching elicits a protective

response which causes simultaneous activation of alpha-motor neurons, undermining the efficacy of the stretching. The mouth-opening and mouth-closing phases of stretching should be monitored in order to ensure that the jaw moves in a straight line at a steady rate. Monitoring is best achieved by the patient using a mirror (as an inexpensive form of biofeedback) and watching the movement of the jaw. An alternative form of this variant on stretching is to maintain the tongue in contact with the palate in order to control mouth-opening in terms of both encouraging primarily rotational movement of the TMJ as well as limiting the overall opening extent; both aspects are sometimes strategically implemented when painful popping is interfering with full stretching. A 3-month period of treatment consisting of education only or education plus a home physical therapy program found that education plus home physical therapy was more effective.[307] Other self-exercises, such as resisted opening, are used for TMD pain, but they tend to be used in a more idiosyncratic manner and any unique therapeutic effects beyond the basic muscle stretch have not been established.

Thermal Modalities

Thermal agents consist of the application of moist heat to the affected areas for 15 to 20 minutes twice daily, as well as ice packs for about 10 minutes.[307] Ice has traditionally been considered to be primarily for acute problems, especially joint injury, but clinical experience has shown that ice seems to be more effective than heat for not all but certainly a larger number of patients with chronic problems than generally thought. Ice is particularly effective when applied to very tender or irritable areas of muscle or joint prior to stretching. When given the opportunity to try each of heat and ice, the patient will discover which works better for them. For some individuals, the use of both (for example, ice first, then heat after stretching; or the reverse) is good. Thermal modalities can be used as often as needed to manage pain.

Self-massage

Manual physical therapy has a long tradition for TMDs, and recent clinical studies support the benefit of soft-tissue manipulation.[308] Similarly, the patient can engage in self-massage; this is particularly true for the masseter muscle, using either cross-fiber technique or stroking the fibers along their length. Patients report nearly as much pain relief from self-massage as they do for thermal modalities.[309] Self-massage may also stimulate large-diameter afferent fibers and thereby facilitate inhibition of nociception at the trigeminal nucleus caudalis.[310] Self-massage also has a real-time educational value: patients can feel muscle tightness and local soreness, helping to integrate body state with perception. Finally, self-massage simply feels good, and that typically has motivational aspects for patients to continue with other self-care methods.

Diet and Nutrition

A common treatment recommendation for TMDs is to eat only softer foods; the rationale is that avoidance of tougher or harder foods will facilitate recovery. Resting a painful body part is a traditional and intuitively understood action, especially for instances of acute tissue damage. However, as clearly shown for bouts of back pain,[311] too much "rest" leads to atrophy and, therefore, via a negative feedback loop emphasized in the pain/fear avoidance model,[231] to further restrictions in activities. Similarly, when extending indefinitely the restriction to only eat soft foods, muscle atrophy and occlusal changes occur, as well as increasing fatigue such as with ordinary speech. Persistent avoidance of normal function decreases the pain threshold and increases the tendency for the patient to believe that trying to function normally will lead to further deterioration of the jaw. In contrast, emphasizing resumption of normal function, such as via usual textured foods, facilitates recovery rather than blocks it.[312] Nutritional needs for those with chronic pain have been largely neglected, though recent attention highlights how little is really understood regarding pain and nutrition.[313–315]

Bilateral Chewing

Unilateral chewing may originate with a missing tooth or a pulpitis; the unilateral chewing pattern tends to persist even after the dental problem is resolved. As part of avoidance behavior, many patients with a TMD will start to chew on only one side, and unilateral chewing is one of the very few local factors associated with TMD.[99] Before resuming a normally textured diet, the patient who chews unilaterally should retrain in order to chew bilaterally; this is best facilitated by judicious use of a mechanical soft diet for perhaps 2 weeks at most, and then gradually resuming more normally textured foods. Hard or brittle food should still be avoided until symptoms substantially improve. Normal chewing restores strength, which balances muscle tone between elevator and depressor muscles, and aids muscle relaxation.

Yawn Control

Yawning is a ballistic movement, leading to rapid translation of the TMJ and rapid stretch of the masticatory elevator muscles; for an individual with a painful TMJ or a myalgia of the masticatory muscles, yawning is painful. Patients instinctively learn to suppress the yawn by co-contraction of the elevator muscles—which opposes the action of the jaw opening muscles under yawn reflex control. The result is that the mandible is torqued during the yawn, and such

suppression is not so effective. A better method of control is to use the lightly formed fist of one hand, applying counter-pressure from beneath the chin. The evidence for controlling yawns in this manner is purely anecdotal.

Parafunctional Behavior Control

Attention to jaw activities that are unrelated to function (such as tooth clenching, jaw-posturing habits, jaw-muscle tensing, and leaning on the jaw) is a critical beginning. Those parafunctional behaviors associated with clinically relevant hyperactivity need to be replaced with restful (neutral) jaw postures, and this should be part of any initial therapy. Parafunctional behavior control is simultaneously the same thing as fully resting or relaxing the jaw, which allows the jaw to assume a neutral position. Parafunction control is helpful in reducing pain in myofascial pain patients.[316] In order to have the skills to appropriately monitor and control their parafunctional behaviors, patients need education, training, support, and reinforcement from their provider.

Implementation of Self-management

Structured provider skills are necessary to strategically implement appropriate escalation of skills, titrate their frequency of use, and evaluate the relative contribution of such behaviors to the aggravation or persistence of symptoms. Table 10-10 illustrates a sample patient instruction sheet.

Clinician Management

Physiotherapy

Appropriate goals of PT are to restore normal muscle tone and resilience, improve joint movement, reduce pain, and improve function. Both passive and active treatments are

Table 10-10 Self-management for TMDs.

Use thermal agents to control pain.
Apply moist heat to the sides of the face and to the temple areas for 10 to 20 min twice daily.
Apply ice packs to targeted areas for 10 mins.
Can alternate ice with heat, and use before and after stretching; discover what works best for you.
Self-massage
Jaw muscles on sides of face can be stretched along their length by pulling the muscles in that direction, or by pulling the fibers to the sides.
Apply gentle massage to the skin overlying the sore areas.
Diet and nutrition
During initial phase of self-management, select foods that do not aggravate your pain or cut your usual foods into smaller pieces. Avoid foods that require wide opening of the mouth or considerable force with the front teeth. Maintain this for about 2 weeks, then gradually resume more normal food textures.
As possible, chew food on both sides of the mouth, alternating sides or splitting food into two parts, one part for each side.
Avoid chewing gum, and the most difficult to chew foods such as hard nuts, tough foods.
Avoid certain postures or movements.
During yawning, support the jaw by providing mild counter-pressure underneath the chin with the thumb and index finger or with the back of the hand.
Avoid the following: lean on or cup the chin when performing desk work or at the dining table; testing the jaw by opening wide or moving the jaw around excessively to assess pain or motion; maneuvering the jaw into positions to assess its comfort or range; habitually clicking the jaw if a click is present.
Do not sleep on the stomach or in postures that place stress on the jaw.
Avoid elective dental treatment while symptoms of pain and limited opening are present.
Be aware of and control oral parafunctional behaviors.
Teeth should only contact during chewing and swallowing.
Monitor jaw at regular intervals through the day for any clenching, grinding, touching, or tapping of teeth or any tensing or rigid holding of the jaw muscles.
Monitor jaw for parafunctional behaviors during specific situations such as while driving, studying, using computer, reading, engaging in athletic activities, when at work, or in social situations, and when experiencing overwork, fatigue, or stress.
Practice neutral jaw posture: Place the tip of the tongue (optimally) behind the top teeth (by saying "N" and retaining the tip of the tongue in that location) or in the floor of the mouth (if the patient cannot manage the tongue in the superior position), separate the teeth slightly, and allow the jaw to "hang" in this position; maintain this position when the jaw is not being used for functions such as speaking and chewing.

commonly included as part of therapy. Although randomized trials necessary to confirm the effectiveness of physiotherapy are generally lacking, the clinical literature suggests that physiotherapy is a reasonable and effective therapy.[308,317] Evidence supporting one type of physical therapy in favor of another has not been demonstrated.[318] Posture therapy has been recommended to avoid forward head positions that are thought to adversely affect mandibular posture and masticatory muscle activity; research evidence, however, suggests that forward head posture, by itself, is not strongly associated with having TMD.[251] This leads to a conundrum in how to best use evidence to guide treatment: clinical practice of physical therapy, when done in a manner that reliably helps symptoms, typically includes many elements, most of which either have not been adequately researched or, as in the case of forward head posture, have disconfirming data. Explanatory models for how physical therapy works are plentiful but critical data are absent; this situation, however, is rapidly changing and better quality evidence will begin to emerge.

Passive modalities such as ultrasound, cold laser, and transcutaneous electrical nerve stimulation (TENS) are typically used initially to reduce pain. Passive modalities are often used as a prelude to active treatments of joint mobilization and soft tissue stretching in order to reduce discomfort associated with the active treatments. Ultrasound relies on high-frequency oscillations that are produced and converted to heat as they are transmitted through tissue; it is a method of producing deep heat more effectively than the patient could achieve by using surface warming. Ultrasound is generally regarded as effective; however, whether it is effective alone is questionable.[319] Cold laser is heavily promoted for its role in effecting cellular metabolism,[320] and it appears to be effective for at least some types of pain;[321,322] its use in chronic pain has, so far, not been supported by strong evidence.[323] TENS uses a low-voltage biphasic current of varied frequency and is designed for sensory counterstimulation for the control of pain. It is thought to increase the action of the modulation that occurs in pain processing at the dorsal horn of the spinal cord and (in the case of the face) the trigeminal subnucleus caudalis of the brainstem. The general principle in the use of TENS is to consider it for therapeutic trial, recognizing that long-term efficacy is highly idiosyncratic. Physical therapists will commonly add more jaw exercises such as active stretching to increase the range of jaw motion, and isotonic and isometric exercises to facilitate strength and coordinated movement. Providing too many exercises too quickly can lead to poor compliance; the addition of exercises to the self-management program should be titrated based on performance and adherence.

Some physiotherapists apply mobilization techniques to increase mandibular motion. These are done passively under the control of the physiotherapist and will usually include distraction and some combination of lateral and protrusive gliding movements. The choice and timing of treatment are individual considerations since the literature is not developed enough to provide specific guidelines.

In addition to the benefits of the therapeutic relationship between the dentist and patient, a physiotherapist trained in managing temporomandibular disorders is likely to interact with the patient regularly for review and coaching regarding physical self-management, education regarding the disorder, and further provision of physical therapy. A physiotherapist can reinforce management from a biopsychosocial approach contributing to a successful treatment outcome.

Intraoral Appliances

Intraoral appliances (variously termed splints, orthotics, orthopedic appliances, bite guards, nightguards, or bruxing guards) are used in TMD treatment. When carefully used, an intraoral appliance is considered to be a reversible form of therapy; however, appliances also have adverse effects as well. A number of studies on splint therapy have demonstrated a treatment effect, although researchers disagree as to the reason for the effect.[282,296,324,325] In an early review of the literature on splint therapy, Clark found that patients reported a 70–90% improvement with splint therapy.[326] Qualitative, quantitative, and systematic reviews have carefully considered the question of appliance treatment, concluding in general that the use of appliances in TMD treatment is beneficial, though whether better than a placebo appliance remains an open question; available high-quality evidence as well as a plausible mechanism of action is still lacking.[90,198,295,327–330] Notably, oral appliances appear to be more effective when TMD is the sole pain disorder; when fibromyalgia, for example, is comorbid with a painful TMD, the efficacy of the oral appliance diminishes considerably.[331]

A decrease in masticatory muscle activity has been associated with splint therapy and might be the reason for the effects of splint therapy.[107] Alternatively, a nonspecific treatment effect has been proposed.[332] Other explanations for the effects of splint therapy include occlusal disengagement, altered vertical dimension, realigned maxillomandibular relationship, mandibular condyle repositioning, and cognitive awareness of mandibular posturing and habits.[333] The nature of treatment effects of appliance therapy will require further research. For the present, however, intraoral appliance therapy is considered to be a reversible treatment. When to include an intraoral appliance differs considerably across practice settings; some practices start treatment with an appliance, while more behaviorally-oriented practices will include an appliance only after specific goals have been met with regard to self-care and behavioral treatments. Early

use of an appliance can facilitate treatment response,[334] but early use can also diminish the value and adherence to the other self-care treatments. Excessive reliance on appliances typically leads to poor treatment outcomes of TMD.

The choice of material for the construction of an appliance remains one of individual preference. In comparing hard versus soft material appliances, a 3-month trial found no difference in outcome when either the hard or the soft appliance was used,[335] and a 12-month trial had the same findings.[336] In contrast to the equivocal study results, a survey of dentists and dental specialists reported that a flat-plane splint made of hard acrylic was used more frequently than any other design or material.[337] Reasons for this preference of hard appliance include adherence to occlusion models and the belief that appliances should replicate an occlusal scheme, belief that dental proprioception facilitated by the hard appliance is beneficial to muscle retraining, greater longevity, and reports by patients that soft appliances often feel bulky or provoke clenching that was not previously present.

The most common purposes advocated for appliance therapy are to provide joint stabilization, protect the teeth, redistribute forces, relax elevator muscles, and decrease or control the effects of bruxism.[333] The appliance most commonly used for these purposes is described as a stabilization appliance or muscle relaxation splint (Figure 10-15). Such appliances are designed to cover a full arch and are adjusted to avoid altering jaw position or placing orthodontic forces on the teeth. Long-term continuous wearing of an occlusal appliance is a risk for a permanent change in the occlusion.[338] This is a greater concern with appliances that provide only partial coverage or that occlude only on selected opposing teeth.[339] Not because of occlusal theory related to TMD, but rather because appliance treatment should not cause teeth to move, the appliance should be adjusted to provide bilateral even contact with the opposing teeth on closure and in a comfortable mandibular posture. Anterior guidance during excursive movements is often preferred and can be achieved with an appropriate acrylic contour; however, anterior guidance patterns do not improve appliance efficacy.[340]

During the period of treatment as symptoms improve, the appliance should be re-examined periodically and readjusted as necessary to accommodate changes in mandibular posture or muscle function that may affect the opposing tooth contacts on the appliance. At the beginning of appliance therapy, a combination of appliance use during sleep and for periods during the waking hours is used by some providers; however, better behavioral management during the waking hours should preclude the need to rely on an appliance except during sleep. Each patient has his or her own needs and characteristics, and these should be monitored to determine the most effective schedule for appliance use. Factors such as tooth clenching when driving or exercising may be managed by increasing splint use during these times, or perhaps such symptom-related events serve as a gateway for referral for stress management. Pain symptoms that tend to increase as the day progresses generally indicate pervasive parafunctional behaviors; the appliance can be used at various times during the day in response to such pain patterns, or behavioral management can be emphasized. Overall, to avoid the possibility of occlusal change, the appliance should certainly not be worn continuously (i.e., 24 hours per day) over prolonged periods, which suggests that behavioral management must remain the primary method for waking parafunction. Full-coverage appliance therapy during sleep is a common practice to reduce the effects of bruxing and is not usually associated with occlusal change. In addition, appliances seem to retain more efficacy if used for shorter periods (e.g., only during sleep) by relying upon behavioral methods for parafunction management during the waking hours.

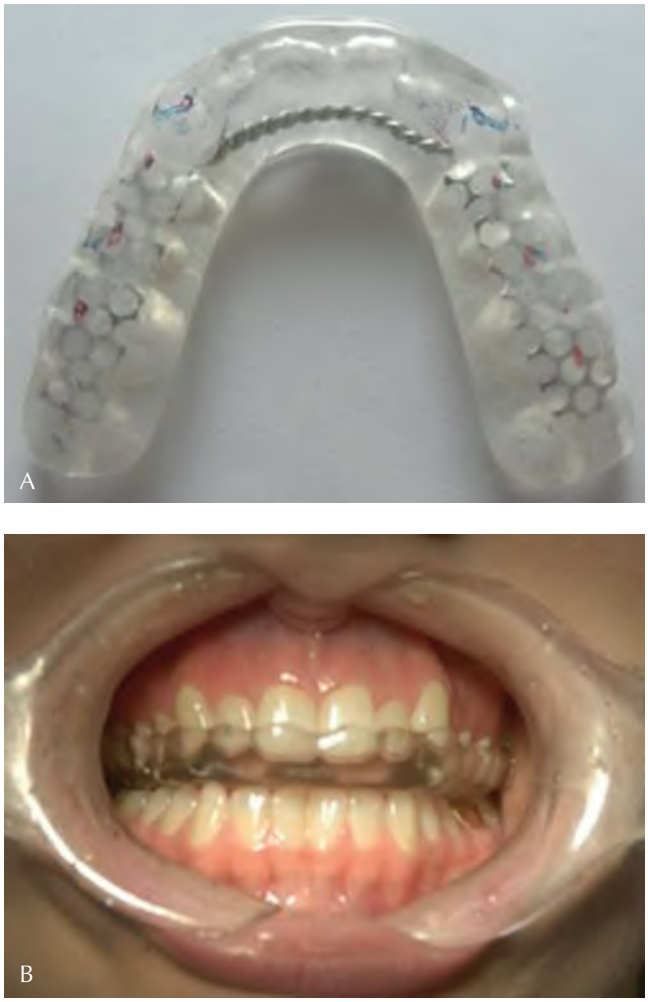


Figure 10-15 Maxillary acrylic full-coverage stabilization splint.

The choice of inserting a stabilizing appliance on the upper or lower arch is a clinical judgment related to how the appliance is to be used and the clinical findings regarding the dentition. Placing the appliance on the arch with missing teeth allows for an increase in occlusal contact position. For patients who are likely to benefit from daytime wear, a lower appliance is usually less visible and does not interfere with speech as much as an upper appliance. When an appliance is to be used only at night, most clinicians choose the upper arch, but this choice seems to be more a function of tradition. There is no evidence that indicates one arch is the better home for an appliance in the treatment of a TMD.

Splints that reposition the mandible anteriorly have been used effectively in treating disc displacements,[341] but they increase the risk of permanently altering the occlusion and should be used with caution if at all.[342] These splints have been made for the upper or lower arch, although the maxillary appliance is better able to maintain a forward mandibular posture by using a ramp extending from the anterior segment that guides the mandible forward during closure. These appliances were used with greater frequency in the past to putatively correct disc position as a step toward more permanently altering mandibular position through permanent changes in the occlusion. This approach was associated with great technical difficulties, and the treatment failed to correct disc displacement in a significant percentage of patients. Evidence supporting the need for such treatment remains lacking. In contrast, repositioning appliances used intermittently for short periods can be useful in controlling symptoms arising from the mechanical instability associated with a problematic disc displacement, such as transient episodes of jaw locking due to disc displacement and accompanied by pain and dysfunction.

In summary, a stabilizing oral appliance that fully covers one arch and does not reposition the mandible or alter the occlusion has been considered a standard part of therapy of TMD. Continuous appliance wear, appliances that only provide partial coverage, and appliances that reposition the mandible and alter the occlusion have a greater chance of adverse effects. The relative importance of an oral appliance for treating a TMD is increasingly questioned in light of the advantages of a purely self-management treatment approach.

Pharmacotherapy

Mild analgesics, nonsteroidal anti-inflammatory analgesic drugs (NSAIDs), antianxiety agents, tricyclic antidepressants, and muscle relaxants are used for treatment of TMD pain. The use of any of these agents, along with the other components of initial therapy, may contribute to improved and more rapid symptom control.[343] The use of medications for TMD management should follow the general principles of analgesic therapy and be used on a fixed dose schedule according to time rather than as needed for pain. Drug therapy requires a thoughtful assessment of the potential risks relative to the benefits, including the clinician's own professional ability and confidence in using the particular drug or drugs. Because of the adverse effects of all of these drugs, short-term or intermittent use is preferred, but a smaller percentage of patients who evolve into a chronic musculoskeletal pain disorder are usually taking combinations of medications long term. The use of multiple drugs and their management as a part of a complex chronic pain disorder is beyond the scope of this chapter. Medication management of pain, particularly chronic pain, is a continually evolving area within the dental profession.

NSAIDs are probably the most commonly prescribed medication for pain control in TMD therapy. The promise of the COX-2 inhibitors (e.g., rofecoxib) as safer alternatives to other NSAIDs has proven unfulfilled due to the association of cardiovascular incidents. There is modest evidence for efficacy of NSAIDs in TMD therapy.[294] For example, ibuprofen 2400 mg daily for 4 weeks did not demonstrate a clear analgesic effect due to the drug,[344] whereas naproxen 500 mg twice daily in a 6-week trial was more effective than placebo or celecoxib.[345] The outcomes of such studies are seldom fully replicated; consequently, successive trials of several systemic NSAIDs in order to identify which one works best for a given patient is a reasonable part of initial therapy. NSAIDs for most TMDs should be short term to supplement the other nondrug therapies that should reduce the need for long-term NSAID therapy. A mild analgesic such as acetaminophen might be a first choice for analgesic drug treatment since it is much less likely to cause adverse side effects when taken in the appropriate dose for short periods; this is particularly so when the pain is regarded as nociceptive rather than inflammatory.[169] A combination of ibuprofen and acetaminophen is commonly regarded as more effective than either medication alone for certain pains—perhaps reflective of a combination of both nociceptive and inflammatory mechanisms—but the data are inconclusive.[346,347]

Topical NSAIDs have demonstrated significant pain-reducing effects in acute and chronic musculoskeletal injuries. NSAIDs can be incorporated in transdermal creams for application on the skin over the painful joint or muscle. Ketoprofen, felbinac, ibuprofen, diclofenac, and piroxicam have significant efficacy. This efficacy holds true for chronic conditions such as arthritis. The incidence of local and systemic adverse events is low and no different from placebo.[348] Capsaicin cream, originally found to be of value in treating postherpetic neuralgia, is a substance-p depleter, a neurotransmitter responsible for increased nerve sensitization. Capsaicin has not been studied for TMD therapy but it has

been recommended as a topical analgesic (0.025% and 0.075%) when applied to the skin over a sore joint or muscle four times daily for at least 2 weeks. Capsaicin therapy is limited due to its burning quality on application, which frequently causes the patient to abandon treatment; careful titration to tolerance of the capsaicin concentration can improve adherence.

Whereas the long-acting benzodiazepine clonazepam was effective in a pilot study of TMD treatment,[349] 10 mg cyclobenzaprine, a muscle relaxant, taken at bedtime was found to be superior to clonazepam at managing jaw pain on awakening.[350] Muscle relaxants are a class of drugs that act in the central nervous system, inhibiting interneurons and depressing motor activity. These medications are used before sleep due to their sedative effects. Some patients taking 10 mg of cyclobenzaprine at bedtime experience continued sedation into the day, but they are able to tolerate a lower dose by splitting the tablet into two or four sections and taking less than the full pill. The sedative effects of cyclobenzaprine may contribute to their efficacy and, in addition, be of value in promoting sleep, which is often also compromised in individuals with pain. Sleep disorders may also require the use of hypnotics or other drug combinations to increase restorative sleep, but behavioral approaches for improving sleep should be considered the primary therapy due to better efficacy.[351–353]

Tricyclic antidepressants, particularly amitriptyline, have proven to be effective in managing chronic orofacial pain. Amitriptyline is analgesic at low doses, has sedative effects, and promotes restful sleep; all of these effects can be helpful in treatment. It is the anticholinergic effects of the drug (dry mouth, weight gain, sedation, and dysphoria) that often make it intolerable. An effective dose can be as low as 10 mg at night but can be increased gradually to 75 to 100 mg, depending on the patient's tolerance of the side effects. Two clinical studies demonstrated a positive treatment effect using low-dose amitriptyline for TMD treatment.[354,355] Depression commonly accompanies chronic pain; referral for depression-relevant dosages of antidepressant medications should be considered.

Opioids were previously considered appropriate for complex chronic pain disorders or briefly for acute injuries to the TMJs or muscles where moderate to severe pain is present. The use of opioids for chronic pain has always been a controversial issue, driven by differing views of pain and suffering as well as owing to the unfortunate practice by some patients of medication diversion. Due to serious adverse events associated with the use of opioid medication for nonmalignant pain, opioid use for chronic pain is now considered inappropriate. A related issue is pseudo-addiction, which is the reliance on adequate dosages of medication (often opioid, but it could be any type) to control a symptom but which is then viewed as "addiction." Knowing one's patient is essential, but careful prescribing is also essential.

Relaxation Techniques and Behavioral Therapy

Integrating relaxation techniques and behavioral therapy in chronic pain management is effective.[356] In some cases, self-management skills, including awareness and attempted control of parafunctional behaviors, may not be sufficient to change behavioral patterns that are contributing to symptoms. A more structured program supervised by a clinician who is competent in behavioral therapy offers a greater chance of addressing issues that are contributing factors. There is general agreement in the literature that behavioral and educational therapies are effective in the management of chronic pain disorders, although the existing research is not sufficient to conclude that any one technique is superior. Relaxation techniques, biofeedback, hypnosis, and CBT have all been used to reduce symptoms in patients with TMD.[357] The mechanism of action of these techniques is likely complex.

Relaxation techniques generally decrease sympathetic activity and (possibly) arousal. Methods include autogenic training, meditation, and progressive muscle relaxation.[356] These techniques are aimed at producing comforting body sensations, calming the mind, and reducing muscle tone. Brief methods for relaxation use self-controlled relaxation, paced breathing, and deep breathing. Hypnosis produces a state of selective or diffuse focus in order to induce relaxation. The technique includes pre- and post-suggestion and is used to introduce specific goals. Individuals vary greatly in their susceptibility to hypnosis and suggestion. Hypnosis does not affect endorphin production, and its effect on catecholamine production is not known.

CBT, which often includes relaxation techniques, is primarily focused on changing patterns of negative thoughts. Hypnosis and CBT have been hypothesized to block pain from entering consciousness by activating the frontal limbic attention system to inhibit pain impulse transmission from the thalamic to the cortical structures.[356] Functional imaging data clearly demonstrate that CNS activity quickly changes in response to changes in thought patterns. A six-session CBT intervention enhanced the treatment effect of usual TMD treatment.[358]

Biofeedback is a treatment method that provides continuous feedback, usually by monitoring the electrical activity of muscle with surface electrodes or by monitoring peripheral temperature. The monitoring instruments provide patients with physiologic information that allows them to reliably change physiologic functions in order to produce a targeted system response similar to that produced by relaxation therapies. The patient develops strategies that are aimed at either lowering the electrical activity of the muscle or raising

peripheral temperature, respectively. Repetitive practice using the biofeedback instrumentation provides the training for the patient to develop better motor control and more accurate proprioception of the targeted muscle(s), with the goal of ultimately achieving a more relaxed state in the targeted muscle(s); central to the success of biofeedback, in terms of generalizing treatment effects from the clinic to the environment, is developing a greater sensitivity to the environmental stimuli that have adverse effects on the individual. A primary limitation to biofeedback treatment is the cost associated with the number of supervised treatment sessions; instrumentation for home use has become much more available, which can help reduce clinician costs and enhance generalized training. However, such instrumentation for home use is primarily oriented towards a general relaxation response rather than muscle activity.

Barriers to integrating behavioral and relaxation therapy exist in standard medical and dental care. The biomedical model of disease is emphasized in medical and dental education. The biomedical model emphasizes the anatomic and pathophysiologic aspects of disease and does not emphasize psychosocial issues, the importance of the patient's experience of disease, or the fundamental importance of self-regulation. In addition, behavioral therapies can be time-intensive and may also not be supported by insurance companies; moreover, clinicians trained for behavioral management of pain can be difficult to identify for referral. Consequently, this is yet one more reason why there is increased emphasis on self-management approaches.

For the patient who does not respond to initial treatment and who continues to have significant pain and disability, additional therapies beyond those described above are usually required. These patients are characterized more as having a chronic pain disorder than as having an anatomic abnormality that is unique to the masticatory system. Treatments used in the management of chronic pain are indicated for this group. A greater focus on behavioral therapies and coping strategies may provide additional benefits. Multidisciplinary pain clinic management may be required. The use of chronic pain medications, including the drugs described as adjuvant analgesics (tricyclic antidepressants, anticonvulsants, membrane stabilizers, and sympatholytics), may be part of a long-term management plan. Chronic pain disorders cause psychosocial changes that require comprehensive management in order to reduce the associated disability.

Trigger Point Therapy

Trigger point therapy has traditionally used two modalities: cooling of skin over the involved muscle followed by stretching, and direct injection of local anesthetic into the muscle. More recently, botulinum toxin injections are being used for trigger points.

"Spray and stretch" therapy is performed by cooling the skin with a refrigerant spray (e.g., fluoromethane) and stretching the involved muscle. Cooling allows for stretching without pain that causes a reactive contraction or strain. Travell and Simons described this technique in detail, introducing the method for the treatment of myofascial pain.[239] Patients who respond to this therapy can use a variation at home by first warming the muscle, then briefly icing it, and then gently stretching the jaw passively. Anecdotal evidence suggests that simply icing the muscle, without preceding heat, and then stretching, can also be effective.

Intramuscular trigger point injections have been performed by injecting local anesthetic, saline, or sterile water or by dry needling without depositing a drug or solution. The choice of solution for injection exists because of the lack of established benefits of any one method.[359] Injection of sterile water was associated with greater injection pain than was injection of saline.[360] In a study in which patients with myofascial pain were treated with injection of lidocaine or with dry needling, both groups reported decreased pain immediately after injection, but the group that received dry needling experienced greater soreness 48 hours after the procedure.[361] Procaine diluted to 0.5% with saline has been classically recommended because of its low toxicity to the muscle,[362] but 1% lidocaine is an alternative.

There are no tested protocols for trigger point injection therapy. A set of three to five weekly sessions has been recommended, and this may be continued with modification of the intervals between injections, depending on the response.[363] Injections can be given to a muscle group in a series of five weekly or biweekly treatments. If there is no response to the initial series of injections, the classic recommendation was that trigger-point injection treatment should be abandoned. Hopwood and Abram analyzed treatment outcomes for 193 patients who received trigger point injection therapy for myofascial pain.[364] They found that: (1) unemployment due to pain increased the odds of treatment failure threefold; (2) a longer duration of pain and greater change in social activity increased the risk of failure twofold; and (3) constant pain (versus intermittent pain) increased the likelihood of treatment failure by 80%. These results emphasize that chronic pain is a multidimensional and complex problem and that a variety of factors will influence treatment outcome.

Nevertheless, treatment failure from traditional injection therapy is now followed by, or is often substituted at the beginning by, use of botulinum toxin injections. Botulinum toxin has been advocated for the treatment of TMDs,[365] but randomized clinical trials question the true efficacy of this treatment for pain beyond that of decreasing muscle tone.[366–368] Moreover, botulinum toxin is not necessarily more effective than the traditional injection approaches for myofascial pain.[369,370] As Travell and Simons established decades ago,

behavioral factors promoting the persistence of chronic myofascial pain must be the primary focus of treatment, for which augmentation by injection therapies can be additionally helpful.[239] Most treatment studies of myofascial pain utilizing injection therapies tend to be standalone injection therapy, and consequently the value of comprehensive treatment remains largely untested.

Other TMD Treatments

The above sections highlight only the most common treatment methods and have not addressed many treatments that have been recommended for the management of TMDs. Acupuncture has been shown to be an effective part of the management of chronic pain. Acupressure, different forms of injection therapy using natural substances, massage therapy, naturopathic and homeopathic remedies, and herbal remedies are just a few of the treatments patients may pursue.[371] The Internet has produced treatment programs that allow patients to evaluate their problem to determine whether the advertised treatment will be of benefit. There is a critical need (which will increase in the future) for dentists to help patients evaluate the treatments and products that are promoted for TMD therapy. Many of these treatments lack publication in the scientific literature that is even descriptive. The large variety of treatments promoted, coupled with the lack of clarity in the scientific research about cause, makes the need to establish a trusting doctor–patient relationship critical.

Restorative Dental Procedures in Individuals with TMDs

Patients who require elective dental treatment should defer such procedures until the TMD symptoms have resolved or are under reasonable control. Patients who develop active dental disease requiring treatment while they report active and problematic TMD pain or mechanical TMJ problem are likely to have increased pain and dysfunction after dental procedures. The dentist should attempt to minimize the effect of a procedure on myalgia or joint strain by using a variety of procedures, as outlined in Table 10-11. One clinically proven method of minimizing symptom aggravation from dental treatment visits is the use of a mechanical support device for the mandible; both pain and fatigue are reduced, and focus groups report that its use by the dentist also minimizes jaw over-extension during dental procedures.[372]

Table 10-11 Managing TMD patients requiring dental procedures.

Prior to the procedure
Use hot compresses to masseter and temporalis areas 10 to 20 minutes two to three times daily for 2 days.
Use a minor tranquilizer or skeletal muscle relaxant (e.g., lorazepam, 1 mg; cyclobenzaprine, 10 mg) on the night and day of the procedure (patient must be accompanied by an adult).
Start a nonsteroidal anti-inflammatory analgesic the day of the procedure.
During the procedure
Use a child-sized surgical rubber mouth prop to support the patient's comfortable opening; remove periodically to reduce joint stiffness. Alternatively, an extraoral device that supports the jaw can be used.
Consider intravenous sedation and/or inhalation analgesia.
Provide frequent rest periods to avoid prolonged opening.
Apply moist heat to masticatory muscles during rest breaks.
Gently massage masticatory muscles during rest breaks.
Perform the procedure in the morning, when reserve is likely to be greatest.
After the procedure
Extend the use of muscle relaxant and NSAID medication as necessary.
Apply cold compresses to the TMJ and muscle areas during the 24 hours after the procedure.

NSAID = nonsteroidal anti-inflammatory drug; TMJ = temporomandibular joint.

Articular Disc Disorders

Description

The TMJ, like other joints, is susceptible to internal derangements of the intracapsular soft tissue. The most common form of internal derangements affecting the TMJ is the disc displacement, an abnormal relationship between disc, condyle, and eminence. Among disc displacements, the evidence is largely limited to those that are oriented in the sagittal plane, and, consequently, the classification of disc displacements reflects the sagittal plane orientation. The most common and by far best studied is the anterior disc displacement (ADD). In an ADD, some part of the disc is displaced anteriorly relative to the normal position on the condyle as described previously. The extent of disc displacement in the closed position of the condyle ranges from minor, such as an elongation of the disc with the anterior band no longer in contact with the condyle in the fully closed position, to complete, where the posterior band is anterior to the condyle. During the opening phase, the disc may return to its normal position, defined as the anterior band and intermediate zone being in the expected functional position on the anterior–superior aspect of the condyle. If the disc returns, the problem is classified as anterior disc displacement with reduction (ADDwR). During the opening phase, the disc may not return to its normal position, and the problem is classified as anterior disc displacement without reduction (ADDwoR). Reduction is an orthopedic term, referring to a return to normal anatomical confirmation. "Locking" of the jaw joint is a commonly used colloquial term indicating a state of nonreduction, and locking can occur acutely with

disc displacements (the acute ADDwoR) and with wide opening of the mandible (subluxation or dislocation).

ADD, during normal jaw opening, may result in abnormal joint sounds, limitation and deviation of mandibular motion, and pain. The majority of individuals with an ADD, with or without reduction and whether in one or both TMJs, have no pain or limitation in functioning; MR studies have demonstrated that ADD is present in 25 to 35% of the normal asymptomatic adult population.[373,374] This is comparable to the finding of asymptomatic clinically insignificant internal derangements that are well documented in the knee and spine.[375,376] Although clinical signs of internal derangement are seen in children,[377] some have reported that ADD of the TMJ does not appear to affect children below the age of 5 years in significant numbers.[378]

A specific etiology in the majority of cases of disc displacement is poorly understood. Some cases result from direct trauma to the joint, such as from a blow to the mandible. With respect to trauma, the particular events and presumed pathophysiology that may result in ADD are often unknown. Clinicians have theorized that indirect trauma from cervical flexion extension injuries (whiplash associated disorders: WAD) may predispose an individual to disc displacement. There is some support that WAD can affect the jaw in adverse ways,[379] but the evidence is weak based on insufficient study designs for assessing causation. It is generally believed that chronic low-grade microtrauma resulting from long-term bruxism or clenching of the teeth or certain types of malocclusion could be a cause of ADD. Arthroscopic examination of the TMJ has demonstrated an association between oral parafunction broadly and intracapsular disorders,[380] but this evidence is insufficient to support direct causation. There is evidence that a generalized laxity of joints is associated with ADD;[381] this is of particular concern for major connective tissue disorders such as Ehlers–Danlos syndrome, but the evidence is presently only anecdotal. Alternations in craniofacial morphology, such as those with an increase in middle anterior facial height and a decrease in the posterior cranial base vertical height, may also play a role in ADD.[382]

The angle or steepness of the mandibular fossa has been considered a contributing factor in the development or aggravation of intracapsular disorders. However, the steep, vertical form of the fossa has been inconsistently associated with disc displacements across studies. Osseous changes appear to occur in response to the disc displacement suggesting that the steepness of the eminence may be a consequence of disc displacement rather than a cause.[383] Differing levels of muscle activity across individuals, as one possible contributing variable, for example, may explain disparate findings regarding the role of the eminence angle on disc position.[384] Collectively, these varied findings regarding joint function and disc displacements highlight the uncertain roles of disc attachment, fossa morphology, bony adaptation, muscle function, and their potentially complex interaction.

One of the most common disc displacements is classically described as anterior and medial to the condyle.[385] The attachment of the superior head of the lateral pterygoid muscle to the TMJ capsule and the direction of pull by that muscle aligns with this classic description of the ADD. Consequently, dysfunction of the lateral pterygoid muscle mediated via its attachment to the capsule is theorized to cause disc displacements. More specifically, the theory suggests that differential hyperactivity of the superior head of the lateral pterygoid is capable of pulling the disc forward from its normal position over the mandibular condyle.[386] While the muscle fibers that do insert into the disc are located primarily at the medial portion, not all such fibers insert directly into the disc but rather only insert into the capsule.[30] Moreover, research on cadaver specimens has indicated that muscle fibers inserting into the disc or the condyle are not adequately differentiated into inferior and superior heads.[30,387] Carpentier and colleagues postulated that the two heads did not have distinct independent actions and concluded that the lateral pterygoid was not likely a significant cause of disc displacement.[30] The inferior lamina of the posterior attachment is considered to be the primary restraint preventing the disc from moving forward. Injury to this ligament has been proposed as the cause of disc displacements,[388] based on evidence in a cadaver model that suggested a superficial injury to the inferior section of the posterior attachment resulted in ADD.

The anterior disc displacement may reflect a shift in location purely in the sagittal plane, or it may, as stated previously, also include some medial aspect (antero–medial displacement) such that the disc is rotated medially as well as well as displaced. Displacements of the disc may also be antero–lateral. Displacements may also occur solely within the coronal plane, such that the intermediate zone of the disc is either medial or lateral to the anatomically normal position, but these are not well-described in the literature.[389] Finally, posterior disc displacement (when a portion of the disc is found posterior to the top of the condyle) is rare but has been reported in the literature.[390]

Based on available evidence and considering the many intersecting proposed mechanisms for articular disc disorders, it is less likely that any particular event causes an internal derangement, and, consistent with TMD as a complex disease, it is more likely that a combination of mechanisms related to the anatomy of the joint and the facial skeleton, connective tissue composition, generalized joint laxity, acute or chronic trauma, and chronic loading of the joint increases the susceptibility of certain individuals to a disturbance of the restraining ligaments and displacement of the disc.

Clinical Manifestations

Disc displacement is divided into stages based on signs and symptoms combined with the results of diagnostic imaging. A variety of staging systems have been proposed (e.g., Wilkes criteria),[391] but a sufficient and simple classification system divides ADD into: (1) anterior disc displacement with reduction (clicking joint); (2) anterior disc displacement with intermittent locking; and (3) anterior disc displacement without reduction (closed lock).[392]

Anterior Disc Displacement with Reduction (ADDwR)

Some part of the articular disc has been displaced anteriorly from its position on top of the condyle due to some combination of elongation of the restraining ligaments, alteration in the form or shape of the disc, or thinning of the posterior band presumably allowing the disc to migrate anteriorly over time. A reducing disc displacement ADDwR is common in the general population, and a clicking or popping joint is of little clinical significance unless it is accompanied by pain, loss of function, and/or intermittent locking. An individual may seek professional advice regarding treatment of an audible click that is not accompanied by pain but that may be socially embarrassing.[209]

Palpation or auscultation of the TMJ may reveal a clicking or popping sound during either opening and closing mandibular movements; if a sound occurs during both opening and closing, it is called a reciprocal click. Any clicking or popping sound due to ADDwR may occur during opening, closing, lateral movements, protrusive movement, or any combination of these movements. The clicking sound of an ADD occurs due to relative movement of the disc while the condyle translates. Clinicians examining patients with ADD may observe a deflection of the mandible early in the opening cycle prior to the click with correction to the midline after the click, but this is a variable finding and deflection due to muscle guarding must be distinguished. Diagnostic sensitivity and specificity of clinical tests for ADD are fair to poor, because joints without ADD may click and joints with ADD may not click. Pain from palpation of the TMJ may be present when ADD is accompanied by capsulitis or synovitis, as seen in some patients, yet the reason the majority of patients with ADD remain asymptomatic across the lifespan is not completely understood.[393,394] The implication for caution regarding necessity of any treatment for this condition is self-evident: an ADD should be left alone in the absence of clear symptoms localized to the joint.

Anterior Disc Displacement with Reduction, with Intermittent Locking

An ADD may be stable over time, or it may, either occasionally or progressively, shift into an intermittent lock, lasting seconds to minutes and which resolves on its own. This limited mandibular opening occurs due to disc interference with the normal translation of the condyle. Specific behaviors, such as opening the mouth during mastication, yawning, or certain speech movements or nonverbal expression, may suddenly result in the inability to fully open the mouth (i.e., fully translate the affected condyle). The sudden restriction may or may not be accompanied by pain. The resolution of the locking episode may occur spontaneously or may occur as a result of the individual moving the mandible in such a manner as to overcome the locking disc.

Anterior Disc Displacement without Reduction (ADDwoR; also termed Closed Lock)

ADD without reduction is often referred to as a (persistent) closed lock and occurs in three variants: acute closed lock that is persistent (i.e., does not resolve in the absence of treatment); chronic closed lock as the extension of an acute lock over time and characterized by continued limitation in jaw range of motion; and the chronic closed lock that exhibits some or complete resolution of the limitation in range of motion. A patient with an acute closed lock will often have a history of a long-standing TMJ click; that click may have also previously occurred with intermittent locking, or that click may have never previously been associated with an intermittent lock but rather abruptly disappeared followed by a sudden initial restriction in mandibular opening. The first-time occurrence of a persistent acute closed lock is typically accompanied by pain localized to the joint and exacerbated during mandibular opening (especially at maximum opening), limited lateral movement to the side contralateral to the affected joint, and deviation of the mandible to the affected side during maximum mouth opening. Collectively, these findings point to the condyle on the affected side which does not translate normally. In addition, the affected condyle will not be as palpable on examination. In chronic closed lock, the symptoms associated with the acute stage typically remit but opening is initially restricted to about the same extent, and over time the disc will deform and maximum mouth opening will gradually improve. The displacement of the disc exposes the posterior attachment to compression by the condyle. The posterior attachment has been shown to react to the change by depositing hyaline in the connective tissue[395] and has been called a "pseudomeniscus" or "pseudodisc."[396,397]

An important caveat to an acute closed lock that is associated with disc displacement without reduction was proposed by Nitzan and Etsion.[398] They suggested that adhesion of the disc in the fossa might cause acute closed lock,[398] which can occur with both normal discs as well as displaced discs. Adhesion occurs when hyaluronic acid and associated phospholipids are degraded. Support for this hypothesis is the immediate and generally stable improvement of

mouth opening after arthrocentesis,[398] a procedure in which saline is injected into the inferior and superior joint spaces in order to temporarily expand the spaces and break any adhesions. In fact, this procedure can probably be an effective treatment for a significant number of patients, but the specific clinical characteristics of those for whom it would be effective remain poorly defined. The phenomenon of adhesions between disc and adjacent bone may have a greater role beyond the acute closed lock, as based on the variability of how the fundamental "types" of disc displacements actually present in patient histories, but this has not been systematically studied. The clinician, however, should consider that while anterior disc displacements are commonly classified as with versus without reduction, a spectrum may be more likely.

Posterior Disc Displacement

Posterior disc displacement has been described as the condyle slipping over the anterior rim of the disc during opening, with the disc being caught and brought backward in an abnormal relationship to the condyle when the mouth is closed. The disc is folded in the dorsal part of the joint space, preventing full mouth closure.[399] The clinical features are: (1) a sudden inability to bring the upper and lower teeth together in maximal occlusion; (2) pain in the affected joint when trying to bring the teeth firmly together; (3) displacement anteriorly of the mandible on the affected side; (4) restricted lateral movement to the affected side; and (5) no restriction of mouth opening.[399]

Coronal Disc Displacement

There is little information regarding coronal plane disc displacements other than as part of an anterior disc displacement (e.g., rotated disc). The little information available suggests that coronal displacements are not associated with any identified characteristics, such as pain complaint, palpation pain, or limitation in mandibular movement. Consequently, coronal plane displacements may have little to no clinical relevance.[389]

Subluxation Associated Disc Displacement

Another type of intracapsular disorder involving the disc occurs when the condyle moves beyond its normal maximal boundary in the open jaw position (subluxation or dislocation of the condyle). Subluxation/dislocation of the condyle often coexists with a disc displacement. The form and steepness of the fossa has been considered a contributing factor in the frequent coexistence of subluxation with disc displacement and highlights the dynamic functional character of the intracapsular disorders. In contrast, Bell[400] pointed to the intrinsic role of muscle tone; he suggested that subluxation (or dislocation) occurs due to a combination of fossa steepness and increased activity of the masticatory elevator muscles preventing the condyle from translating posteriorly around the eminence during the closing phase of mandibular movement.

Management

The clinician must distinguish the patient with myofascial pain and coincidental TMJ clicking from the patient whose pain is directly related to disc displacement. In making this distinction, the clinician will be able to formulate an appropriate treatment selection.

Longitudinal studies demonstrate that most symptoms associated with ADD resolve over time either with no treatment or with minimal conservative therapy.[401] One study of patients with symptomatic anterior disc displacement without reduction experienced resolution without treatment in 75% of cases after 2.5 years.[402] A 30-year outcome study of natural course demonstrated similar findings.[403] Since symptoms associated with anterior disc displacement with and without reduction tend to decrease with time, painful clicking or locking should initially be treated with conservative therapies aimed at reducing symptoms and allowing the body to respond adaptively. Similarly, the clinician should not treat asymptomatic clicking on the assumption that such clicking will inevitably progress to painful clicking or locking.

Recommended treatments for symptomatic ADD include, as a starting point, self-management strategies: patient education, regular use of thermal agents, pain-free chewing, yawn control, simple joint mobility, and reducing parafunctional behaviors. In addition to these core methods, the following can be added based on indication: splint therapy, physical therapy including manual manipulation, and anti-inflammatory drugs. Finally, for more advanced problems involving ADD that have failed conservative therapy, arthrocentesis, and arthroscopic lysis and lavage, arthroplasty, and vertical ramus osteotomy may be considered. Although most of these nonsurgical and surgical techniques are effective in decreasing pain and in increasing the range of mandibular motion, the abnormal position of the disc is not usually corrected.[207]

Anterior Disc Displacement with Reduction

Patients with TMJ clicking or popping that is not accompanied by pain or locking ***do not require*** therapy. Both flat-plane stabilization splints that do not change mandibular position and anterior repositioning splints have been used to treat painful clicking. Anterior repositioning splints maintain the mandible in an anterior position with the disc in a reduced position, preventing the condyle from closing posterior to the disc. One meta-analysis concluded that repositioning splints were more effective than stabilization splints in eliminating both clicking and pain in patients with

ADD.[404] However, it also appears that appliances may only reduce symptoms quicker, with noted outcomes being the same at 3 months regardless of whether an appliance was added to the self-management treatments or not.[405] Clinicians must weigh the potential benefits of using repositioning splints against the potential adverse effects that include tooth movement and open bite. Clinicians have advocated techniques that are designed to "recapture" the disc to its normal position, but splint therapy, arthrocentesis, or arthroscopy rarely correct disc position and function.[406]

Anterior Disc Displacement without Reduction

Some patients with closed lock may present with little or no pain, whereas others have severe pain during mandibular movement. Treatment options should depend on the degree of pain and limitation associated with the ADD. Management of a locked TMJ may be nonsurgical or surgical. The goals of successful therapy are to eliminate pain, restore function, and increase the range of mandibular motion. Correcting the disc position is not necessary to achieve these goals.

Patients who present with restricted movement but minimal pain frequently benefit from manual manipulation and an exercise program designed to increase mandibular motion. A flat-plane occlusal stabilization appliance to decrease the adverse effects of sleep bruxism on the affected joint is appropriate. There is no evidence to suggest that repositioning the mandible using oral appliance therapy is indicated as a treatment for ADD without reduction. Sato and colleagues reported that a combination of a flat-plane stabilization splint and anti-inflammatory drugs was successful in reducing pain and increasing the range of motion in over 75% of patients.[401] The success of this therapy was attributed to decreased inflammation and to the gradual elongation of the posterior attachment, permitting increased translation of the condyle. In a multigroup RCT, Schiffman and colleagues[407] randomized individuals with severe closed lock to medical management, rehabilitation, arthroscopic surgery, or arthroplasty; each of the surgical treatments included post-operative rehabilitation. At 5 years, all treatments resulted in equal improvement as based on symptoms and examination findings, and no treatment was superior, indicating that medical management or rehabilitation should be regarded as sufficient treatments.

Patients with severe pain on mandibular movement may benefit from either arthrocentesis or arthroscopy. Flushing the joint and deposition of intra-articular corticosteroids to decrease inflammation or sodium hyaluronate to increase joint lubrication and decrease adhesions have been reported to decrease pain associated with nonreducing disc displacements.[408,409] A significant reduction in the range of movement preprocedurally was considered a risk factor for delay in postprocedural improvement.[410]

Kurita and colleagues reported on a 2.5-year follow-up on patients with ADD without reduction. During the observation period, approximately 40% of patients became asymptomatic, 33% continued to have symptoms but at a decreased level, and 25% had no improvement. An association was noted between continued TMD symptoms and radiographically detectable degenerative changes.[411]

Subluxation Associated Disc Displacement

Surgical treatments that modify the steepness or flatten the eminence have been recommended, but controlled outcomes do not yet exist for any treatment approach.

Temporomandibular Joint Arthritis

Osteoarthritis (Degenerative Joint Disease, DJD)

Description

Degenerative joint disease (DJD), is primarily a disorder of articular cartilage and subchondral bone, with secondary minimal inflammation of the synovial membrane. It is a localized joint disease without systemic manifestations. The process begins in loaded articular cartilage that thins, clefts (fibrillation), and then fragments leading to sclerosis of underlying bone, subchondral cysts, and osteophyte formation.[412] The articular changes are essentially a response of the joint to chronic microtrauma or pressure. Microtrauma may be in the form of continuous abrasion of the articular surfaces as in natural wear associated with age or due to increased loading related to chronic parafunctional activity. The fibrous tissue covering in patients with degenerative disease is preserved.[413] This may be a factor in remodeling and the recovery that is usually expected in osteoarthrosis and osteoarthritis of the TMJs.[414]

The relationship between internal derangements and DJD has been, until recently, unclear. A higher frequency of radiographic signs of DJD was observed in cross-sectional studies of subjects with disc displacement without reduction[413], and similarly a significant association was observed between an anterior displaced disc and osteoarthritis of the TMJ.[415] Yet, longitudinal observation (8 years) utilizing reliable imaging interpretation indicates that the majority of both disc displacement and DJD diagnoses (76%, and 71%, respectively) remain stable, that approximately equal proportions worsen and improve diagnostically across time, and that change in soft tissue and hard tissue are unrelated.[416] Consequently, DJD of the TMJ remains best considered a disease of aging in which genetic factors play an important role. By the age of 40 a majority of individuals have radiographic evidence of DJD of the TMJ. Secondary DJD results from a known underlying cause, such as trauma, congenital dysplasia, or metabolic disease.

Risk factors for symptomatic DJD include gender, diet, genetics, and psychological stress. Epidemiologic studies suggest a female predisposition to TMDs overall, including osteoarthritis.[52] The possibility that a diet of excessively hard or chewy foods might cause increased loads on the joints and lead to degenerative changes has been proposed. Psychological stress leading to parafunctional activities such as tooth clenching or bruxism has been proposed as a factor which increases loading at the TMJ. The present disease model for DJD of the TMJ suggests that excessive mechanical loading on the joints produces a cascade of events leading to the failure of the lubrication system and destruction of the articular surfaces. These events include the generation of free radicals, the release of proinflammatory neuropeptides, signaling by cytokines, and the activation of enzymes capable of matrix degradation.[417]

Clinical Manifestations

DJD of the TMJ begins early in life and has been observed in over 20% of the TM joints in individuals older than 20 years.[418] A study of patients younger than 30 years old presenting to a TMD clinic demonstrated that two-thirds of the patients had degenerative changes detected on tomograms.[419] The incidence of degenerative changes increases with age. Degenerative changes are found in over 40% of patients older than 40 years. Many patients with mild to moderate DJD of the TMJ have no symptoms, although arthritic changes are observed on radiographs.

Degenerative changes of the TMJ detected on radiographic examination may be incidental and may not be responsible for facial pain symptoms or TMJ dysfunction; however, some degenerative changes may be underdiagnosed by conventional radiography because the defects are confined to the articular soft tissue. These soft tissues changes are better visualized with MRI,[420] but whether such improvement in detection is reflected in a better outcome by more targeted treatment provided earlier has not been evaluated.

Patients with symptomatic DJD of the TMJ experience pain directly over the affected condyle, limitation of mandibular opening, crepitus, and a feeling of stiffness after a period of inactivity. Examination reveals tenderness and crepitus on intra-auricular and pre-auricular palpation. Deviation of the mandible to the painful side is a characteristic finding. Radiographic findings in DJD may include narrowing of the joint space, irregular joint space, flattening of the articular surfaces, osteophyte formation, anterior lipping of the condyle, and the presence of subchondral cysts. These changes may be seen best on CT scans (see Figures 10-13A and 10-13B). The presence of joint effusion is most accurately detected in T2-weighted MRIs; while interexaminer reliability for detection of effusions is overall acceptable (kappa = 0.64),[421] smaller effusions are more difficult to reliably identify. Whether MR-depicted effusion in the TMJ is important clinically has not yet been determined.[264]

Management

DJD of the TMJ can usually be managed by conservative treatment with an emphasis on physical therapy and NSAIDS that control both pain and inflammation. In osteoarthritis, significant improvement is noted in many patients after 9 months, and a "burning out" of many cases occurs after 1 year.[422] Nonsurgical management may consist of jaw self-management, including behavior modification, heat application, soft diet, physical therapy including jaw exercises, and NSAIDS. Occlusal appliances may be helpful when sleep bruxism is an etiologic factor. When nonsurgical management is not effective in reducing either pain or dysfunction, a more invasive method may be indicated, such as a corticosteroid injection.[423]

Arthrocentesis is a relatively conservative joint procedure if intra-articular steroid injection is ineffective.[424] Arthroscopy, arthroplasty, and arthrotomy and joint replacement are surgical procedures that may be indicated in a small percentage of cases depending on the response to more conservative treatment and the severity of pain and disability.[425] It seems prudent to manage a patient with conservative treatment for at least several months before considering surgery unless severe pain or dysfunction persists after an adequate trial of nonsurgical therapy. Only when there is significant TMJ pain or disabling limitation of mandibular movement is surgery indicated.

Rheumatoid Arthritis

Description

Rheumatoid arthritis (RA) is an inflammatory, autoimmune disease primarily affecting periarticular tissue and secondarily bone. The disease process starts as a vasculitis of the synovial membrane. It progresses to chronic inflammation marked by an intense round cell infiltrate and subsequent formation of granulation tissue. The cellular infiltrate spreads from the articular surfaces eventually to cause an erosion of the underlying bone. The percentage of RA patients with TMJ involvement ranges from 40% to 80%, depending on the group studied and the imaging technique used.[420,426] Studies using conventional radiography and tomography find fewer abnormalities than changes detectable on CT.[420] TMJ changes on CT were found in 88% of RA patients, but changes were also detected in more than 50% of controls.[426] Moreover, changes detected using conventional CT do not correlate well with clinical complaints. Yet, using high-resolution CT, condylar changes are detected in approximately 80% of RA patients.[427] It should be noted that many patients with radiographic TMJ changes do not report pain

and have few other symptoms or clinical signs, so a diagnosis of a clinically significant TMD requiring treatment should not be based on imaging alone.

Radiographic changes in the TMJ associated with RA may include a narrow joint space, destructive lesions of the condyle, and limited condylar movement. There is little evidence of marginal proliferation or other reparative activity in RA in contrast to the radiographic changes often observed in DJD. High-resolution CT of the TMJs in RA patients shows erosions of the condyle and glenoid fossa that are not detected on conventional radiography.[420]

Clinical Manifestations

The TMJs in RA are usually involved bilaterally. Pain is usually associated with the early acute phase of the disease but is not a common complaint in later stages. Other symptoms often noted include morning stiffness, joint sounds, and tenderness and swelling directly over the joint.[428] The symptoms are usually transient in nature, and only a small percentage of patients with RA of the TMJs experience permanent clinically significant disability. The most consistent clinical findings include pain on joint palpation, limited mouth opening, and crepitus. Micrognathia and an anterior open bite are commonly seen in patients with juvenile idiopathic arthritis. Ankylosis of the TMJ related to RA is rare.

If RA is suspected after a history and physical exam, laboratory tests including rheumatoid factor, antinuclear antibody, ESR, and C reactive protein should be ordered. Patients with positive laboratory results should be referred to a rheumatologist or their family physician.

Seronegative Spondyloarthropathies

Several arthropathies are distinct from RA and are not associated with positive serology (rheumatoid factor). These disorders, characterized by arthritis, are known as the seronegative spondyloarthropathies and include ankylosing spondylitis (AS), psoriatic arthritis (PA), and reactive arthritis (Reiter's syndrome). The TMJs can be involved in these arthropathies. The clinical manifestations are joint pain with function, limited mouth opening, and erosion of the superior surface of the condyle on radiography. There are no specific findings that are pathognomonic of involvement of the TMJs.

AS primarily involves the spine, although other joints are often involved. It causes inflammation that can lead to new bone formation, causing the spine to fuse, reducing mobility and producing a forward, stooped posture. The disease usually involves the sacroiliac joints where the spine joins the pelvis. TMJ involvement has been reported in AS, but the prevalence has not been established. TMJ involvement has been estimated at about 15–20% of patients with AS.[429] Significantly decreased mouth opening, TMJ pain, crepitus, and muscle pain are frequent clinical findings.[430]

PA is a chronic disease characterized by psoriasis and inflammation of the joints. Approximately 10% of patients who have psoriasis develop joint inflammation. The skin lesions may precede the joint involvement by several years. PA commonly involves the fingers and spine and pitting of the nails is common.

The masticatory system is affected in about 50% of patients with PA.[431] The symptoms of PA of the TMJ are similar to those noted in RA, except that the signs and symptoms are likely to be unilateral. TMJ pain with chewing is a common finding,[431] and limitation of mouth opening may occur.[432] The most common radiographic finding is erosion of cortical outline of the mandibular condyle.

Reactive arthritis, also called Reiter's syndrome, is a nonpurulent joint inflammation triggered by infection elsewhere in the body, such as a gastrointestinal Salmonella infection or a chlamydial genital infection. The symptoms include polyarthritis, conjunctivitis, and superficial oral ulcers. The arthritis is characteristically unilateral and most frequently involves the joints of the lower extremity.[433] A clinical and radiographic study of patients with reactive arthritis demonstrated that approximately 10% had temporomandibular joint involvement.[434]

Connective Tissue Disease

Connective tissue diseases that affect the TMJ include systemic lupus, systemic sclerosis (scleroderma), undifferentiated connective tissue disease, and mixed connective tissue disease. These disorders are addressed in Chapter 19 "Immunological Diseases." When the TMJ is involved, the clinical presentation is similar to other disorders causing inflammation and subsequent degenerative changes. The history will usually be positive for involvement of other joints. A clinical examination of the masticatory system supplemented with diagnostic imaging, as indicated based on the history of other joint involvement, is usually adequate to confirm involvement of the TMJ.

Diseases Associated with Crystal Deposits in Joints

Gout is a disease that includes hyperuricemia, recurrent arthritides, renal disease, and urolithiaisis. The disease primarily affects men. Acute pain in a single joint is the characteristic clinical presentation. The TMJ is rarely involved. Calcium pyrophosphate deposition is also known as pseudogout. Deposits of microcrystals in affected joints are responsible for the clinical manifestations. Examination of aspirated synovial fluid from the involved joint by polarized light and detection of monosodium urate crystals confirms the diagnosis.

Treatment includes colchicine, NSAIDs, and intra-articular steroid injection. Pseudogout affecting the TMJ has been treated with colchicine and arthrocentesis.[435]

Synovial Chondromatosis

Synovial chondromatosis (SC) is an uncommon benign disorder characterized by the presence of multiple cartilaginous nodules of the synovial membrane that break off resulting in clusters of free-floating loose calcified bodies in the joint. It is theorized that SC originates from embryonic mesenchymal remnants of the subintimal layer of the synovium that become metaplastic, calcify, and break off into the joint space.[436] SC most commonly involves one joint, but cases of multi-articular SC have been reported.[437] Some cases appear to be triggered by trauma, whereas others are of unknown etiology. The knee and elbow are the most commonly involved joints.

More sophisticated imaging techniques, such as CT and arthroscopy, have revealed cases of SC that previously would have received other diagnoses, causing authors of recent publications to suspect that SC is more common than previously believed.[438] Extension of SC from the TMJ to surrounding tissues (including the parotid gland, middle ear, or middle cranial fossa) may occur.[439]

Slow progressive swelling in the preauricular region, pain, and limitation of mandibular movement are the most common presenting features. TMJ clicking, locking, crepitus, and occlusal changes may also be present. The extension of the lesion from the joint capsule and involvement of surrounding tissues may make diagnosis difficult, causing SC to be confused with parotid, middle ear, or intracranial tumors. Cases of SC that were mistaken for a chondrosarcoma have been reported. Intracranial extension may lead to neurologic deficits such as facial nerve paralysis. Panoramic radiographs may not lead to the diagnosis due to superimposition of cranial bones that may obscure the calcified loose bodies.[440] A CT scan or an MRI should be obtained if SC is suspected after clinical evaluation. The lesion may appear as a single mass or as many small loose bodies.[441]

Treatment should be conservative and consist of removal of the mass of loose bodies. This may be done arthroscopically when only a small lesion is present, but arthrotomy is often required for larger lesions.[442,443] The synovium and articular disc should be removed when they are involved. Lesions that extend beyond the joint space may require extensive resection.

Septic Arthritis

Septic arthritis of the TMJ most commonly occurs in patients with previously existing joint disease, such as RA or underlying medical disorders—particularly diabetes. Patients receiving immunosuppressive drugs or long-term corticosteroids also have an increased incidence of septic arthritis. The infection of the TMJ may result from blood-borne bacterial infection or by extension of infection from adjacent sites, such as the middle ear, tonsils, maxillary molars, and parotid gland.[444] Gonococci are the primary blood-borne agents causing septic arthritis in a previously normal TMJ, whereas *Staphylococcus aureus* is the most common organism involved in previously arthritic joints.[445]

Symptoms of septic arthritis of the TMJ include trismus, deviation of the mandible to the affected side, severe pain on movement, and an inability to occlude the teeth owing to the presence of inflammation in the joint space. Examination reveals redness and swelling over the involved joint. In some cases, the swelling may be fluctuant and extend beyond the region of the joint.[446] Large tender cervical lymph nodes are frequently observed on the side of the infection. Diagnosis is made by detection of bacteria on Gram's stain and culture of aspirated joint fluid.

Serious sequelae of septic arthritis include osteomyelitis of the temporal bone, brain abscess, and ankylosis. Facial asymmetry may accompany septic arthritis of the TMJ, especially in children. Diagnosis is aided by MRI, CT, and synovial fluid analysis.

Evaluation of patients with suspected septic arthritis must include a review of signs and symptoms of gonorrhea, such as purulent urethral discharge or dysuria. The affected TMJ should be aspirated and the fluid obtained tested by Gram's stain and cultured for *Neisseria gonorrhoeae*.

Treatment of septic arthritis of the TMJ consists of surgical drainage, joint irrigation, and 4–6 weeks of antibiotics.

OTHER DISORDERS

An additional set of less common disorders is described below for purpose of differential diagnosis and contrast with the more common conditions, above.

Myositis

In addition to the far more prevalent myalgia and myofascial pain, the masticatory muscles may be occasionally affected by inflammation. The inflammation may be local as well as systemic in nature. Localized inflammation, known as myositis, has been reported as a result of direct trauma to the muscle, infections such as a submasseteric abscess or pericoronitis, and procedures such as third molar extraction or routine dentistry.[447,448] When calcifications result from the inflammation of the muscle, the condition is referred to as myositis ossificans. These calcifications can be detected on

either CT or MRI. Inflammation of the masticatory muscles can also result from diseases such as polymyositis or dermatomyositis (see Chapter 19 "Immunological Diseases").

The patients characteristically have a history of unilateral jaw pain and decreased mandibular range of motion. Examination findings include erythema, tenderness, and swelling over the affected muscle, usually the masseter, and a restricted range of mandibular movement. The tenderness to palpation is usually severe when injury is the cause of the myositis, such that only very light palpation will be permitted by the patient and the pain is classified as allodynia. Laboratory tests will show elevated white blood cells in patients with acute infection and elevated serum muscle enzymes in patients with an inflammatory myopathy such as dermatomyositis and polymyositis.

Treatment of myositis resulting from infection includes use of antibiotics and surgical drainage when necessary. For myositis not resulting from infection, NSAIDS and rest have been reported as helpful in the initial phase, supplemented by mobility exercises and physical therapy after the initial allodynia has subsided.

Contracture

Contracture of the muscles of mastication can result from fibrosis of muscle, ligament, and tendon tissue related to trauma, infection, or head and neck radiation therapy. Contracture also occurs in response to persistent limitation in muscle range of movement, such as a myalgia that is inadequately treated with mobilization to regain normal muscle length. The limited mandibular range of motion may be mistaken for articular disc displacement or muscle guarding, although contracture does not directly result in pain or tenderness of the muscle or joint.[187,449] The differential diagnosis of limited movement can be particularly difficult when anterior disc displacement without reduction results in limited jaw opening and the nonreducing disc does not respond over time to permit normal condylar movement; the masseter muscle can undergo contracture due to the limited mobility of the condyle. Long-term, it is both the nonreducing disc and the masseter contracture that may restrict movement.

Examination will reveal a decreased maximum mandibular opening with a reproducible firm stop, deviation of the jaw to the affected side with an absence of tenderness.

Treatment of contracture is slow and difficult; with increasing chronicity, the outcome is increasingly unpredictable with respect to expected therapeutic gains. While stretching alone may help, typically manual mobilization of the soft tissue is required. Identifying an end-point for such treatment is important, with maintenance of the restricted mobility becoming the more realistic therapeutic goal.

Trismus

Trismus is a CNS-driven activation of the motor neurons resulting in muscle contraction as a protective behavior. Trismus, myositis, and contracture exhibit similar restriction in mobility, but they are distinguished by history and examination: trismus is a noninflammatory secondary response to injury (e.g., needle injection during mandibular block) or nociception (cancer pain) to a tissue different from the source of the restriction.

In order to minimize trismus resulting from head and neck radiation, a range of motion exercises should be instituted as early as possible. Management of trismus interfering with function includes instruction in home exercises and treatment by a physical therapist when necessary (see Chapter 8).

Developmental Disturbances

Developmental disturbances involving the TMJ may result in anomalies in the size and shape of the condyle. Local factors, such as trauma or infection, can initiate condylar growth disturbances, such as hyperplasia, hypoplasia, agenesis, and the formation of a bifid condyle, all of which may be evident on radiographic examination of the joint. True condylar hyperplasia usually occurs after puberty and is completed by 18 to 25 years of age. Limitation and deviation of mouth opening and facial asymmetry may be observed.

Facial asymmetry often results from disturbances in condylar growth because the condyle is a site for compensatory growth and adaptive remodeling. The facial deformities associated with condylar hyperplasia involve the formation of a convex ramus on the affected side and a concave shape on the normal side. If the condylar hyperplasia is detected and surgically corrected at an early stage, the facial deformities may be prevented. Bone scintigraphy is recommended as part of a presurgical evaluation to identify activity in the joint.[450]

Condylar aplasia is a congenital condition where the condyles did not develop before birth, while hypoplasia can occur as a result of a congenital or acquired anomaly. When congenital, it is usually associated with syndromes such as Treacher Collins Syndrome, Pierre Robins syndrome, or other syndromes affecting the first and second branchial arches (Figure 10-14). Deviation of the mandible to the affected side and resultant facial deformities are associated with unilateral agenesis and hypoplasia of the condyle. Rib grafts have been used to replace the missing condyle to minimize the facial asymmetry in agenesis. In cases of hypoplasia, there is a short wide ramus, shortening of the body of the mandible, and antegonial notching on the affected side, with elongation of the mandibular body and flatness of the

face on the opposite side. Early surgical intervention is again emphasized to limit facial deformity.

Hyperplasia of the coronoid process is an uncommon cause of restricted mouth opening but may be missed in the differential diagnosis of restricted mouth opening. One study estimated that 5% of 163 patients had restricted mouth opening due to elongation of the coronoid process.[451] Careful clinical examination can include coronoid hyperplasia into the differential diagnosis, readily confirmed by plain or CT imaging.

The bifid condyle is a rare condition affecting less than 1% of the population and can occur unilaterally or bilaterally. It is seen as a groove or depression midline of the condylar head. Even though this is usually an incidental finding on radiographs, some patients with bifid condyle present with limited range of motion and/or arthralgia.

Fractures

Fractures of the condylar head and neck often result from a blow to the chin (see Figure 10-16). The patient with a condylar fracture usually presents with pain and edema over the joint area and limitation and deviation of the mandible to the injured side on opening. Bilateral condylar fractures may result in an anterior open bite. The diagnosis of a condylar fracture is confirmed by diagnostic imaging. Intracapsular nondisplaced fractures of the condylar head are usually not treated surgically. Early mobilization of the mandible is emphasized to prevent fibrous or bony ankylosis.

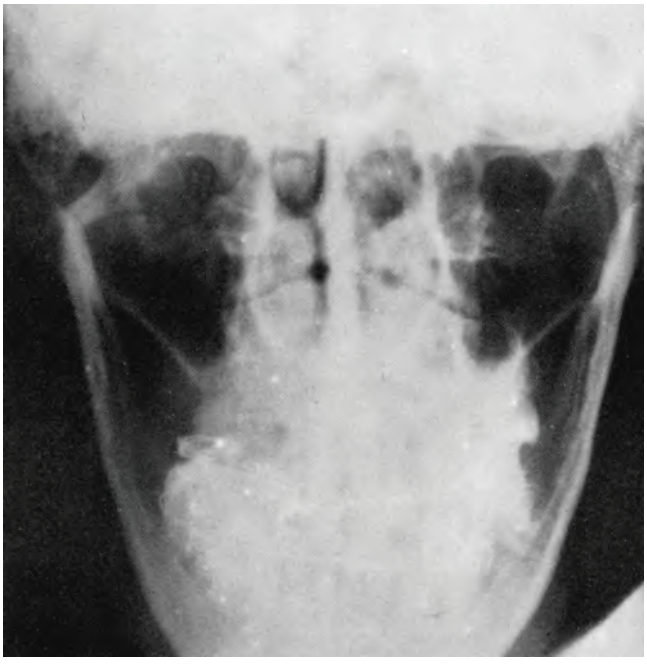


Figure 10-16 Fractured and medially displaced condyle.

Dislocation

In dislocation of the mandible, the condyle is positioned anterior to the articular eminence and cannot return to its normal position without extrinsic manipulation. This disorder contrasts with subluxation, in which the condyle moves anterior to the eminence during wide opening but is able to return to the resting position without extrinsic manipulation. Notably, subluxation is a variation of normal function and the normal range of motion of the condyle is not limited to the fossa but does extend anterior to the height of the eminence.

Dislocation of the mandible can occur from both traumatic and atraumatic causes. Traumatic causes include procedures such as endotracheal intubation or any other procedure that involves oral access to internal organs. Atraumatic mandibular dislocation usually results from muscular incoordination in wide opening during eating, yawning, or laughing. Mandibular dislocation may be unilateral or bilateral. The typical complaints of the patient with dislocation are an inability to close the widely open jaws and pain related to muscle spasm. On clinical examination during dislocation, a deep depression of the skin may be observed in the preauricular region corresponding to the condyle being positioned anterior to the eminence.

The condyle can usually be repositioned without the use of muscle relaxants or sedation. If muscle spasms are severe and reduction is difficult, the use of intravenous diazepam (approximately 10 mg) can be beneficial. The practitioner who is repositioning the mandible should stand in front of the seated patient and place his or her thumbs lateral to the mandibular molars on the buccal shelf of bone; the remaining fingers of each hand should be placed under the chin. The condyle is repositioned by a downward and backward movement. This is achieved by simultaneously pressing down on the posterior part of the mandible while raising the chin. As the condyle reaches the height of the eminence, it can usually be guided posteriorly to its normal position.

Postreduction recommendations consist of limiting mandibular movement and the use of NSAIDs to lessen inflammation. The patient should be cautioned not to open wide when eating or yawning because recurrence is common, especially during the period initially after repositioning. Long periods of immobilization are not advised due to the risk of fibrous ankylosis.

Chronic recurring dislocations have been treated with surgical and nonsurgical approaches. Injections of sclerosing solutions have been used but are no longer frequently utilized because of difficulty in controlling the extent of fibrosis and condylar limitation. Various surgical procedures have been advocated for treating recurrent dislocations of the mandible; these include bone grafting to the eminence, lateral pterygoid myotomy, eminence reduction, eminence augmentation with implants, shortening the temporalis ten-

don by intraoral scarification, plication of the joint capsule, and repositioning of the zygomatic arch.

Ankylosis

True bony ankylosis of the TMJ involves fusion of the head of the condyle to the temporal bone. Trauma to the chin is the most common cause of TMJ ankylosis, although infections also may be involved.[446] The primary sources of these infections were the middle ear, teeth, and the hematologic spread of gonorrhea. Children are more prone to ankylosis because of greater osteogenic potential and an incompletely formed disc. Ankylosis frequently results from prolonged immobilization following condylar fracture. Limited mandibular movement, deviation of the mandible to the affected side on opening, and facial asymmetry may be observed in TMJ ankylosis. Osseous deposition may be seen on radiographs. Ankylosis has been treated by several surgical procedures. Gap arthroplasty using interpositional materials between the cut segments is the technique most commonly performed.

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11

Neuropathic Orofacial Pain

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INTRODUCTION

Pain is a multifaceted experience involving physiological, cognitive, and emotional aspects. Reflecting this complexity, pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1]

Acute pain resulting from injury or a painful stimulus generally results in a withdrawal reaction, ensuring minimal or no damage to the organism. If tissue damage occurs, a local inflammatory response is initiated causing increased sensitivity in peripheral nociceptors (peripheral sensitization) and in dorsal horn neurons associated with pain transmission (central sensitization). Usually, the injured area becomes sensitive to light touch (allodynia) and hypersensitive to painful stimuli (hyperalgesia). The injured area is painful during the healing phase, in most cases the pain is resolved with no residual disability following healing.

Chronic pain, on the other hand, is not directly associated with injury; it continues beyond healing and has no value for the organism's survival. It may be associated with primary or reactive changes in the nervous system that perpetuate the sensation of pain even in the absence of an active injury. Chronic pain is often not a symptom but a disease in itself that inflicts severe physical and emotional suffering on the individual. Chronic orofacial pain may be subdivided into three main symptomatic classes: musculoskeletal, neurovascular, and neuropathic.[2]

This chapter focuses on neuropathic orofacial pain (NOP); that is, painful neuropathies affecting oral and facial structures.

NEUROPATHIC PAIN

Neuropathic pain (NP) is defined as "pain arising as a direct consequence of any lesion or disease affecting the somatosensory system,"[3,4] which induces chronic pain that may originate from a peripheral nerve, a ganglion, the dorsal root, or from the central nervous system (central NP).

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The best estimate of NP prevalence is between 6.9–10% of population.[5] The exact prevalence is unclear, in part due to inconsistent definitions and clinical criteria. The prevalence of syndromes involving NP is expected to increase together with life expectancy and disease survival rates. The relatively limited existing treatment options for NP, largely pharmacologic, may lead to impaired quality of life and extensive usage of health care facilities.[6,7]

The International Headache Society's (IHS's) classification and the International Classification of Headache Disorders (ICHD) can serve as the basis for the definitions and descriptions of the clinical NOP syndromes described in this chapter.[8] We review all the painful orofacial neuropathies except for the rarer pain conditions, such as optic neuritis, ischemic ocular motor nerve palsy, Tolosa–Hunt syndrome, paratrigeminal oculosympathetic (Raeder's) syndrome, and recurrent painful opthalamoplegic neuropathy.

The quality of pain across many NPs is often described as burning, sharp, or electric. The pain may be evoked (stimulus-dependent; e.g., mechanical, thermal) or spontaneous (stimulus-independent)[9] with hyperalgesia, allodynia (e.g., positive sensory sign) and/or numbness (e.g., negative sensory signs).[10] Quantitative Sensory Testing (QST) can be used to evaluate the patients. In the absence of advanced QST tools, sensory function can be assessed using a simple pin, a blunt instrument, warmed and cooled implements, or cotton wool.[11]

Neuropathic Orofacial Pain

Neuropathic orofacial pain (NOP), sometimes termed as trigeminal neuropathic pain is an umbrella term that includes conditions related to painful lesions of the cranial nerves.[12] The most common clinical entities are trigeminal neuralgia, painful post-traumatic trigeminal neuropathies, and burning mouth syndrome.

NOP may be generally classified as peripheral or central, or based on the symptomology as episodic and continuous. Episodic neuropathies are characterized by short, sharp, or electrical like paroxysmal pain similar to trigeminal neuralgia, while post-traumatic neuropathy or inflammation in nerve structures (neuritis) are commonly characterized by continuous burning pain.

NOP shares mechanisms and features with spinal neuropathic pain, yet it demonstrates inimitable characteristics. Conditions such as burning mouth syndrome or trigeminal neuralgia occur solely in this region, while other conditions such as painful diabetic neuropathy, one of the most common neuropathic conditions, rarely affects the orofacial region. This may be explained in part by trigeminal nerve injury studies that show divergent responses to physical and inflammatory insults compared to spinal nerves injury.[13,14]

There is no single, common, easy method to diagnose NOP. The diagnosis is based on self-reports, symptoms, as well as physiological and behavioral methods. Occurrence of NOP may be spontaneous (stimulus-independent) or touch-evoked (stimulus-dependent); these episodes may also be superimposed as a result of constant pain.

Some sensory signs and symptoms, particularly thermal or mechanical allodynia, are frequently associated with NOP. Evaluation of sensory changes is best performed by Quantitative Sensory Testing (QST), a method that utilizes noninvasive assessment and quantification of normal and abnormal responses of the nervous system to various stimuli.[15] Typically, mechanical or thermal stimuli selectively activate different sensory nerve fibers (e.g., heat activates C-fibers, cold stimuli and punctuate mechanical stimuli activate Aδ-fibers and light touch activates Aβ fibers). Sensory evaluation can be performed using sophisticated equipment or using simple pin, blunt instruments, warmed and cooled implements, and cotton wool. Data obtained from QST can support treatment decisions; for example, when the pathology is mainly peripheral microsurgical repair or topical, treatment should be considered, while in cases where the pain has a strong central nervous system component, centrally acting drugs should be the treatment of choice.

Painful Trigeminal Neuropathies

The term "painful trigeminal neuropathy" (PTN) is an umbrella term bringing together a number of facial pains in the distribution(s) of one or more branches of the trigeminal nerve caused by a disorder associated with the trigeminal neuralgias and indicative of neural damage.[8]

The primary pain in PTN is continuous, and commonly described as burning, squeezing, or as pins and needles. Superimposed brief pain paroxysms can be present, but not as the main type of pain. Sensory changes within the trigeminal distribution—such as mechanical allodynia, cold hyperalgesia, and numbness—are prevalent findings in PTNs. Allodynic areas are different from trigeminal neuralgia's trigger zones; they are generally much larger than the punctate trigger zones, and allodynic areas lack both the "latency" and "refractory period" associated with trigeminal neuralgia triggers.

Painful Trigeminal Neuropathy Attributed to Acute Herpes Zoster

Acute herpes zoster (HZ) or shingles is a reactivation of latent varicella virus infection that may occur even decades after the primary infection. The exact mechanisms leading to viral reactivation and the subsequent appearance of acute HZ are unknown. Clinical presentation of HZ includes a dermatomal vesicular eruption. The symptoms are more severe in immunocompromised patients and

include a prolonged course, recurrent lesions mimicking a typical zoster infection, and involvement of multiple dermatomes.[16]

Diagnosis of HZ is based on the clinical presentation and laboratory testing.[17] The clinical features important to the diagnosis include a painful prodrome, a unilateral dermatomal distribution, a vesicular or papular eruption, a history of a rash in the same distribution, and pain.[16] Identification of viral DNA in vesicular or cerebrospinal (CSF) fluid provides a more definitive diagnosis.1[8] Additionally, identification of HZ DNA in saliva has been suggested as a possible and less invasive diagnostic test.[18]

HZ Etiology and Pathophysiology

Peripherally, viral replication induces epithelial cell degeneration and ballooning, followed by invasion of giant cells. In rare cases, necrosis and bleeding are observed. The vesicles rupture and release infectious contents.

Activation of varicella zoster virus at the spinal root or cranial nerve neurons results in an inflammatory response that may also include the leptomeninges. Nerve damage following inflammation around the nerve trunk with lymphocytic infiltration of the nerve root contributes to pain in HZ. The ongoing inflammation may induce neuronal loss, fibrosis, and focal necrosis of nerve cells and satellite cell bodies.[19] Infected DRG cells demonstrate cell degeneration and accumulation of glia cells. The distribution of sensory changes and development of hyperalgesia are associated with the spread within the spinal cord.

HZ Epidemiology

HZ does not generally appear in epidemics and does not follow a seasonal pattern. The annual incidence of HZ has been reduced significantly since the introduction of the first varicella vaccination in 1995.[20]

HZ incidence increases with age, approximately 0.3% of the population will develop HZ.[20] More than 50% of patients over the age of 80 are at risk to develop HZ, and the overall lifetime risk to develop HZ is estimated as 30%.[20] HZ is not common among young patients, and it remains to be determined when the presence of HZ in young patients should be interpreted as sign of underlying immunosuppressive disease.

Clinical Features of Acute HZ

Acute HZ is characterized by a unilateral, dermatomal, red macopapular rash that matures into vesicular eruptions over 3–5 days. The vesicles dry within another 7–10 days, but complete healing may take a month. HZ virus most commonly affects the thoracic nerves, followed by the lumbar region. The trigeminal nerves are affected in 8–28% of cases. Among the trigeminal cases, the ophthalmic branch involvement is most common, occurring in 80% of cases. Ophthalmic nerve involvement can result in keratitis, a vision-threatening condition. When the maxillary or mandibular branches are affected, the vesicles may appear intraorally. Cervical nerves are affected in 13–23% of cases.

Pain in HZ is constant with superimposed piercing attacks. Evoked pain may be the prominent feature in some patients. The pain quality varies: burning (26%), stabbing (15%), shooting (15%), tingling (10%), and aching (9%) are common descriptors used.[21] Its intensity is moderate to severe (VAS 6.2 average), but up to 25% of patients have no pain.[22] High pain severity correlates with an increased incidence of Post Herpetic Neuralgia (PHN).[22] In three-quarters of the patients, acute HZ presents with prodromal pain, headache, itching, malaise, and fever.[16,23–25] The pain develops 2–3 days (< 7) prior to acute HZ and may last with varying intensity up to 3–6 months after healing.[24] Acute HZ patients may have mechanical allodynia and altered sensory thresholds that can spread to adjacent dermatomes, but is rarely bilaterally. Motor weakness may occur, but is usually transient.

Dermatomal pain with no rash, termed "*zoster sine herpete*," is very rare and its diagnosis requires evidence of concurrent viral reactivation.[26]

HZ Management

Acute HZ treatment is focused on pain control, reducing the risk of complications such as spreading and local secondary infection, post herpetic neuralgia (PHN), as well as efforts to accelerate healing.[24] Early initiation of antiviral treatment (less than 72 hours following rash onset), mainly in patients older than 50 years, shortens the rash duration and reduces pain severity and frequency.[22,27] Meta-analyses, however, did not find significant reductions in PHN incidence following oral acyclovir therapy[28]

Antiviral Medications The antiviral medications used to treat acute HZ include valacyclovir (1000 mg x 3/d), acyclovir (800 mg x 5/d), and famciclovir (500 mg x 3/day). Valacyclovir is more efficacious than acyclovir in terms of pain resolution. Famciclovir is well-tolerated therapy that has the advantage of reduced frequency of dosing.[17] Brivudin is an antiviral medication that is available in some countries for the early treatment of HZ, mainly in immunocompetent adults. Overall, brivudin (125 mg daily) is superior to acyclovir (800 mg x 5/d), however it has a mixed efficacy profile.[29] Brivudin and famciclovir (250 mg x 3/d) are comparable in effectiveness on pain and rash with similar tolerability. Severe drug interactions have been reported between brivudin and 5- fluorouracil (FU) and other 5-fluoropyrimidines; therefore, brivudin should not be used along with 5-FU or its derivatives, capecitabine, floxuridine, or flucytosine.[29] Newer anti-HZ drugs, such as the bicyclic nucleoside

analogue FV-100, the helicase-primase inhibitor ASP2151, and valomaciclovir, have been evaluated in clinical trials and offer promising improved efficacy, reduced daily doses, and side effects.[30]

Systemic administration of corticosteroids in combination with antiviral medication offers clinically significant benefits for acute pain and quality of life outcomes when administered systemically within 72 hours of rash onset.[29]

Pain medications Analgesics such as paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) should be used to control fever and pain. Stronger pain may require analgesic/NSAID combinations or short-term opioid treatment, mainly for nonresponsive pain. Amitriptyline and gabapentin are centrally acting analgesics that can also provide some pain relief. Amitriptyline may be associated with cardiovascular effects, which limit its use in the elderly and medically complex patients.

Trigeminal Post-Herpetic Neuralgia (PHN)

Post-Herpetic Neuralgia (PHN) is a complication of acute HZ (shingles). It is a neuropathic pain syndrome that develops following herpes virus-induced nerve injury. Affected nerve fibers induce burning pain that lasts long after the rash and blisters disappear.

Multiple risk factors contribute to the development of PHN, including age and severe symptoms such as pain and rash.[25,31] Advanced age (> 50 years old) and intense pain independently predict PHN at 3 months after the acute infection.[31,32] It is not clear when acute HZ transitions into PHN.[33,34] HZ-associated pain may be best classified into three phases: acute HZ (lasting less than 30 days); subacute HZ (more than 30 days but less than 120 days); and PHN (more than 120 days).[16] This classification is in line with evidence suggesting that acute HZ and PHN have distinct pathophysiologies.[35]

Varicella vaccine may offer an effective method of preventing HZ and PHN in individuals at risk. The live attenuated zoster vaccine was shown to be effective in reducing the incidence of PHN among older adults[36] as well as reducing the duration and severity of the acute disease.[37] The vaccine has been shown to be 70% efficacious, safe, and effective. The efficacy of the vaccine appears to decrease with age; however, this can be overcome by vaccine modifications.[30] Zoster vaccines are approved and recommended for individuals over the age of 50.[38] The recombinant version was approved in the United States in 2017 and is safe and effective.[39] A recent metanalysis concluded that the adjuvant recombinant subunit vaccine might be more effective[39] at preventing herpes zoster than the live attenuated vaccine, but the recombinant vaccine also has a higher risk of local adverse events.

Varicella vaccine is contraindicated in immunosuppressed individuals, a group that is at high risk of infection. Instead, passive immunity with an immune globulin preparation should be considered for these patients following exposure to varicella.[17,30]

PHN Etiology and Pathogenesis

Some of the characteristics commonly found in PHN patients include scarring of sensory ganglia and peripheral nerve damage (often bilateral) with loss of large myelinated nerve fibers.[19] Both peripherally and centrally generated mechanisms are involved in PHN and the extent to which each of the processes contributes to PHN will affect the clinical presentation.[40] Patients with the least residual epidermal neurites following acute HZ more often develop PHN, suggesting mechanisms secondary to nerve damage.[19] In trigeminal PHN patients, neurophysiological abnormalities in the A-delta and C fibers were associated with the intensity of the constant burning pain, while dysfunctions of A-beta fibers were associated with paroxysmal pain.[41,42]

PHN patients do not usually present with an active viral infection. PHN patients develop spinal dorsal horn atrophy, which does not exist in acute HZ patients that do not progress to PHN.[19] Postmortem examination has revealed bilateral, severe, peripheral nerve pathology in an ophthalmic PHN patient;[43] while the trigeminal ganglion and trigeminal root were unaffected, suggesting that PHN progresses from peripheral to central structures. It is assumed that ongoing activity in peripheral nociceptors plays an important role in the early PHN stages (< 1 yr) while central mechanisms have more prominent role in later stages.[44]

PHN Epidemiology

The specific incidence of PHN in the trigeminal region is not known; however, the overall PHN incidence is estimated at 3.9–42.0/100,000 person per year.[5] The frequency of persistent pain 3 months following acute HZ increases with age, ranging from 0.3% in patients under 44 years old to 9% in those 75 and older.[19] Between 5–40% of acute HZ patients will report pain 6 months following initial onset,[16,36] and it has been estimated that after 1 year, 5–10% of the patients will report persistent pain.[16,36] There is some variability in the reported durations of pain following acute HZ.

PHN Clinical Features

The ophthalmic division of the trigeminal nerve is most commonly involved in trigeminal PHN.[45] The quality of pain associated has been described as burning, throbbing, stabbing, sharp, or shooting. Most PHN patients will report a constant, deep, burning or aching pain. However, variable temporal patterns of pain have been reported, with some

PHN patients presenting with constant pain and others with paroxysmal pain as the leading symptom.[41]

Between 30–50% of PHN patients report itching of the affected area, termed post-herpetic itch (PHI).[46] Although PHI is usually mild to moderate, in some cases it may be extremely bothersome and is often subjectively graded as worse than pain.[19] PHI may be accompanied by anesthesia and may result in self-injury from persistent scratching.[46] PHN pain is typically severe with VAS ratings of 8. When present, background pain fluctuates from moderate to excruciating.

The affected areas are usually hypoesthetic or anesthetic, with pale or red/purple scars. These "anesthetic" scars often exhibit allodynia and hyperalgesia. No different from other neuropathic pain conditions, a heterogeneous mix of sensory signs and symptoms are observed in PHN.[41] Most patients with PHN develop allodynia and diminished responses to temperature and pinprick.

PHN Treatment

Several evidence-based treatment options are available for PHN. It appears that early treatment improves treatment effectiveness.[47,48] TCAs present an effective treatment option for PHN with an overall Number Needed to Treat (NNT) of 2.6. Amitriptyline is the most extensively studied Tricyclic Antidepressant (TCA); however, other available TCAs such as nortriptyline or desipramine may also be used. Gabapentin (NNT of 4.4) and pregabalin (NNT 3.3–4.93) have been proven to be efficacious and are relatively safe in elderly patients.[47,48] Opioids (NNT ~ 2.7) and tramadol (NNT of 4.8) are a treatment option; however, the risk of Opioid Abuse Disorder (OAD) should be considered.[47,48] In the presence of allodynia, lidocaine patches (NNT ~4) are useful, with significantly fewer side effects compared to systemic drugs.[49–51] High concentrations of topical capsaicin (8%) (NNT of 8.8) was shown[52] as a safe treatment option.[52] For trigeminal PHN, however, capsaicin patches are not recommended and extreme care should be taken when applying treatments around the eyes.[53] Post-herpetic itch (PHI) is extremely difficult to treat; local anesthetics provide some temporary relief, but it does not usually respond to antihistamines.

More invasive PHN treatment options include epidural and intrathecal steroids, sympathetic and sensory nerve blocks, spinal cord stimulation, and neurosurgical techniques with dorsal root entry zone (DREZ) lesion.[54,55]

Painful Post Traumatic Trigeminal Neuropathy (PTTN)

Neuropathy (sensory change) is a disease resulting from damage to or malfunctioning of the somatosensory nervous system. When accompanied by pain it is termed as painful neuropathy.

Neuropathies can be divided into: peripheral neuropathy, when pain originates in peripheral nerve; ganglionopathy, when the ganglion is involved; radiculopathy, when affecting the dorsal root; or central neuropathic pain, when this originates from the central nervous system. Often there are overlapping conditions. This section focuses on Painful Traumatic Trigeminal Neuropathy (PTTN): pain resulting from damage to the trigeminal nerve. PTTN has been previously termed in the literature as: phantom tooth pain, atypical odontalgia, and atypical facial pain.

Craniofacial or oral trauma are probably the most common PTTN etiologies;[56,57] however, minor dental interventions such as nerve blocks, root canal treatment, and third molar extractions may also result in PTTN.[58–62] Other causes include infection (i.e., AIDS), metabolic abnormalities (i.e., diabetes), malnutrition, vascular abnormalities (i.e., trigeminal neuralgia), infarction (i.e., central post stroke pain), neurotoxins, radiation, and autoimmune diseases. In most cases, occurrence of iatrogenic PTTN or other post-traumatic neuropathies does not reflect on the quality of the surgical intervention.[63]

PTTN Etiology and Pathogenesis

The pathophysiology of painful traumatic neuropathies involves a series of events in the nervous system, involving changes in functional, biochemical, and physical characteristics of neuronal and glial cells. These changes are time dependent and progress from the peripheral to the central nervous system.[64–71] Selected aspects of these events are discussed in the subsequent section.

Peripheral Sensitization Peripheral sensitization is usually initiated in response to a variety of stimuli or types of tissue damage. Inflammatory mediators that are released at the damaged area directly activate or indirectly sensitize nociceptors. Development of sensory changes such as hyperalgesia and/or allodynia are characteristic of peripheral sensitization.

It has been shown that perineural inflammation along the nerve trunk (not necessarily in the nociceptor area) can induce ectopic activity and spontaneous pain at the target organ supplied by the nerve.[72,73] Inflammation can affect nerve function either by secretion of mediators such as cytokines or by local pressure induced by edema.[74] The inflammatory process and the peripheral sensitization progress rapidly; however, the condition is reversible. Nevertheless, if inflammation persists, it may induce nerve damage.[75]

Nerve Injury and Ectopic Activity Trauma or severe inflammation may result in neuronal tissue injury leading to subsequent cell death. However, if the proximal stump survives,

healing may occur, which often involves disorganized sprouting of nerve fibers that form a neuroma. Neuroma formation may be dependent on the degree of nerve damage and usually occurs when the perineurium is damaged. Milder injuries, such as nerve constriction or compression, may induce focal demyelination and regions of neuroma formation, which are characterized by ectopic neural activity partially caused by upregulation of specific sodium and calcium channels and downregulation of potassium channels. Mechanical and chemical stimulation of the neuroma can induce ectopic activity, resulting in pain when the injured area (and the neuroma) is touched. Ectopic activity is also seen in the cell bodies of injured nerves in the dorsal root or trigeminal ganglia; this may in part explain spontaneous neuropathic pain. Experimentally, trigeminal nerve neuromas are less active than those in sciatic nerve, suggesting relative resistance of the trigeminal nerve to trauma-induced hyperactivity.

Phenotypic Changes Nerve injury results in altered expression of neuropeptides in trigeminal ganglion, suggesting functional modifications. For example, under normal circumstances, Aβ fibers transmit innocuous stimuli; however, in the presence of persistent inflammation or injury there is a phenotypic change and they begin to express substance P.[67] Aβ fibers thus acquire the ability to induce painful sensations in response to peripheral stimulation, partially explaining the phenomenon of allodynia.

Sensitivity to Catecholamines During periods of stress or anxiety, which are accompanied by increased sympathetic activity, patients may report increased pain in the injured area. This may be due to upregulation of α-adrenoreceptors in the dorsal root ganglion and the site of injury that induce sensitivity to circulating catecholamines. Additionally, sensory-sympathetic interactions can be amplified by basket-like sprouting of sympathetic fibers around large neuronal cell bodies within the dorsal root ganglion. This phenomenon has not been detected in the trigeminal ganglion and may explain the relative rarity of sympathetically maintained craniofacial pain.[13]

Central Sensitization Ongoing or bursts of activity from primary afferents transmitted to the dorsal horn neurons (DHN) may trigger changes in the central nervous system. Repeated input from primary nociceptive afferents increasingly depolarizes DHNs leading to augmented responses ("wind up"). Prolonged DHN depolarization results in activation of the NMDA receptor (NMDAr), a calcium channel normally blocked by a magnesium ion. Upon activation, the magnesium ion blocking the NMDAr is removed, allowing calcium ion influx to the DHN and initiating a variety of intracellular events. Activation of NMDAr is thought to contribute to central sensitization by enhancing neuronal activity. Repeated nociceptive afferent input also leads to activation of other calcium channels (L-, P-, and N-type) resulting in increases in intracellular calcium and DHN hypersensitivity, which manifests as hyperalgesia and/or allodynia.

Prolonged hypersensitivity may activate adjacent DHNs, probably by diffusion of neurotransmitters or by unmasking of silent inter-DHN connections. Activation of adjacent DHNs expands the receptive field area, leading to perception of pain in areas not normally innervated by the involved peripheral nerve. The increase in receptive field can be detected clinically as sensitivity in the uninjured areas in the vicinity of the injury, named secondary hyperalgesia. The phenomenon of central sensitization accounts for increased pain and spread of pain to adjacent structures in patients with severe facial pain. The early neuronal excitability responds well to treatment as it is activity dependent. However, prolonged stimulation and long-term changes originating in the DRG and DHNs involve modified gene expression and downregulation of repressor mechanisms that lead to further excitability. It is important to note that central sensitization characterized by hyperalgesia, temporal summation, and abnormal sensation may also develop following a minor injury such as third molar extraction or root canal treatment.[76,77]

Some months after nerve injury, neuronal death occurs (mainly C-fibers) and sprouting of Aß fibers from deeper lamina follows as injured C-fiber terminals withdraw from lamina I/II. The sprouting of Aß fibers results in increased pain induced by light touch.[78]

Glial and Satellite Glial Cells Spinal cord glial cells have been shown to play an important role in the normal development, connectivity, and plasticity of the central nervous system.[64] They also have a role in the initiation and maintenance of chronic pain and pain modulation. Glia cells express receptors and transporter proteins for many neurotransmitters and are able to release excitatory molecules, such as pro-inflammatory cytokines, glutamate, nitric oxide, and prostaglandins, in response to neuronal signals. This leads to the enhancement of DHN hyperexcitability and neurotransmitter release from primary afferents.[64,79] Glial cells may be an attractive therapeutic target because they participate in pathological pain and not in acute nociceptive responses.[80,81]

PTTN Epidemiology

Traumatic injuries to the trigeminal nerve largely result in either no residual deficit or in a nonpainful neuropathy; only

a small proportion develop a painful neuropathy. There is wide interindividual variability in the onset and features of PTTN following identical injuries.

Macro trauma Mild hypoesthesia of the infraorbital nerve is frequently observed following zygomatic complex fractures; however, neuropathic pain develops in only 3.3% of patients followed up for 6 months[56] compared to around 5–17% in other body regions.[82,83]

Dental Implants Neuropathy secondary to direct or indirect neuronal trauma may develop following implant placement. Between 0.6–36% of patients will experience neurosensory disturbances following implant placement[84–89] as a result of damage to adjacent nerves that may also lead to pain.[90–92] The large incidence range for neurosensory disturbances may imply that both transient and permanent changes were included. However, the exact incidence of postimplant PTTN is unclear. Direct damage may occur during site preparation and/or implant insertion, and indirect damage may result from bleeding and pressure buildup around the nerve or a perineural inflammatory response.

In some cases a major nerve trunk, usually the inferior alveolar nerve, may be impinged to a variable degree,[93,94] especially when the implant is over inserted. In these cases, significant sensory dysfunction is immediately present postoperatively and the neuropathy is believed to result from inflammation and direct physical damage caused by the preparation and/or the implant.[95]

A small group of patients develop pain in spite of normal healing and in the absence of apparent complications. Pain and "sensitivity" to mechanical (chewing, brushing) and often thermal stimuli develop in these patients following implant loading. In some cases, the pain resolves when the implant is unloaded. The underlying mechanism for this pain is unclear; however, it is believed to be neuropathic.[96]

Mandibular and Third Molar Extraction Between 0.3–1% of third molar extractions may be associated with altered sensation in the lingual or inferior alveolar nerve that persists for varying periods.[97,98] Lingual nerve damage is observed less frequently than inferior alveolar nerve injuries[99–101] but may reach 4% in extraction techniques involving nerve retraction.[102]

Nonpainful neuropathies that may develop following dental interventions have a reasonably good prognosis and most patients report improvement.[103]

Root Canal Treatment Multiple factors, including apical infection or inflammation[104,105] accidental injection or leakage of hypochlorite rinsing solution[106–108], and extrusion of filling materials[109,110] have been reported to cause chemical/physical injury that may contribute to nerve damage following endodontic therapy. Between 3–13% of cases report persistent pain following successful endodontics[58,111–114], and 5% of surgical endodontics cases will develop chronic neuropathic pain.[115] Multiple factors have been associated with persistent pain following endodontic treatment, including: long duration of preoperative pain, marked symptomatology from the tooth, previous chronic pain problems, and history of painful treatment in the orofacial region.[113,114] Patients with persistent pain following endodontic treatment may have a deficient endogenous inhibitory system.[77] The importance of preoperative pain parameters implies that some sensitization may have occurred, predisposing to chronic pain.

Local Anesthetic Injections Nerve injury may occur following local anesthetic injection secondary to physical trauma by the needle or by chemical insult from the anesthetic solution.[116–119] Injuries more commonly occur during blocks to the inferior alveolar and lingual nerves, with lingual nerve injuries being more permanent.[62] Lingual nerve injury is more likely during repeated injections and when the injection was reported as painful.[62] The signs associated with injury due to local anesthetic injection are similar to other PTTNs and include burning pain, paraesthesia, allodynia, or hyperalgesia. It has been suggested that the degree of injury may be dependent on the type and toxicity of anesthetic agent used.[120,121] Articaine 4%, when used as an inferior alveolar nerve block, was shown to be significantly associated with nerve injury and clinical symptoms.[122] Therefore, its use for nerve blocks should be limited.

PTTN Diagnosis

Trauma cases should be carefully assessed to detect fractures, other injuries, and extent. Depending on the case, plain radiography or cone beam computerized tomography (CBCT) may be used.

Sensory testing is recommended, preferably with quantitative dynamic assessment,[11,123] to evaluate the degree of injury.[124,125] When advanced quantitative sensory testing (QST) equipment is not available, dental instruments may be adapted to assess gross sensory changes associated with PTTN. For example, pin-prick sensation can be tested with a dental probe, thermal sensation with warm/cool instruments, and mechanosensation with cotton wool. The affected areas should be carefully mapped, marked, and photographed to become part of the patient's documentation, evaluation, and follow-up.

PTTN Clinical Features

PTTN is more prevalent in females and commonly occurs around 45–50 years of age.[61,126–128] The pain is in the injured

area and the affected nerve dermatome accompanied by evident sensory dysfunction.[126] The pain may spread across dermatomes, but rarely crosses the midline. However, in more extensive injuries, where multiple nerves are affected, bilateral pain may occur. The pain is usually burning or shooting, with a moderate to severe intensity (VAS 5-8)[59,60,126,127,129] continuous, and long lasting.[126] Paroxysmal spontaneous pain and pain triggered by touch or function has also been reported.[59] Unlike trigeminal neuralgia, triggering areas are usually not accompanied by a latency or refractory period.[126] Allodynia or a positive Tinel's sign occurs more frequently in PTTN than in trigeminal neuralgia.[59]

Painful neuropathies may be associated with positive (e.g., dysesthesia) and negative symptoms (e.g., numbness).[123,126,127] The sensory symptoms frequently associated with PTTN include thermal and mechanical allodynia.[130] Extensive changes in the central nervous system somatosensory processing may induce additional sensory changes.[11,131,132] The sensory changes may be described by the patients as swelling, a foreign body, numbness, hot or cold, local redness, or flushing, but these are not always demonstrable.[59,126]

Patients with PTTN may present with elevated levels of depression and pain catastrophizing and reduced quality of life. Quality of life and emotional problems, but not anxiety, can by predicted based on the intensity of the pain.[127,133]

PTTN Management

PTTN is characterized by a poor prognosis, improvement is observed in less than one-third of patients and only 10–20% will report a significant improvement.[103,127] Approximately half of the patients reported no improvement or worsened pain. Some degree of pain was experienced by most cases even at an average of 13 years after onset.[127] Prevention is obviously preferable; however, it is not always possible.

Approaches for Preventing PTTN It is unclear why some patients develop persistent postinjury (or postsurgical) pain and others do not. The factors contributing to the development of persistent pain may be grouped into three phases:[134] (1) the preoperative phase includes risk factors specific to each patient, such as psychosocial parameters, genetically controlled pain modulatory mechanisms, the presence of related preoperative pain (i.e., painful surgical site), and comorbidities such as other pain disorders, obesity, and sleep disorders;[135] (2) the intraoperative phase includes surgery dependent factors, such as technique, associated nerve and tissue injury, as well as the analgesic regimens; (3) the postoperative phase involves the patient's coping ability, postoperative pain intensity, healing with scar formation, as well as possible additional confounding factors such as chemotherapy or other unrelated treatments.[134,136]

Preventive analgesia (pre-emptive analgesia) is often recommended to avert the development of persistent postsurgical pain. Preventive intervention may involve various modalities and the recommended protocol varies with pre-, intra- and postoperative components. Currently there is not enough evidence supporting a routine implementation or a unified protocol,[137] yet a preventive strategy should be employed in selected cases. This may include selection of an alternative surgical approach that can minimize tissue damage and nerve involvement, preoperative anti-inflammatory and analgesic treatments, deep local or regional anesthesia, and adequate postoperative analgesics to ensure no perioperative pain. Gabapentin employed 2 hours preoperatively and continued for 1–5 days postoperatively may reduce the incidence of persistent postsurgical pain.[136] Preoperative anesthetic blocks have been suggested to reduce postoperative pain, but no protocol has been broadly accepted.[138,139] The use of local anesthetic blocks during surgery (under general anesthesia) to prevent the injury-associated afferent barrage and resultant central sensitization has been proposed; however, results are inconsistent. Local anesthetics have been shown to suppress postoperative pain and reduce analgesic consumption, but the effect on preventing chronic pain is unknown.[140]

A less efficient pain modulatory capacity has been shown to be indicative of patients' risk to develop postoperative chronic pain.[141–143] This could eventually translate to a chairside screening test to identify at patients at risk.

Factors contributing to lack of success in preventive strategies include inadequate management of the injury related sensory barrage and inadequate pain treatment duration.[139] Preventive programs for selected patients (at risk) should include preoperative and perioperative analgesics, deep local or regional anesthesia, and excellent postoperative analgesics.

Approaches for Established Painful Traumatic Trigeminal Neuropathies

Pharmacotherapy Anti-inflammatory therapy is indicated for the treatment of postoperative clinically symptomatic temporary perineural inflammation (neuritis), as inflammation and neuritis has been shown to have a significant role in the pathophysiology of NP. Standard NSAIDs (for example, naproxen 500 mg b.i.d., ibuprofen 400 mg t.i.d.) are recommended to treat mild cases. The use of steroids such as prednisone, 40–60 mg initially then tapered over 7–10 days, or dexamethasone, 12–16 mg initially then similarly tapered, may be warranted in severe cases with sensory alterations or significant pain. Animal studies show that early dexamethasone may reduce neuropathic pain[144] but there is no support for this concept from rigorous clinical studies. Treatment with steroids should be as short as possible and tapered to

reduce side effects from consistently high dosages. If treatment is successful, patients may be transferred to a NSAID with an antacid treatment for a further 7–10 days.

PTTNs are extremely difficult to manage.[145] Estimation of the Number Needed to Treat (NNT) for neuropathic pain induced by peripheral nerve injury is challenging due to the insufficient number of controlled trails. However, traumatic neuropathies are the most recalcitrant to treatment.[145,146] Antiepileptic drugs (AEDs) and tricyclic antidepressants (TCAs) remain the mainstays of NP treatment.[47,48,147]

The available pharmacotherapies (antidepressants, anticonvulsants, opioids) may provide improved quality of life, sleep, and mood, but usually require high doses for NP, resulting in significant side effects. In NP patients, a 30–50% reduction in pain is considered significant pain relief, and only 20–40% of patients attain this.[148–152]

Drugs with mixed serotonin/noradrenaline (e.g., amitriptyline and nortriptyline) or serotonin and noradrenaline reuptake inhibitors (e.g., venlaflaxine and duloxetine) have been shown to be superior to the selective serotonin reuptake inhibitors.[153,154] The NNTs for TCAs such as amitriptyline in painful polyneuropathies is relatively good and estimated to be 2.1.[147] The more novel antidepressant drugs, the serotonin and noradrenaline reuptake inhibitors (SNRIs) demonstrated less efficacious pain relief (NNT = 5) for NP; however, they have significantly fewer side effects and therefore may be considered as an alternatives for the treatment of painful polyneuropathy.[147]

As a group, anticonvulsant drugs (ACD) are inferior to the antidepressants in the management of painful polyneuropathies. However, ACDs are heterogeneous in their efficacy for painful neuropathies.[155,156] Carbamazepine or oxcarbazepine are efficacious in painful polyneuropathies (NNT = 3.7), but have more side effects than pregabalin (NNT = 4.5) or gabapentin (NNT = 6.4).[147] Based on the efficacy of pregabalin and gabapentin in other peripheral neuropathies, they are theoretically good options for managing PTTN.

Opioids are not considered an effective treatment for traumatic neuropathies (NNT = 5).[147] Combinations of drugs with different modes and sites of action may offer improved efficacy with reduced side effects. In diabetic polyneuropathy or postherpetic neuralgia, combinations of nortriptyline and gabapentin, or nortriptyline and morphine, have been shown to be more efficacious than monotherapy.[157,158] Similarly, patients with painful diabetic neuropathy who did not respond to gabapentin monotherapy showed significant pain improvement when treated with the combination of gabapentin and venlafaxine.[159] An oxycodone–gabapentin mix was shown to be more efficacious than gabapentin alone in diabetic neuropathy patients.[160] Lower doses of gabapentin and morphine may also be combined to achieve significant analgesia in patients with PHN and diabetic neuropathy .[161] Combining gabapentin and an opioid was shown to be superior to gabapentin alone in the treatment of neuropathic pain in adults, but this combination increases the risk of side effects.[162] On the other hand, a combination of duloxetine and pregabalin was reported to provide no significant advantage over high-dose monotherapy in the treatment of diabetic peripheral neuropathy.[163] To date, there is a lack of clear evidence supporting recommendation of any one specific drug combination for neuropathic pain.[162]

Based on the available evidence, TCAs/SNRIs or gabapentin/pregabalin are the first drugs indicated in painful peripheral neuropathy.[47,48,147] In patients initiated on amitriptyline that develop severe side effects, imipramine, desipramine, duloxetine, or venlafaxine should be considered. If these fail or are contraindicated, gabapentin or pregabalin offer the best chances for success. Similarly, in patients on gabapentin/pregabalin, treatment failure is an indication for a trial of TCAs or SNRIs. Combination therapy of SNRI or TCA with gabapentin or pregabalin should be considered if the above treatment options are partly successful.[147] Opioids or tramadol may be used only as third line monotherapy or add on therapy. It is important to keep in mind that opioid treatments pose a risk of addiction and abuse potential. Therefore, screening, preventive measures, and careful monitoring should be in place in all clinics prescribing opioids. Cannabinoids are increasingly being tested[147] and have NNTs of 3–5 in peripheral and central neuropathic pain.[164,165]

When applying a widely accepted pharmacotherapy protocol for neuropathic pain in a cohort of PTTN patients, unfortunately only 11% of patients achieved a ≥ 50% reduction in pain intensity, and patients with higher pain intensity scores were less likely to benefit from the therapy.[145] Comparable response rates have been reported in other painful neuropathies,[147] emphasizing the need for new drugs and treatment options for chronic neuropathic pain.

Topical treatments offer the benefit of minimal side effects, fewer drug–drug interactions, and improved patient tolerance; however, the affected areas are not always amenable to treatment.[166,167] Evidence-based topicals include lidocaine or capsaicin (low and high concentrations) patches and locally injected onabotulinum toxin A.[168] Individually prescribed topical formulations are also in use.[166]

Cognitive behavioral therapy (CBT) CBT does not have significant effects on pain intensity and quality of life measures in neuropathic pain patients.[169] Nonetheless, NP patients should be offered psychosocial therapy as anxiety and depression are frequently comorbid.

Surgical Options Surgery is recommended to improve sensation in injured patients with nonpainful neuropathies.[170–172] Roughly 50% of repaired cases will recover complete sensory function within 7 months[173] if treated within 1 year of injury.[171,174–177] Inferior alveolar nerve injuries have a marginally better prognosis with surgical treatment compared to lingual nerve injuries[178,179] and the presence of a neuroma is a negative prognostic factor.[173,177]

The role of surgery for painful trigeminal neuropathies is not clear. Often, patients with painful traumatic trigeminal neuropathy end up with more pain following peripheral surgical procedures (exploration, further apicoectomies). Therefore, patients with painful traumatic neuropathies should not undergo further surgery unless there are specific indications.[180] Surgical intervention for PTTN patients may be indicated for the release of scar tissue, decompression, and neuroma excision, all of which have been shown to have good success rates.[180]

Decompression of an injured nerve by shortening or removing the implant completely may promote healing and prevent neuropathy. Each situation needs to be weighed individually according to the time elapsed since insertion, type, and degree of the nerve injury. Early removal or replacement of the implants (< 24–48 hours after placement) has been suggested to reduce incidence of neuropathy and pain.[180,181] Microsurgical repairs may be considered for total resections of nerve bundles such as the inferior alveolar. Pharmacotherapy may be considered in management of early nerve injury and evidence of neuritis.

Osseointegrated implant removal may induce substantial collateral damage; therefore, implant removal must be weighed against the potential tissue damage and loss of function.

Central Surgery In refractory cases, central nervous system procedures may be considered.[182,183] Trigeminal dorsal root entry zone (DREZ) surgery may be performed.[183] However, the primary choice of surgery should be minimally invasive, such as computed tomography (CT)-guided percutaneous trigeminal tractotomy-nucleotomy (surgical division of the descending fibers of the trigeminal tract in the medulla) aimed to ablate pathways that carry sensation from the face.

Orofacial Complex Regional Pain Syndrome (CRPS)

Complex Regional Pain Syndrome (CRPS) is a category of chronic, painful neuropathic disorders resulting from injury.[184] Three types of CRPS have been defined: CRPS I (reflex sympathetic dystrophy); CRPS II (causalgia); and CRPS-NOS (not otherwise specified) to allow inclusion of patients not meeting all the criteria.[185] CRPS's clinical presentation includes spontaneous pain, allodynia, and hyperalgesia not limited to dermatomal regions.186

The specific signs that differentiate CRPS from non-CRPS neuropathic pain include regional changes in skin color, temperature, and motor function, sweating, edema, and thermal allodynia.[187] CRPS I may develop as a result of relatively minor local trauma with surgery, fractures, crush injuries, and sprains being the most common causes.[188] Injections, local infection, and burns resulting in minor or not identifiable nerve lesions with disproportionate pain have also been associated.[189] CRPS II occurs less frequently and results from substantial injury to a major nerve, most often following high velocity trauma or surgery. The major distinguishing characteristic of CRPS is the disproportionate severity of the syndrome relative to the injury and nondermatomal spread of pain over time.[184] Pain is commonly felt in the most distal part of the affected limb. CRPS I and CRPS II are often difficult to differentiate.[189]

It is not clear if CRPS occurs in the craniofacial region. The cases reported justify the diagnosis only on interventions aimed at interfering with sympathetic input,[190] although sympathetic involvement is not always essential for CRPS diagnosis.[191] With the exception of trophic and motor changes, CRPS criteria are similar to PTTN and other neuropathic pain conditions.

Classic Facial Neuralgias

The classic neuralgias that affect the craniofacial region are a unique group of neurologic disorders involving the cranial nerves and are characterized by: (1) brief episodes of shooting, often electric shock-like pain along the course of the affected nerve branch; (2) trigger zones on the skin or mucosa that precipitate painful attacks when touched; and (3) pain-free periods between attacks and refractory periods immediately after an attack, during which a new episode cannot be triggered. These clinical characteristics differ from other neuropathic pain disorders, which tend to be constant and have a burning quality without the presence of trigger zones.

Neuropathic pain involving the spinal nerves tends to be constant, whereas involvement of the cranial nerves may result in either constant pain or the classic brief episodes of shooting pain depending upon both the nature of the underlying disorder and the position of the lesion along the course of the nerve. For example, tumors involving the trigeminal nerve between the pontine angle in the posterior cranial fossa and the ganglion in the middle cranial fossa will usually result in the lancinating electric shock pain of classic TN, whereas more peripheral lesions will usually result in more constant pain. The classic craniofacial neuralgias include trigeminal neuralgia, glossopharyngeal neuralgia, occipital neuralgia, and geniculate neuralgia.

Trigeminal Neuralgia (TN)

TN, once also called tic douloureux, is the most common of the cranial neuralgias and chiefly affects individuals older than 50 years of age. The ICHD-3 subdivides TN into three subtypes that may only be diagnosed following imaging. Classical trigeminal neuralgia (CTN) occurs with "demonstration on MRI or during surgery of neurovascular compression (not simply contact), with morphological changes in the trigeminal nerve root." Compression is typically associated with nerve atrophy or displacement. Secondary trigeminal neuralgia is reserved for a typical TN phenotype associated with a local or systemic disease. Finally, idiopathic trigeminal neuralgia has been introduced for patients with typical TN not associated with nerve compression, local or systemic disease. Both classical and idiopathic trigeminal neuralgia are subdivided into purely paroxysmal and those with concomitant persistent pain.

TN Etiology and Pathogenesis

Approximately 10% of TN cases are symptomatic and have detectable underlying pathology, such as a tumor of the cerebellopontine angle, a demyelinating plaque of multiple sclerosis, or a vascular malformation. The most common tumor associated with TN is a meningioma of the posterior cranial fossa.

The most widely accepted theory is that a majority of cases of classic TN are caused by an atherosclerotic blood vessel (usually the superior cerebellar artery) pressing on and grooving the root of the trigeminal nerve. This pressure results in focal demyelinization and hyperexcitability of nerve fibers, which will then fire in response to light touch, resulting in brief episodes of intense pain.[192] Evidence for this theory includes the observation that neurosurgical decompression of the nerve root from the vessel eliminates the pain in a majority of cases.[193] Additional evidence for this theory was obtained from a study using tomographic magnetic resonance imaging, which showed that contact between a blood vessel and the trigeminal nerve root was significantly more frequent on the affected side.

Evidence against this theory explaining all cases of classic TN includes the observation by neurosurgeons that vascular compression is not always detected and manipulation of the area of the nerve root may eliminate the painful episodes even when an atherosclerotic vessel is not pressing on the nerve root. Neurovascular compression (NVC) is not identifiable in a significant number of CTN patients. For example, in a series of 219 patients with paroxysmal TN, 28.3% had no imaging evidence of NVC[194] and up to 17% of patients undergoing surgery for TN had no NVC.[195,196] Moreover, NVC is prevalent both on the symptomatic and asymptomatic side (89% versus 78%) in TN patients, but severe NVC is more prevalent on the symptomatic side (53% versus 13%).[197] Interestingly, pain recurrence after initially successful MVD is often not accompanied by renewed nerve compression.[198]

Furthermore, 17% of age-matched TN-free controls have imaging evidence of NVC.[199–203] Moreover, 14% of cadavers with no history of CTN demonstrate vascular contacts, although these had minimal grooving.[199,200] Classifying CTN and ITN separately allows further study of these groups. TN patients with no NVC are typically younger and three times more likely to be female,[204] supporting the clinical value of the new classification.

Observing neurovascular contact of itself, therefore, has low predictive value in establishing a diagnosis of CTN. The presence of anatomical changes associated with the neurovascular contact increases specificity and positive predictive value.[203] Although NVC clearly plays a role in individual patients, at a population level, the high prevalence of NVC and the rarity of CTN suggest that a finding of NVC in CTN may often be insignificant. Current evidence postulates that TN is a far more complex disease (or cluster of diseases) than previously appreciated.

The pathophysiology of TN seems complex. Around 2% of all TN cases may be familial, and family clusters of TN indicate that it may have a genetic origin.[205] Some of the suggested causes include: inherited anatomical changes affecting the base of the skull, which would promote compression of the trigeminal nerve by vascular structures; mutations in the gene encoding calcium channels resulting in hyperexcitability;[205] as well as mutations in the serotonin transporter gene (5-HTTLPR).[206] Therefore, certain individuals may be prone to develop pain following neurovascular compression while others may be resistant, as in traumatic neuropathies.

TN Clinical Features

The majority of patients with TN present with characteristic clinical features, which include episodes of intense shooting, stabbing pain that lasts for a few seconds and then completely disappears. The pain characteristically has an electric shock-like quality and is unilateral except in a small percentage of cases. The maxillary branch of the trigeminal nerve is the branch that is most commonly affected, followed by the mandibular branch, and, rarely, the ophthalmic branch. Involvement of more than one branch occurs in some cases.

Pain in TN is precipitated by a light touch on a "trigger zone" present on the skin or mucosa within the distribution of the involved nerve branch. Common sites for trigger zones include the nasolabial fold and the corner of the lip. Shaving, showering, eating, speaking, or even exposure to wind can trigger a painful episode, and patients often

protect the trigger zone with their hand or an article of clothing. Intraoral trigger zones can confuse the diagnosis by suggesting a dental disorder, and TN patients often first consult a dentist for evaluation. The stabbing pain can mimic the pain of a cracked tooth, but the two disorders can be distinguished by determining whether placing food in the mouth without chewing or whether gently touching the soft tissue around the trigger zone will precipitate pain. TN pain will be triggered by touching the soft tissue, whereas pressure on the tooth is required to cause pain from a cracked tooth. Just after an attack, there is a refractory period when touching the trigger zone will not precipitate pain. The number of attacks may vary from one or two per day to several per minute. Patients with severe TN may be severely disabled by attacks that are triggered by speaking or other mouth movements and in severe cases there can be significant weight loss due to inability to eat without severe pain.

In some patients, a dull continuous pain called pretrigeminal neuralgia precedes the typical shooting pain by weeks or months. In this stage, trigeminal neuralgia is more difficult to diagnose and is more often confused with dental pathology.

TN Diagnosis

The diagnosis of TN is based on the history of shooting, electric shock-like pain along a branch of the trigeminal nerve, the presence of trigger zones and refractory periods. A routine cranial nerve examination will be normal in patients with idiopathic TN, but sensory and/or motor changes may be evident in patients with underlying tumors or other CNS pathology. A clinical examination alone may be insufficient to distinguish symptomatic from classic TN; in some cases, electrophysiological testing of trigeminal reflexes is more accurate. Local anesthetic nerve blocks, which temporarily eliminate the trigger zone, and painful episodes are also good diagnostic tools.

Since approximately 10% of TN cases are caused by detectable underlying pathology, enhanced MRI of the brain is indicated to rule out tumors, multiple sclerosis, and vascular malformations.[207] Magnetic resonance angiography may also be needed to detect difficult to visualize vascular abnormalities.

TN Management

Initial therapy for TN should consist of trials of drugs that are effective in eliminating the painful attacks. Anticonvulsant drugs are most frequently used and are most effective. Carbamazepine is the most commonly prescribed drug and is an effective therapy for greater than 85% of newly diagnosed cases of TN. The drug is administered in slowly increasing doses until pain relief has been achieved. Skin reactions, including severe cases of erythema multiforme and toxic epidermal necrolysis, are serious side effects. Patients receiving carbamazepine must have periodic hematologic laboratory evaluations because serious life- threatening blood dyscrasias occur in rare cases. Monitoring of hepatic and renal function is also recommended. Patients who do not respond to carbamazepine alone may obtain relief by combining carbamazepine with baclofen or gabapentin. Oxcarbazepine is the 10-ketoanalogue of carbamazepine with a similar mode of action and is often better tolerated than carbamazepine. Routine serial testing for blood dyscrasias is not required, but hyponatremia may be a problem for elderly patients, especially those with cardiovascular disease such as an atrioventricular heart block.

Gabapentin, another anticonvulsant with fewer serious side effects than carbamazepine, may be effective in milder cases, but does not appear to be as reliable as carbamazepine or oxcarbazepine.

Other drugs that are effective for some patients include phenytoin, lamotrigine, baclofen, topiramate, and pimozide. Since TN may have temporary or permanent spontaneous remissions, drug therapy should be slowly withdrawn after a patient remains pain free for 3 months.

In cases where drug therapy is ineffective or when the patient is unable to tolerate the side effects of drugs after trials of several agents, surgical therapy is indicated. A number of surgical procedures that result in temporary or permanent remission of the painful attacks have been described, these include: procedures performed on the peripheral portion of the nerve, where it exits the jaw; at the gasserian ganglion; and at the brainstem, at the posterior cranial fossa.

Peripheral surgery includes cryosurgery on the trigeminal nerve branch that triggers the painful attacks. This procedure is most frequently performed at the mental nerve for cases involving the third division and at the infraorbital nerve for cases involving the second division. The potential effectiveness of this procedure can be evaluated prior to surgery by determining whether a long-acting local anesthetic eliminates the pain during the duration of anesthesia. This procedure is usually effective for 12 to 18 months, at which time it must be repeated, or another form of therapy must be instituted.

One procedure performed at the level of the gasserian ganglion is percutaneous radiofrequency thermocoagulation, although some clinicians continue to advocate glycerol block at the ganglion or compression of the ganglion by balloon microcompression. A severe complication of peripheral procedures is severe neuropathic pain including anesthesia dolorosa, which is numbness combined with severe intractable pain.

The most extensively studied and most successful surgical procedure is microvascular decompression of the nerve root at the brainstem where the artery is separated from the nerve root. Over 70% of patients experience long-term relief of symptoms.[193] It should be noted that 30% of the patients experienced a recurrence of symptoms and required a second procedure or alternative therapy. Complications are rare but include stroke, facial numbness, and facial weakness.

Gamma knife stereotactic radiosurgery is a minimally invasive technique for the treatment of TN.[208] The technique uses multiple beams of radiation, converging in three dimensions to focus precisely on a small volume of brain tissue. The method relies on precise MRI sequencing that helps localization of the beam and allows a higher dose of radiation to be given to targets inside the skull (for TN treatment: the trigeminal nerve where it enters the brainstem) with more sparing of normal tissue. This technique is not as effective as microvascular decompression, but is particularly helpful for elderly patients with a high risk of complications from surgery.

In summary, therapy for TN presently includes a variety of both medical and surgical approaches, each of which is effective for some patients. Drug therapy, including trials of several drugs or combinations of drugs, should be attempted before surgery is recommended. When surgery is necessary, the patient should be carefully counseled regarding the advantages and disadvantages of the available surgical procedures. Clinicians should also remember that since spontaneous remissions are a feature of TN, procedures resulting in temporary relief might be all that is necessary in some cases.

Glossopharyngeal Neuralgia (GN)

Glossopharyngeal neuralgia is a rare condition that is associated with paroxysmal pain that is similar to, although usually less intense than, the pain of TN. The location of the trigger zone and pain sensation follows the distribution of the glossopharyngeal nerve, namely, the pharynx, the base of the tongue, external ear canal, and infra-auricular retromandibular region.[209] Pain is triggered by stimulating the pharyngeal mucosa during talking or swallowing. The pain may be confused with geniculate neuralgia because of the common ear symptoms or with a temporomandibular disorder since pain may be associated with mandibular movements.

Glossopharyngeal neuralgia may occur with TN and, when this occurs, a search for a common central lesion is essential. Glossopharyngeal neuralgia also may be associated with vagus nerve involvement, which may cause syncope, asystole, bradycardia, hypotension, and cardiac arrest. Insertion of a pacemaker may be required to prevent syncopal episodes. The application of a topical anesthetic to the pharyngeal mucosa eliminates glossopharyngeal nerve pain, which can aid in distinguishing GPN from other cranial neuralgias.

The most common causes of glossopharyngeal neuralgia are intracranial or extracranial tumors and vascular abnormalities that compress the ninth cranial nerve. Treatment is similar to that for TN, with a good response to carbamazepine and oxcarbazepine. Refractory cases are treated surgically with microvascular decompression, percutaneous radiofrequency thermocoagulation, or gamma knife radiosurgery.[210,211]

Nervus Intermedius (Geniculate) Neuralgia

Nervus intermedius (geniculate) neuralgia is an uncommon paroxysmal neuralgia of CN VII, characterized by pain in the ear and less frequently the anterior tongue or soft palate. The location of pain matches the sensory distribution of this nerve (i.e., the external auditory canal, a small area on the soft palate, and the posterior auricular region). Pain may be provoked by the stimulation of trigger zones within the ipsilateral distribution of the nerve. The pain is not as sharp or intense as in TN, and there is often some degree of facial paralysis, indicating the simultaneous involvement of the motor root. Disorders of taste or lacrimation may also be present.[212]

Geniculate neuralgia results from vascular compression of the nerve root or herpes zoster of the geniculate ganglion and nervus intermedius of CN VII. This condition, referred to as Ramsay Hunt syndrome, is characterized by viral vesicles in the ear canal or on the tympanic membrane and pain. Since the symptoms result from inflammatory neural degeneration, a short course (2 to 3 weeks) of high-dose steroid therapy is beneficial. Use of an antiherpes drug such as acyclovir or valacyclovir significantly reduces the duration of the pain.

A recombinant herpes zoster vaccine has been developed and approved, which is effective in preventing herpes zoster and post herpetic neuralgia in 90% of individuals who have received the recommended two doses.[213]

Patients with geniculate neuralgia can be treated successfully with oxcarbazepine, carbamazepine, and/or gabapentin. Patients who do not respond to these medications may have a regional nerve blockade and, if this fails, undergo surgery for excision of the nervus intermedius and geniculate ganglion or microvascular decompression.[214]

Occipital Neuralgia (ON)

ON Etiology and Pathogenesis

Occipital neuralgia (ON) affects the distribution of the greater, lesser, or third occipital nerves and can stem from multiple causes, chiefly pressure on the affected nerve from

surrounding muscular and vascular structures, congenital deformities, neoplasms, myelitis, or degenerative joint disease.[215,216] Injuries to the affected nerve after surgery, whiplash injury, or multiple sclerosis may also cause ON.[216,217] The most common cause is nerve entrapment by surrounding muscles, which may be either secondary to or independent of joint changes.[215,218,219]

ON Epidemiology

The incidence and prevalence of occipital neuralgia has not been definitively determined. The greater occipital nerve is involved in 90% of cases, and 85% are unilateral.[215,220] Cases show no variation in temporal or seasonal frequency.[218]

Clinical Manifestations

Occipital neuralgia presents as "unilateral or bilateral paroxysmal, shooting or stabbing pain in the posterior part of the scalp, in the distribution(s) of the greater, lesser and/or third occipital nerves."[8] Like TN and GFN, each attack lasts seconds to minutes and consists of a severe sharp pain. The pain can include aching, allodynia, dysesthesia, or paresthesia, which may persist between attacks. The affected area can extend up the back of the head toward the vertex of the scalp and even to the ipsilateral frontal and orbital areas through connections to the trigeminal spinal nuclei.[220,221]

Clinical tests can help to confirm the presentation of ON, including Tinel's sign, in which patients feel tingling upon light pressure to the nerve, and the pillow sign, when patients feel pain upon neck extension while supine.[219]

ON Differential Diagnosis

Misdiagnosis of occipital neuralgia is common, owing in part to its similarity in presentation to multiple headache disorders. Tenderness and trigger points in the posterior neck muscles and joints causing both migraine headache and cervicalgia may be mistaken for the classic sign of tenderness in the affected nerve in ON.[222] Cervicogenic headache is also often confused with ON, but is due to pain referred from the underlying structures and occurs after injury to the affected area.[218,219] For this reason, palpation sensitivity of the posterior scalp in the area of either the greater or lesser occipital nerves is considered highly suggestive but not specific for diagnosis.[215] Patients with ON do not show worsening or triggering of symptoms with movement of the neck, distinguishing ON from other causes of neck pain.

ON Laboratory Findings

Imaging studies such as MRI or plain film are used to rule out an underlying cause of pain, including pathology affecting the area of the upper cervical spine or posterior neck muscles and central space occupying lesions.[216]

ON Management

Management of ON should begin with physical therapy, including applications of cold and heat, exercise, massage, and transcutaneous electrical nerve stimulation (TENS).[219,220] Blocks of the affected nerves are both diagnostic and therapeutic and may be administered with local anesthetic, corticosteroid, or onabotulinum toxin to decrease inflammation to the nerve.[217–220] For patients requiring additional treatment, systemic medications used in ON include nonsteroidal anti-inflammatory drugs, muscle relaxants, tricyclic antidepressants, and anticonvulsants.[220]

For persistent and unresponsive cases of ON, peripheral nerve and occipital nerve stimulation, pulsed radiofrequency, radiofrequency ablation, rhizotomy, neurolysis, and C2 dorsal root ganglionectomy can be considered.[218,219] Occipital nerve stimulation is particularly promising as a minimally invasive and reversible option which has been endorsed by the Congress of Neurological Surgeons. Radiofrequency ablation, which uses thermal insult to destroy A-delta and C fibers, may be effective in those patients with positive but insufficient responses to nerve blocks or those with ON affecting the third occipital nerve.[215,219] More destructive procedures carry increased risk of complications, including causalgia and neuroma formation.

Neck-Tongue Syndrome (NTS)

NTS Etiology and Pathogenesis

Neck-tongue syndrome (NTS) occurs when the C2 ventral ramus is compressed, entrapped, or stretched against the atlantoaxial joint as a result of underlying joint laxity. Afferent fibers from the lingual nerve are compressed in the same manner while transiting via the ventral ramus of C2 after anastomosing with hypoglossal nerve fibers. NTS can manifest secondary to minor or major trauma to the cervical joints.[223]

NTS Epidemiology

Approximately 50 cases of NTS have been reported to occur, primarily in childhood and adolescence with equal gender prevalence. It usually resolves with age.[223,224] NTS tends to cluster in families, likely due to susceptibility to joint laxity.[225, 226]

NTS Clinical Manifestations

NTS consists of severe sharp pain of the posterior neck or occiput together with numbness or involuntary movement of the ipsilateral tongue, both occurring after sudden movement of the neck.[8,227] Symptoms of NTS last between seconds to 2 minutes as in TGN, GPN, and ON.[226,227] Other headache symptoms, including pain shooting up the back of the head, can occur. Autonomic activation may also occur causing flushing and sensitivity to light and sound.[224,226,228]

The history is often positive for muscle guarding habits and the clinical examination is usually unremarkable, but may include tight cervical muscles and pain to palpation of the upper neck.

NTS Differential Diagnosis

The posterior neck pain in NTS may in its character and location resemble multiple other headache disorders, including cranial neuralgias and cervicogenic headaches. The main distinguishing factors of NTS are the simultaneous tongue symptoms.

NTS Laboratory Findings

NTS is usually self-limiting and does not require additional laboratory or imaging work up.[228]

NTS Management

Many patients with NTS will improve with time, and the symptoms are often rare and temporary enough to not require active treatment. Some patients may improve with exercises, postural correction, and habit awareness.[224] Spinal manipulation is not recommended as a treatment given the risk of adverse effects.[226] When necessary, patients can benefit from topical lidocaine application, local anesthetic and steroid injection to the posterior skull, and systemic medications including nonsteroidal anti-inflammatory drugs, steroids, tricyclic antidepressants, antiepileptics, and muscle relaxants.

Persistent Idiopathic Facial Pain (PIFP)

Persistent idiopathic facial pain (PIFP) is defined as "persistent facial and/or oral pain, with varying presentations but recurring daily for more than 2 hours per day over more than 3 months, in the absence of clinical neurological deficit."[222] This definition may include a large number of chronic facial pain disorders. PIFP has historically been termed atypical odontalgia (AO) or atypical facial pain (AFP). The diagnosis of AFP includes a heterogeneous group of patients since it was used when no other diagnosis was suitable.

Many cases diagnosed as PIFP could also be classified as chronic myofascial pain, traumatic neuropathy, pre- or atypical trigeminal neuralgia, facial migraine, or neurovascular orofacial pain.

PIFP Etiology and Pathophysiology

Studies of PIFP patients revealed increased neuronal excitability at the brainstem level,[229–231] disturbed inhibitory function of the prefrontal cortex,[232] and alterations in the dopamine systems associated with either/both pain transmission and its modulation.[233] Additionally, sensory changes consistent with a neuropathy or neuropathic pain have been shown employing QST in patients with PIFP.[128,230,234] The data seem to indicate that PIFP is a neuropathic pain syndrome similar to PTTN. PIFP and PTTN may represent extremes of a spectrum of clinical presentations. PIFP patients often have a history of mild trauma and subclinical sensory changes, while PTTN patients have history of a significant trauma and usually detectable sensory changes. Neurophysiologic and quantitative sensory examinations performed on PIFP patients by Forssell et al.[230] suggested that PIFP might be a heterogeneous entity representing one extreme of a continuum that ranges from definitive neuropathic pain syndromes to idiopathic pains with an unclear "neuropathic" involvement.[230]

PIFP Epidemiology

The estimated incidence of PIFP is 4.4 per 100,000 person years[235] and lifetime prevalence is around 0.03%,[236] with the majority of patients being females in their mid 40s.[237] PIFP may coexist with chronic orofacial pain syndromes such as chronic myogenic pain.[238]

PIFP Clinical Features

Minor surgical or other invasive dental or otolaryngologic procedures are often reported as the initiating event.[239,240,241]

Although there should be no clinically evident neurosensory deficits in PIFP[222] hypoesthesia has been reported in studies using quantitative sensory testing (QST).[128,230,234] This is confusing, since patients with a neuropathic type pain following surgery or other trauma with neurosensory changes should be diagnosed with painful traumatic trigeminal neuropathy (PTTN), as defined by the IHS.[126,222]

Pain in PIFP can be deep or superficial,[222] is poorly localized, radiates, and is unilateral in about 60% of the cases.[237] It is commonly described as aching, burning, throbbing or stabbing;[128,222,230,231,234,237,242] the pain severity is variable (rated 7 on an 11-point VAS) and it may be aggravated by emotional stress.[222,237] Most PIFP patients report persistent, long lasting (years) daily pain[237] that tends to spread in a nondermatomal pattern with time.[222] Typically, pain characteristics, location, and associated features change over time and pain free or remitting periods are very rare.[237] PIFP may coexist with other chronic orofacial pain or headache syndromes.[237]

Psychiatric and psychosocial disability have often been associated with PIFP,[243] although one study on 14 PIFP patients found no significant comorbid psychiatric disorders compared to controls.[231] PIFP patients reporting higher pain intensity tend to have increased scores for anxiety and depression,[244] suggesting that a psychiatric screening should be performed.[245] An interdisciplinary approach is needed for the diagnosis and management of PIFP.[246]

PIFP Management

The lack of a clear pathophysiological basis complicates the development of a treatment protocol. The approach to the management of PIFP patients should consider the effect of the pain disorder on the patients' personal lives.[247] Multidisciplinary approaches addressing comorbidities such as psychiatric disorders and the chronic course of the condition should be undertaken.[248] Considering the chronicity and resulting distress, behavioral interventions and medications known to have an effect in painful neuropathies, such as antidepressants and antiepileptic drugs, may be indicated. Patient education is also needed to clarify the diagnosis and to elucidate the risk of further invasive interventions aimed at pain relief in the absence of clear associated pathology.

Case series using tricyclic antidepressants,[249] an open study on duloxetine,[250] a randomized controlled trial on venlafaxine,[251] and open studies on anticonvulsants[252,253] and low level laser[254] have all shown beneficial effects but the level of evidence is low.

Occipital nerve blocks have not been efficient in PIFP patients.[255] Noninterventional novel therapies such as virtual reality,[256] hypnosis,[257] or complementary and alternative medicine[258] may have some benefit for PIFP patients. However, the evidence for psychosocial interventions is limited due to the lack of controlled studies.[259] Invasive procedures carry the risk for inducing a traumatic neuropathy and therefore may end up increasing pain.

It is important to note that available evidence for any of the treatments listed above is limited and randomized clinical trials are missing. Therefore a conservative, multidisciplinary approach based on experiences with comparable chronic orofacial pains or headaches is recommended.[248]

Atypical Odontalgia

Atypical Odontalgia (AO) is defined by the IASP as a severe throbbing pain in the tooth without major pathology and is considered a subentity of PIFP. AO has been referred to as phantom toothache, suggesting a neuropathic etiology.[260–262] It is also possible that various studies included some heterogeneous groups of patients with localized neuropathic or neurovascular syndromes. Repeated dental interventions aimed at pain relief in AO patients or undiagnosed orofacial pain cases may lead to nerve injury and PTTN. Chronic orofacial pain patients undergo extensive and often misguided surgical interventions[240,263] that are known to exacerbate pain in 55% of patients. About 5% of AO patients are misdiagnosed, which results in serious sequelae and delay of necessary treatment.[240]

Due to the ambiguity in the terminology it has been suggested that AO should not be used,[264] similarly to the way that AFP is no longer advocated. Patients with neuropathic pain following surgery or other trauma should be diagnosed as PTTN. However, in clinical reality, a number of patients with intraoral pain do not neatly fit any diagnostic category. These patients usually have persistent pain in the dentoalveolar region and have been grouped into a diagnosis of "primary persistent dentoalveolar pain" (PDAP).[265,266] Since AO seems to be an intraoral representation of PIFP, the term "persistent idiopathic dentoalveolar pain" seems very suitable.

Burning Mouth Syndrome (BMS)

There are many oral mucosal diseases that cause burning sensations as a result of observable local pathology. However, Burning Mouth Syndrome (BMS) refers specifically to burning pain involving the oral mucosa in the absence of either local pathology or underlying medical causes.[267] Over the years, the condition has also been known as stomatodynia, burning tongue, stomatopyresis, glossopyresis, glossodynia, and idiopathic glossodynia.

BMS Etiology and Pathogenesis

Before a diagnosis of BMS can be made, local and systemic causes of the symptoms must be ruled out.[268] These include oral mucosal lesions, candidiasis, and salivary gland disorders, as well as systemic causes such as anemia, diabetes, and deficiencies of iron, folate, and vitamin B12. In addition, antihypertensives in the angiotensin-converting enzyme (ACE) inhibitors class are known to cause oral burning as a side effect and, if suspected as the cause, the clinician prescribing these drugs should be consulted as to whether another class of antihypertensive drugs can be substituted.

Studies of BMS patients using laboratory investigations and imaging have shown an increased incidence of BMS in women after menopause. This has led to the suspicion of an association between BMS and hormonal changes,[269] but to date minimal evidence supports this theory.

Centrally, functional MRI of the brain of BMS patients demonstrates brain activation patterns similar to other neuropathic pain disorders as well as decreased dopamine levels. Locally, it has been hypothesized that dysfunction of the chorda tympani branch of the facial nerve may inhibit trigeminal nerve function causing reflex hyperactivity of the lingual nerve.[270,271] On incisional biopsy, patient with BMS are found to have local increases in ion channels associated with neural growth factors.[15,17,19] Salivary markers in affected patients also show altered immune mediator and mineral concentrations and increased markers of stress.[267,269]

BMS has also been associated with psychological disorders, particularly depression and anxiety. BMS patients may also suffer from gastrointestinal and chronic fatigue

syndromes, and other orofacial or generalized pain disorders.[272] The rates of psychiatric comorbidities observed in BMS, however, are approximately equal to those in other chronic pain disorders. Patients with BMS are also frequently found to exhibit altered sleep quality, although all of these may result from the correlation with anxiety and depression and not as a direct effect of BMS.[267] It is likely that some cases of BMS have a strong psychological component while in other cases factors including low-grade trauma and parafunctional habits (e.g., rubbing the tongue across the teeth or pressing it on the palate) play a larger role.[268] Sensory changes and altered pain modulation have been reported in BMS patients.[273,274]

Historical disagreement about the definition of this condition and the heterogeneity of patients included in studies have long led to confusion about patient characteristics, natural course of BMS, and effective management. For this reason, many have called for studies with standardized diagnostic classification and increased scientific rigor.

BMS Epidemiology

The estimated prevalence of BMS varies based on study design and diagnostic criteria between 3.7–15%.[272] Women experience symptoms of BMS 5 to 7 times more frequently than men, with the difference becoming most pronounced after menopause.[269,272] When questioned, 10–15% of postmenopausal women are found to have a history of oral burning sensations, and these symptoms are most prevalent 3 to 12 years after menopause.[275] Of patients with BMS, 30–60% also exhibit other neuropathic pains, decreased cold and heat sensitivity, and decreased pain thresholds.[267] Estimates may not capture the full burden of this condition, however, as patients commonly experience delays in diagnosis (mean 34 months) and misdiagnoses from multiple providers (mean 3.1 providers seen before receiving effective treatment).[269]

BMS Clinical Manifestations

The tongue is the most commonly affected structure in BMS, with pain in 71–78% of patients occurring in the anterior two thirds or tip of the tongue.[269] In half of the patients, the tongue is the only site affected. When more widespread, the dorsum and lateral borders of the tongue (72%), lips (24%), and anterior palate (25%) are frequently involved, although in some cases the burning pain may also affect the gingivae and pharynx.[269,272] Regardless of location, pain is usually bilateral and does not follow dermatomes.[272] There is no paroxysmal component of BMS. Pain may begin after dental treatment or another traumatic event in up to one third of patients.

Pain is most commonly described as burning or hot and intensity varies from mild to as severe as a toothache with average VAS 3.1–5.1/10.[269,272] Patients also describe the sensation as itching, tingling, tender, scalding, numb, raw, annoying, and uncomfortable.[269,271] The pain is long standing with variable intensity day to day, increasing toward the end of the day.[272,275]

BMS can be intermittent or constant, but eating, drinking cold drinks, or placing candy or chewing gum in the mouth characteristically relieves the symptoms, possibly due to activation of large neuronal fibers.[272] Common aggravating factors include personal stressors, fatigue, and specific foods (acidic, hot, spicy, and alcohol-containing).[268] More than two-thirds of patients complain of paresthesia, dysesthesia, or altered taste sensation[8,27] often described as metallic, bitter, or foul.[272] The subjective feeling of dry mouth is also common and although stimulated salivary flow is normal, unstimulated salivary flow may be decreased.

BMS is most common in patient with Type C personalities; those exhibiting fearful and neurotic tendencies.[267] Patients may also have symptoms that suggest depression, such as decreased appetite, insomnia or poor sleep quality, and a loss of interest in daily activities.[269] Women with BMS show more symptoms of obsessive-compulsive disorder, somatization, and paranoia than unaffected women, and men with BMS show more symptom distress than matched controls. Patients are also likely to exhibit multiple other nonspecific complaints, be taking other medications, and relate a history of severe menopause.[275]

BMS Differential Diagnosis

Other causes of oral burning must be eliminated by examination and laboratory studies. Patients with unilateral symptoms should have a thorough evaluation of the trigeminal and other cranial nerves to eliminate a neurologic source of pain. A careful clinical examination for oral lesions resulting from candidiasis, lichen planus, ill-fitting prostheses, allergy, or other mucosal diseases should be performed.[272,274] Patients complaining of a combination of xerostomia and burning should be evaluated for the possibility of a salivary gland disorder including Sjogren's syndrome, particularly if the mucosa appears dry and the patient has difficulty swallowing dry foods without sipping liquids.[268]

BMS Laboratory Findings

Laboratory studies should be reviewed or performed in order to rule out an underlying systemic cause of burning. In patients with no lesions or other systemic symptoms, clinicians should check complete blood count with a differential, metabolic panel including fasting blood glucose, hemoglobin A1C, iron, vitamin B12, and folic acid.[272,274,275] Other tests may be ordered on an individual basis according to examination findings.

BMS Management

Once the diagnosis of BMS has been made, the patient should be reassured that the burning is not caused by a serious or life-threatening disorder. Counseling the patient, acknowledging the condition, and connecting patients with other sufferers are helpful in management, and may be adequate for individuals with mild burning sensations. When necessary, consultation should be sought for any suspected underlying serious psychiatric disorder.[272,274,275]

BMS is often resistant to therapy and there are few evidence-based treatments, each of which has been evaluated only in small studies that lack long term follow up.[271] In addition, many BMS patients respond to placebo, complicating evaluation of treatment options.[275] Patients with parafunctional tongue habits often benefit from use of a protective soft dental splint.

Topical clonazepam is the most reliably effective drug therapy for BMS, although it is not effective for every patient.[276–278] A combination of topical and low doses of systemic clonazepam is also used.[279] It should be stressed to the patient that this drug is being used not to manage psychiatric illness but for its well-documented analgesic effect. Clinicians prescribing these drugs should be familiar with potential side effects including xerostomia, fatigue and lethargy, spasmophilia, euphoria, and the risk of dependence.[267,275] Systemic clonazepam carries the additional risks of memory and cognitive impairment.[272]

Many other topical and systemic medications have been proposed and studied in patients with BMS. These include pregabalin, histamine receptor agonists (lafutidine), other anxiolytics (chlordiazepoxide, diazepam), dopamine agonists (levodopa, pramipexol), and supplements including catuama (a mixture of guarana, catuaba, ginger, and muira puama).[268,269,272,274,280] A medication used topically is capsaicin, which depletes substance P to desensitize pain response.[267,271] Alpha lipoic acid (ALA), a mitochondrial antioxidant co-enzyme that increases neural growth factors, has also been studied.[281–284] Results to date are mixed but this treatment may be helpful, particularly in combination with other therapies.[271] Treatment with ALA can cause headache and gastrointestinal upset in some patients.[267,275]

Nonpharmacologic management strategies have also been proposed in BMS. The most commonly recommended is cognitive behavioral therapy (CBT), in which a trained counselor uses biofeedback, relaxation, exposure, and cognitive restructuring among other modalities to redefine the patient's pain experience. This is effective in finding coping strategies, addressing catastrophizing, and improving mood disorders.[267,272,285,286] Other defocusing strategies including psychotherapy, exercise regimens, yoga, tai-chi, and acupuncture may also be beneficial[269,271,287] and tongue protectors and other appliances can address any parafunctional habit.[269,272]

Central Causes of Facial Pain

Direct damage to the central nervous system (stroke or spinal cord trauma) or indirect damage induced by diseases such as epilepsy, Parkinson's disease, and multiple sclerosis may result in central pain (CP). These pains are usually associated with decreased sensation and are termed anaesthesia dolorosa and deafferentation pain. Painful peripheral traumatic neuropathies may involve central mechanisms; however, the initiating events are peripheral.

Central Post Stroke Pain (CPSP)

CPSP is characterized by constant or paroxysmal pain accompanied by sensory abnormalities such as decreased perception and frequently allodynia. Severity and prevalence of CPSP may be underestimated as many post-stroke patients are unable to self-report their pain.[288]

CPSP Epidemiology

CPSP occurs within 6–12 months in 2.7–11% of all stroke patients and 25% of brainstem infarct patients.[289–291] Women and younger patients seem to be at higher risk of CPSP following stroke.[290] CPSP is commonly located in the upper extremity (37.9%), the lower extremity (20.7%), and in both upper and lower extremities (10.3%). The pain is located more rarely in the head (16.0%) and in both head and lower extremity in (3.4%). The entire side of the body is affected in around 10%.[290,292]

CPSP Pathophysiology

Although the exact pathophysiology of CPSP is unclear, it is thought to result from imbalance in facilitatory and inhibitory pathways and ectopic activity in damaged neurons induced by the stroke. CPSP is often associated with lesions of the ventrocaudal thalamic nuclei and particularly within the ventroposterior inferior nucleus, suggesting that the pain is associated to thalamus pain pathways. Spinothalamic pathways and cortical processing have also been shown to be associated to CPSP.[293] However, not all patients with spinothalamic pathway damage following stroke develop pain, suggesting that this cannot be the sole pathophysiologic mechanism leading to CPSP.

CPSP Clinical Features of Head/Face

Brainstem lesions induced by lateral medullary infarct may induce pain in the face that is usually unilateral in the periorbital area.[294] The pain quality is most frequently described as burning or hot, aching, pricking, stinging, lacerating, and pressure like.[292] Patients with thalamic stroke frequently describe the quality of pain as lacerating. The pain intensity is moderate to severe that can be exacerbated by light touch, cold, and movement.[294]

According to IHS criteria, symptoms must occur within 6 months of a stroke to be classified as CPSP. The onset is usually within 1 month (range 3–6 months), although a gradual onset of CPSP within 6 years has been reported.[292] The pain is usually constant, around one quarter of CPSP patients reported persistent pain with superimposed attacks and 42% reported paroxysmal pain lasting seconds to minutes.[294]

Motor impairment and a variety of sensory symptoms may occur, depending on the location and extent of the lesion. Constant or evoked dysesthesia is the most common abnormal sensation;[289] however, other symptoms include unilateral pain and/or dysesthesia associated with loss of sensation to pin-prick, temperature, and touch.[292] Thermal sensory impairment has been reported in the majority of CPSP cases and sensory dysfunction that correlates with the presence of pain occurs in over half of cases.[294] About 60% of CPSP patients present with muscle spasticity.

CPSP Management

Antidepressants, such as amitriptyline, as well as anticonvulsants, such as lamotrigine, are effective in CPSP and should be considered first.[293,295,296] Gabapentin is a good second choice drug.[293] Intravenous treatment with lidocaine or propofol may provide short-term pain relief.[293] Poststroke patients may not respond well to tricyclic antidepressants, therefore anticonvulsants may be a better option.[297]

PAIN ASSESSMENT

Pain measurement is an essential element in any medical assessment, including diagnosis, monitoring of disease progress, and evaluation of treatment effectiveness. Unfortunately, there is no one common or easy method of pain measurement. Pain is difficult to measure; it is a personal and private experience that cannot be seen or felt by others. The methods used for pain assessment may include indirect, self-report, physiological, and behavioral methods.

Pain intensity and frequency are probably the most important features measured to assess a patient's wellbeing; however, pain quality, onset, duration, localization, and other additional factors that alleviate or aggravate the pain, occurrence of pain elsewhere in the body, and associated psychosocial problems should be assessed as well.

Drawing the painful area on a body map and a pain diary may provide necessary information. These methods should be standardized and used consistently with each patient.

Pain Scales

The visual analog scale (VAS) is the most frequently used method to assess pain intensity. The scale is usually a horizontal[298,299] or vertical 10 centimeter (cm) line[300] labeled at each end by descriptors such as "no pain" and "worse pain ever." The patient marks the line to indicate pain severity and level is quantified by measuring the distance in cm from zero (no pain) to the patient's marked rating. This method has been validated in a number of studies,[301] but was found to be insufficient in others.[302] A popular variation of the VAS that was designed for children or for patients that do not have the verbal skills to describe their symptoms is the Faces Pain Rating Scale, which is comprised of a series of faces with different expressions in a continuum from a happy face for "no pain" to a very sad face for intense pain.[303,304]

In the Numerical Rating Scale (NRS), patients are asked to rate their pain on a scale from 0 to 10 or 0 to 100, in which "0" is no pain and the other end of the scale represents the worst possible pain.[305] Verbal descriptive scales incorporate specific words organized to express the increasing and progressive intensity of pain. A category scale is a simple form of a verbal scale and in clinical trials is usually composed of four pain descriptions, such as none, mild, moderate, and severe. Simple category scales can be used for rough comparisons or in addition to other pain scales and the number of categories can be increased to achieve greater resolution. Hybrid scales combine verbal scales with graphic rating or with numerical scales; the descriptors are placed in appropriate locations on the analogue scale.[306,307]

There is no simple guide to the choice of pain scale; however, numerical, visual, and verbal scales have been validated in numerous studies and the choice must be specifically established considering the individual patient or research project in question.

Most visual analog, numerical, or verbal pain scales rate pain as a unidimensional experience. More sophisticated questionnaires have been developed that address the multidimensional experience that pain induces.

Pain Questionnaires

The McGill Pain Questionnaire (MPQ)[308] is the most frequently used questionnaire for the multidimensional assessment of pain. The MPQ assesses three separate components of the pain experience: the sensory intensity, the emotional impact, and the cognitive evaluation of pain. Patients are presented with 78 adjectives in 20 groups, or dimensions, and are instructed to select one from each of the groups that most closely matches their own pain experience. An overall score for each major dimension is obtained from the sum of either weighted scores or ranking the chosen words within the group.

The translation of the MPQ to many languages has shown that people from different ethnic and educational backgrounds use similar adjectives to describe the same pain

conditions.[309] The MPQ has been found to be sensitive to pain interventions, and therefore can evaluate treatment efficacy.[310–312] In the orofacial region, the MPQ has been validated in trigeminal neuralgia, atypical odontalgia, toothache, and Burning Mouth Syndrome.[313,314] A short form (MPQ-SF) is available that consists of 15 selected adjectives that patients score on a four-point scale and a VAS that is used for measurement of pain intensity.[315–318]

Other multidimensional questionnaires have also found common psychological patterns for patients in pain, regardless of etiology, location, treatment, and the medical or dental diagnosis.[319,320]

Quantitative Sensory Testing

The term Quantitative Sensory Testing (OST) embraces several methods used to quantify sensory nerve function. QST utilizes noninvasive assessment and quantification of sensory nerve function in patients with suspected neurological damage or disease. The common concepts in QST methods are that the assessment of normal and non-normal responses to various stimuli provides information about the functioning of the peripheral and central nervous system and that these responses can be quantified by the amount of physical stimuli required to evoke specific levels of sensory perception. The response to gross external stimuli has been part of the formal neurological evaluation since the late 19th century. The concept is still valid, and years of research and development of new tools have improved the benefit gained from such tests. External stimuli are usually mechanical and thermal.

QST is an accepted tool for the assessment of diabetic neuropathies[321] and other sensory abnormalities.[322] However, although it is an important tool, currently QST cannot be used alone to diagnose neuropathies.[321]

The establishment of normal QST ranges is complicated by numerous variables including probe or electrode size, stimulus frequency, site, rate of stimulus change, clinical environment, gender, age, and ethnicity. A significant attempt for QST standardization was made by The German Research Network on Neuropathic Pain.[323] Systematic sequences of thermal and mechanical QST were employed on patients suffering from various neuropathic pain conditions. The findings were categorized as gain or loss of sensation. Ninety two percent of the patients presented at least one sensory abnormality and a sensory profile was suggested for each neurological syndrome. However, combinations of gain and loss sensations were found to exist across the syndromes.

The use of QST in the trigeminal system or other orofacial areas requires further research before being used in routine clinical practice; however, the field is sufficiently developed to aid diagnosis and the evaluation of treatment.[123]

Dynamic Pain Psychophysical Testing

A growing body of evidence suggests that the use of a new generation of "dynamic" pain psychophysical testing can be used to evaluate pain modulation processes. The dynamic testing relies on the fact that pain perception is transmitted from the periphery to the CNS, and then modulated in the CNS before its arrival in the cortex. Similar external stimuli may be perceived differently among individuals, depending on their modulation processes. Two modulation components are routinely tested in the lab; Temporal Summation (TS), which is thought to be the psychophysical correlate of second/third order neuron wind-up, probably reflecting central sensitization, and Central Pain Modulation (CPM), which is thought to measure endogenous pain inhibition. TS is associated with excessive activation of N-methyl-D-aspartate (NMDA) receptors in response to extensive nociceptive input. The clinical manifestation may be allodynia and hyperalgesia.[324–326] TS is tested by application of identical repetitive stimuli, an increase in pain scores is documented along or in the end of the stimuli. CPM represents the endogenous analgesia system, where descending pathways induce modulatory effects on incoming painful stimuli.[327] CPM is tested by using two remote noxious stimuli with one, the "conditioning" pain inhibiting the other, the "test" pain. In recent years, many reports used both TS and CPM to demonstrate altered pain modulation in chronic pain patients. Enhanced TS was found in chronic pain patients such as fibromyalgia,[328–331] tension headache and musculoskeletal pain,[332,333] migraine,[334] chronic low back pain,[335] and Temporomandibular Disorders (TMD).[336–340] Similarly, less-efficient CPM response was found in many of the idiopathic pain syndromes such as TMD,[341] fibromyalgia,[331,342–344], tension headache,[345] BMS,[274] and Irritable Bowel Syndrome.[346] Among healthy subjects, reduced pain-modulatory capacity was demonstrated in older subjects[347] and among females compared to males.[348] A combination of reduced CPM and enhanced TS was found among patients with chronic postendodontic treatment pain.[77]

It has been suggested that the pain modulatory system can define susceptibility to the development of chronic pain disorders.[349–352] Patients who presented an altered pain modulation were found to be more prone to develop postoperative (thoracotomy) chronic pain.[141] Moreover, recent studies have shown that painful diabetic neuropathy patients with less efficient CPM benefit more from treatment with duloxetine,[353] which has the potential to enhance the descending pain inhibition by inhibiting reuptake of spinal noradrenalin (NA) and serotonin.[353–355]

	PTTN[1]	BMS[2]	PIFP[3]
Epidemiology	0.3–36% depending on the cause	0.7–15%	0.03% lifetime prevalence 4.4/100,000 person years incidence rate
Pathophysiology	Trauma, implants, mandibular third molar extraction, root canal therapy, local injection	Neuropathic pain state; hormonal and psychosocial factors implicated; altered salivary composition, epithelial changes in the tongue, reduced innervation	Neuropathic pain syndrome; trauma
Pain Quality	Burning, shooting, severe throbbing; continuous; unilateral	Burning or hot; spontaneous onset; chronic unremitting pattern	Aching, burning, throbbing, stubbing; deep, poorly localized, radiating, mostly unilateral
Pain Severity	Moderate to severe (VAS: 5–8)	Mild to moderate (VAS: 3–7)	Mild to severe (VAS: 7–8)
Diagnostic criteria[4]	A. Facial and/or oral pain in the distribution(s) of one or both trigeminal nerve(s) and fulfilling criterion C B. History of an identifiable traumatic event to the trigeminal nerve(s), with clinically evident positive (hyperalgesia, allodynia) and/or negative (hypoesthesia, hypoalgesia) signs of trigeminal neve dysfunction C. Evidence of causation demonstrated by both of the following 1. Pain is localized to the distribution(s) of the trigeminal nerve(s) affected by the traumatic event 2. Pain has developed < 6 months after the traumatic event D. Not better accounted for by another ICHD-3 diagnosis	A. Oral pain fulfilling criteria B and C B. Recurring daily for > 2 hrs. per day for > 3 months C. Pain has both of the following characteristics: 1. Burning quality 2. Felt superficially in the oral mucosa D. Oral mucosa is of normal appearance and clinical examination including sensory testing is normal E. Not better accounted for by another ICHD-3 diagnosis	F. Facial and/or oral pain fulfilling criteria B and C G. Recurring daily for > 2 hrs. per day for >3 months H. Pain has both of the following characteristics 1. Poorly localized, and not following the distribution of a peripheral nerve 2. Dull, aching or nagging quality I. Clinical neurological examination in normal J. A dental cause has been excluded by appropriate investigations K. Not better accounted for by another ICHD-3 diagnosis

[1]Post-traumatic trigeminal neuropathy (PTTN)
[2]Burning Mouth Syndrome (BMS)
[3]Persistent idiopathic facial pain (PIFP)
[4]http://www.ihs-headache.org

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12

Common Headache Disorders

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- ❒ CLASSIFICATION
- ❒ DIAGNOSING HEADACHES
- ❒ PRIMARY HEADACHES
  - Migraine (ICD-10: G43)
  - Tension-Type Headache (ICD-10: G44.2)
  - Trigeminal Autonomic Cephalalgias (ICD-10: G44.0)
  - Hemicrania Continua
- ❒ SECONDARY HEADACHES
  - Headache Attributed to Nontraumatic Subarachnoid Hemorrhage (ICD-10: G44.812)
  - Headache Attributed to Giant Cell Arteritis (ICD-10: G44.812)
  - Headache Attributed to Idiopathic Intracranial Hypertension (ICD-10: G44.820)
  - Headache Attributed to Intracranial Neoplasm (ICD-10: G44.822)
  - Sleep Apnea Headache (ICD-10: G44.882)

Headaches are the most prevalent neurologic disorder. It is estimated that approximately 50% of the general population have headaches during any given year and more than 90% report a lifetime history of headache. Tension-type headache (TTH) is the most common form of primary headache, with a lifetime prevalence of about 52% compared to the lifetime prevalence of migraine of 18%. Chronic headache, defined as 15 or more headache days a month, affects 1.7–4% of the world's adult population. Despite regional variations, headache disorders are a worldwide problem, affecting people of all ages, races, income levels, and geographic areas. Headaches are relatively rare in children but increase with age. Headache in general, and migraine specifically, increases in frequency during adolescence, particularly in women of childbearing age.

CLASSIFICATION

The International Classification of Headache disorders (ICHD-3; Table 12-1) classifies headaches based on specific inclusion and exclusion criteria, and is a flexible operational tool for both clinical and research application.[1] In this classification there are three domains, namely primary headaches; secondary headaches; and neuropathies, facial pains, and other headache disorders. Nearly 300 different types of headaches and facial pain are described in the ICHD-3. While some types of headaches are significantly more common than others, one must be mindful that the rate of misdiagnosis is probably equivalent to one's knowledge (or lack thereof). Diagnostic challenges are compounded by the fact that many patients experience more than one type of headache, and that some patients are, unfortunately, unable to provide an accurate headache history, which is one of the most important aspect of the diagnostic work-up.

DIAGNOSING HEADACHES

The diagnosis of headache is largely based on clinical symptoms and therefore an accurate history represents a crucial element of the diagnostic process. A comprehensive history

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

Table 12-1 ICHD-3 (International Classification of Headache Disorders, 3rd Edition).

Part I: The Primary Headaches
1) Migraine
2) Tension-type headache (TTH)
3) Trigeminal autonomic cephalalgias (TACs)
4) Other primary headache disorders
Part II: The Secondary Headaches
5) Headache attributed to trauma or injury to the head and/or neck
6) Headache attributed to cranial or cervical vascular disorder
7) Headache attributed to nonvascular intracranial disorder
8) Headache attributed to a substance or its withdrawal
9) Headache attributed to infection
10) Headache attributed to disorder of homeostasis
11) Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure
12) Headache attributed to psychiatric disorder
Part III: Neuropathies and Facial Pains and Other Headaches
13) Painful lesions of the cranial nerves and other facial pain
14) Other headache disorders

Source: Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*, 2018;38(1):1–211.

needs time, interest, focus, and establishment of rapport with the patient. When to ask what question to elicit specific information is an art that is acquired by practice and improves with experience. Rather than relying on the patient to report pertinent symptoms, the clinician must possess sufficient knowledge to know what questions to ask in succession and what symptoms to explore.

Many patients experience more than one type of headache. Patients may distinguish various types of headaches according to location, severity, triggering factors, or associated factors. For each type of headache, the following elements need to be determined as part of the complete headache history, starting with the headache of greatest importance to the patient: (1) headache location, (2) onset, (3) precipitating factors, (4) quality, (5) intensity, (6) frequency and duration, (7) triggering factors, (8) aggravating factors, (9) relieving factors, and (10) associated factors. Ascertaining the characteristic pain quality may help distinguish one type of headache from another. For instance, while most TTHs are described as tight "band-like" pain or pressure, migraines tend to be described as "throbbing" or "pounding." While the pain intensity of a migraine is often rated as severe, that of a TTH is often mild or moderate. Associated factors may include photophobia or phonophobia, which is relevant for the diagnosis of migraine, or the presence of autonomic symptoms, which is relevant for the diagnosis of trigeminal autonomic cephalalgias (TACs). It is often helpful for the patient to complete a headache diary (Figure 12-1; numerous versions are available for download as smartphone apps), as an aid to establishing a diagnosis, monitoring the headache symptoms, and/or evaluating the response to treatment.[2]

A critical consideration in evaluating headache is ruling out an underlying structural lesion or systemic disease, such as intracranial tumor, severe infection, aneurysm, uncontrolled hypertension, or stroke (i.e., secondary headaches). The systematic SNNOOP10 is an important and useful screen for secondary headaches (Table 12-2).[3] A neurologic examination with emphasis on the gross function of the cranial nerves is essential when the history is suggestive of a secondary headache. Diagnostic imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), is useful in screening for intracranial pathology. An MRI and magnetic resonance angiography (MRA) of the brain with contrast is the diagnostic modality of choice in nonemergent cases. In the presence of a normal neurologic examination, the prevalence of vascular and neoplastic findings is low, 6.6% and 1.4%, respectively.[4] In 2020, the American Headache Society recommended against the need for neuroimaging for migraines in the absence of atypical features (Table 12-2).[5]

Headaches are highly comorbid with oral and facial pain. The International Classification of Orofacial Pain emphasizes three types of interactions between headaches and orofacial pain.[6] First, headache patients can experience additional facial pain during headache attacks; second,

DATE	**TIME** (start/finish)	**INTENSITY** rate 1–10 (most severe being 10)	**PRECEDING SYMPTOMS**	**TRIGGERS**	**MEDICATION** (and dosage)	**RELIEF** (complete/moderate/none)

Figure 12-1 Headache diary. *Source:* American Headache Foundation.

Table 12-2 SNNOOP10 red flags to identify secondary headache.

	Sign or Symptom
1	Systemic symptoms including fever
2	Neoplasm in history
3	Neurologic deficit or dysfunction (including decreased consciousness)
4	Onset of headache is sudden or abrupt
5	Older age (after 50 years)
6	Pattern change or recent onset of headache
7	Positional headache
8	Precipitated by sneezing, coughing, or exercise
9	Papilledema
10	Progressive headache in atypical presentations
11	Pregnancy or puerperium
12	Painful eye with autonomic features
13	Post-traumatic onset of headache
14	Pathology of the immune system such as HIV
15	Painkiller overuse or new drug at onset of headache

Source: Do TP, Remmers A, Schytz HW, et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. *Neurology*. 2019;92(3):134–144.

headaches may be replaced by facial pain of the same quality, intensity, and duration; and third, facial pain resembling primary headaches may present in headache-naïve patients. It is not unusual for headaches to present in the midface or dentoalveolar region, mimicking dental pain. Another important comorbidity is psychopathology, especially depression, anxiety, and somatization. Evidence from Genome-Wide Association Study (GWAS) data suggests significant shared genetic underlying mechanisms for migraine and depression.[7] The psychologic status of the patient may need to be assessed by a clinical psychologist, given the well-demonstrated relationship between chronic head pain, poor sleep, and elevated psychosocial distress. Assessment of disability or limitation of activities, during and after a headache episode, should also be considered, especially for migraineurs. The extent of disability can be gauged using instruments such as a Migraine Disability Assessment (MIDAS) questionnaire and the Headache Impact Test (HIT-6).[8]

PRIMARY HEADACHES

The ICHD-3 classifies headaches into primary and secondary headaches.[1] The primary headaches represent the vast majority of headaches and are defined as headaches without an underlying disease or structural cause. These headaches include migraine, TTH, TAC, and other primary headache disorders (Table 12-1).

Migraine (ICD-10: G43)

Migraine is more than "just a headache." It is a complex but relatively benign neurologic disorder with head pain as one of its clinical manifestations. It is also associated with a broad spectrum of other symptoms caused by the involvement of several brain structures. There are 23 International Classification of Diseases, Tenth Revision (ICD-10) codes for migraine diagnosis, reflecting the complexity of its subtypes.

Epidemiology

The global prevalence of migraine is approximately 14.4% and it is three times more frequent in females than males.[9] In children, abdominal migraine is a subtype of functional abdominal pain affecting about 13.5% of children worldwide. A high incidence of infant colic has been reported in migraineurs compared to controls.[10] In females, there is a sudden increase in prevalence during puberty and a decline following menopause. Considering the high prevalence during the most productive years of a patient's life, there is, consequently, a substantial cost to society due to decreased productivity and increased healthcare utilization. According to the 2016 Global Burden of Disease (GBD) study, migraine is the second most disabling condition in the world (second to low back pain).[11] The consequential impaired functioning and decreased quality of life make migraine a debilitating neurologic disease.[12] It is therefore no surprise that an increased risk of suicidal behavior has been reported in chronic migraineurs.[13] About a third of migraineurs also experience auras, and female migraineurs who experience auras are more susceptible to ischemic stroke.[14]

Pathophysiology

Migraine is a complex neurovascular headache.[15] Its etiopathophysiology is not completely understood. The phenomenon underlying the migraine pain and aura is cortical spreading depression (CSD), which is a self-propagating neuronal and glial depolarization that spreads across the cerebral cortex. This process results in neuronal dysfunction, substantiated by recent evidence of microstructural abnormalities of the trigeminal nerve in migraineurs.[16] The headache also involves recurrent activation of the trigeminocervical complex by neurotransmitters, such as neuropeptides, of which the calcitonin gene-related peptide (CGRP) is known to be a key player, and other inflammatory mediators, which cause neurogenic inflammation and neuronal sensitization.[17] Research on gut–brain interaction suggests

that the gut microbiota profile also plays a role in migraine pathogenesis.[18]

There appears to be a genetic and familial risk, as more than half of all migraineurs report having other family members who suffer from migraine. In addition, specific mutations leading to rare causes of vascular headache have been identified.[15] Hemiplegic migraine, for example, is caused by mutations in genes that encode ion channel and transport proteins. Genetic mutations cause impaired neurotransmission and cortical hyperexcitability, which result in increased susceptibility to CSD and impaired sensory processing. The gene and environment interaction has received much attention in the last decade. This epigenetic link in migraine suggests that DNA methylation of numerous genes is also involved in migraine pathogenesis.[19]

Migraine is a spectrum disorder. In some people, episodic migraine increases in frequency and evolves into chronic migraine, a process known as transformation. The pathophysiologic mechanisms responsible for chronification are not well understood, but likely involve genetic and epigenetic factors, neurogenic inflammation, and central sensitization. In recent years, TTH and migraine have been considered to be part of the same continuous spectrum rather than individual and distinct disease states.

Migraine, especially greater headache pain intensity and frequency, is significantly comorbid with insomnia, depression, anxiety, gastric ulcers, angina, and epilepsy.[20] The comorbidity of migraine and temporomandibular disorders (TMD) is also well established.[21] Individuals suffering from both TMD and migraine also had higher prevalence of bodily pain and systemic diseases.[22] A prospective cohort in the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study identified migraine as a risk factor for the development of TMD.[23] Therefore, prompt management of migraine may reduce the risk of developing TMD.

Clinical Features

The migraine headache is a moderate to severe, pulsating, unilateral head pain that is aggravated by routine physical activity (such as walking or climbing stairs). In addition, nausea and/or vomiting, or photophobia and phonophobia, are present. Osmophobia has been reported to increase the diagnostic sensitivity of migraine.[24] The headache begins with gradual onset, reaching a peak in 2–4 hours. The pain typically lasts 4–72 hours untreated or unsuccessfully treated. Migraine may present as isolated facial pain, rendering it an important differential diagnosis for dental pain and TMD.[25] Orofacial migraine is an episodic or chronic pain that presents exclusively in the orofacial region, without head pain, with the characteristics and associated features of migraine as described in the ICHD-3.[6] The three-item ID Migraine screener is a valid and reliable screening instrument for migraine, which is especially useful in primary care and epidemiologic settings.[26]

In migraine with aura, the headache is preceded or accompanied by one or more fully reversible aura symptoms. An aura is a unilateral, stereotyped, sensory, motor, visual, speech, brainstem, or retinal focal neurologic symptom. The aura symptoms usually develop gradually and last minutes. Visual aura is the most common. Sensory aura such as paresthesia follow a cortical somatotopic pattern and may involve the face, lips, and tongue. Rarely, focal motor weakness may occur. Prodromal symptoms such as fatigue, poor concentration, and neck stiffness may begin hours to a few days before a migraine. These symptoms should not be confused with aura symptoms. What was previously misconstrued as migraine triggers, such as eating chocolate and bright light, is now known to be prodromal symptoms warning of the impending migraine. These symptoms announce the arrival of the migraine and precede the head pain. Patients should be taught to recognize these prodromal symptoms so that abortive medications can be administered early in the migraine attack for maximum efficacy. Similarly, postdromal symptoms, such as fatigue or mood change, may last hours or a few days following the migraine.

Migraines occurring at least 15 days per month for more than 3 months fulfill the criteria for chronic migraine, although patients with 8 or more migraine days per month are similarly disabled.[27] Data from the Chronic Migraine Epidemiology and Outcomes (CaMEO) study suggests that the presence of noncephalic pain (pain in the face, neck, back, arms, legs, chest, abdomen, and other locations) may identify episodic migraineurs who are at risk of chronicity.[28] The American Academy of Neurology recommends neuroimaging only for migraine with atypical headache patterns or neurologic signs.[29]

Management

The management of migraine includes patient education, in addition to pharmacologic and nonpharmacologic strategies. The patient needs to be educated about the diagnosis, etiology, trigger avoidance (if applicable), and management strategies. Generally, pharmacotherapy is divided into prophylactic or preventative therapy, and acute or abortive therapy.

Patients experiencing four or more migraine headache days per month, patients whose migraines significantly interfere with daily routine despite acute treatment, and patients in whom acute treatment is contraindicated, has failed, or is overused (defined as use in 10 or more days per month) are candidates for prophylactic therapy.[30] First-line migraine preventatives (Table 12-3) include anticonvulsants (such as topiramate, which is the only US Food and Drug Administration (FDA)-approved oral chronic migraine

Table 12-3 Migraine preventative medications listed in order of most established efficacy.

Drug Class	Examples
Anticonvulsants	Topiramate, valproate sodium, divalproex sodium
Beta-adrenergic blockers	metoprolol, propranolol, timolol
Onabotulinum toxin	Onabotulinum toxin A
Calcitonin gene-related peptide monoclonal antibodies (CGRP MABs)	Erenumab, fremanezumab, galcanezumab
Triptans	Frovatriptan
Antidepressants	Amitriptyline, venlafaxine

Table 12-4 Migraine-abortive medications (listed in order of most established efficacy).

Drug Class	Examples
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Aspirin, ibuprofen, diclofenac, naproxen
Ergot alkaloids	Dihydroergotamine, ergotamine
Triptans (5HT receptor agonists)	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, lasmiditan
Gepants (calcitonin gene-related peptide [CGRP] receptor antagonists)	Ubrogepant, rimegepant
Opioids	Butorphanol

preventative), β-adrenergic receptor blockers (metoprolol, propranolol, and timolol), frovatriptan, and onabotulinum toxin A. Second-line therapy includes amitriptyline, venlafaxine, atenolol, and nadolol. The oral prophylactics must be taken daily and usually have a 2–6-week period before an effect is observed. Onabotulinum toxin A is FDA approved for the management of chronic migraine and is injected every 3 months via the PREEMPT protocol using a total of 155 units into 31 injection sites.[31] Onabotulinum toxin A acts via blocking the release of pro-inflammatory and excitatory neurotransmitters and reducing the pronociceptive ion channels on the afferent neurons. Monoclonal antibodies (MABs) targeting the CGRP receptor (such as erenumab, fremanezumab, and galcanezumab) have been recently approved by the FDA for the prevention of migraine.[32] CGRP pathway blockers are the first mechanism-specific migraine treatment. The CGRP MABs are injected subcutaneously monthly and are devoid of drug interaction concerns. The most common adverse effects are injection site discomfort, constipation, and hypertension. They are indicated upon failure of at least two oral preventatives or inadequate response to at least two quarterly injections of onabotulinum toxin A.[30] A reasonable goal for preventative therapy is a 50% reduction in migraine headache days, a significant decrease in migraine duration or pain intensity, improved response to acute treatment, reduction in migraine-related disability, or improvement in quality of life.

Episodic migraine can often be managed with abortive therapy alone. While most individual attacks are successfully managed with oral agents, parenteral drugs may be necessary when nausea and/or vomiting accompany the attacks. Abortive agents for migraine (Table 12-4) include the nonsteroidal anti-inflammatory drugs (NSAIDs), ergotamine derivatives, the triptans (5-$HT_{1B/1D/1F}$ agonists), opioids, and the gepants (CGRP receptor antagonists). Ergotamine and its derivatives are nonselective 5-hydroxytryptamine (5-HT_1) receptor agonists, whereas the triptans are selective 5-HT_1 receptor agonists. Triptans are available in oral, nasal, and parenteral formulations, and in combination with NSAIDs. They are contraindicated in ischemic vascular conditions, uncontrolled hypertension, and other significant cardiovascular disease. A novel selective 5-HT_{1F} receptor agonist, lasmiditan, is devoid of vasoconstrictor properties.[33] Lasmiditan acts presynaptically to block the release of pro-nociceptive neurotransmitters, and therefore has a high positive response rate. It is also a more specific agonist, resulting in fewer side effects, most commonly dizziness. Novel CGRP receptor antagonists, the gepants (such as ubrogepant and rimegepant), have also been recently approved by the FDA for the acute treatment of migraine.[34] The gepants do not have a vasoconstrictor effect either. The blockage of the CGRP pathway in the form of both abortive agents and prophylaxis has blurred the line in the concept of acute versus preventative therapy. It is noteworthy that the presence of cutaneous allodynia increases the likelihood of poor response to treatment for all oral abortive agents, urging the need for prompt administration at migraine onset and the use of intranasal and injectable agents (due to faster onset compared with oral agents).[35] It is also noteworthy that frequent use of migraine-abortive medications may cause medication-overuse headaches (defined as the use of abortive medication for 10–15 days per month and that the abortive is causing the increase in headaches).

Nonpharmacologic management plays an important role in the management of migraine. This includes biobehavioral therapies such as relaxation training, biofeedback, cognitive behavioral therapy, mindfulness and meditation, and other forms of complementary and alternative therapies such as acupuncture treatment.[36] These modalities are important for patients in whom pharmacologic management is contraindicated and for those who prefer nonpharmacologic management. In addition, when combined with pharmacotherapy,

they may enhance the clinical therapeutic outcome or permit a reduction in the amount of medications used. Pericranial nerve blocks, including occipital nerve blocks and sphenopalatine ganglion blocks, have been investigated for both migraine abortion and prevention.[37] They are associated with few contraindications, good safety, and are generally well tolerated. Percutaneous implantation of neurostimulators and surgical decompression procedures have also received much attention despite the lack of well-designed clinical trials. Neuromodulation approaches such as single-pulse transcranial magnetic stimulation, noninvasive vagus nerve stimulation, and external trigeminal nerve stimulation have been approved by the FDA for migraine treatment.[38] Last but not least, adequate management of migraine comorbidities is integral to the success of migraine management. Comorbid depression, anxiety, insomnia, and widespread pain (including TMD) should be identified and their management prioritized.

Tension-Type Headache (ICD-10: G44.2)

Epidemiology

TTH affects 26.1% of individuals worldwide.[11] The GBD study estimated that 1.89 billion people worldwide had TTH while a lower number, 1.04 billion, had migraine. Although TTH has a similar, if not higher, socioeconomic impact compared to migraine, much less recent research has been conducted on TTH compared to migraine research. This is possibly because TTH is less disabling. Over 80% of adults experience TTH periodically. Some contrasts between TTH and migraine include that (1) TTH is rarely disabling in its severity (unlike migraine); (2) the female:male ratio for TTH is 5:4, indicating that women are only slightly more likely to be affected than men (in contrast with the preponderance of female migraineurs); and (3) the average age of onset of TTH is higher than that for migraine, namely 25–30 years.

Pathophysiology

Although TTH is common, the pathophysiology remains unclear. Contrary to what its name suggests, electromyography has not revealed an increase in resting muscle tension in TTH. Pericranial muscle tenderness is not a universal finding in TTH, leading to the hypothesis that central mechanisms are likely responsible for the peripheral pain. The overlap between TTH and myofascial pain has also been well described. There were significantly more active trigger points in the head, neck, shoulder, and upper back muscles of patients with chronic TTH (CTTH) compared with controls.[39] In a randomized controlled trial, dry needling significantly reduced the intensity, frequency, and duration of CTTH compared to sham dry needling.[40] Therefore, a peripheral mechanism in the pathogenesis of TTH cannot be excluded either. The generalized lowered pressure pain threshold in myofascial pain may contribute to the central sensitization in TTH. In addition, the overlap between TTH and Headache Attributed to TMD (TMDH) is also noteworthy (see Chapter 10). TMDH is a secondary headache caused by a disorder of the structures in the temporomandibular region. While the need to screen and rule out secondary headaches cannot be overemphasized, the experience of more than one headache type is not uncommon and can complicate the diagnosis.

Genetic twin association studies in monozygotic twins suggest that shared genetic factors likely account for the comorbidity of migraine and TTH. In a longitudinal population-based study, 23.3% of migraineurs evolved into definite TTH 5 years later, while 14.7% of those with TTH evolved into definite migraine.[41] Only 32.3% remained as TTH. The transition from migraine to TTH and vice versa over time is therefore not unusual. TTH and migraine are thus believed to be on the same continuous spectrum rather than distinct entities.

Similar to migraine, TTH is highly associated with sleep disturbances (especially CTTH) and psychiatric comorbidity such as stress, anxiety, and depression.[42,43] A higher prevalence of excessive daytime sleepiness has been reported in CTTH compared with episodic TTH (ETTH) and no headache.[44] The frequency of suicidality was significantly higher in TTH, especially in CTTH, compared with controls.[45]

Clinical Features

The ICHD-3 classifies TTH into four categories, namely infrequent ETTH, frequent ETTH, CTTH, and probable TTH. At least two of the following headache characteristics must be present: bilateral location; pressing or tightening (nonpulsatile) quality; mild to moderate intensity; and not aggravated by routine physical activity. Nausea or vomiting is absent, either photophobia or phonophobia may be present, and the headaches may or may not be associated with pericranial tenderness upon palpation of the frontalis, temporalis, masseter, pterygoid, sternocleidomastoid, splenius, or trapezius muscles. The headache duration is between 30 minutes and 7 days. While infrequent ETTH occurs fewer than 12 days per year (i.e., <1 day per month), frequent ETTH occurs between 12 and 180 days per year (between 1 and 14 days per month for more than 3 months), and CTTH occurs more than 180 days per year (at least 15 days per month for more than 3 months).

Management

Guidelines on the management of TTH have not changed since the European Federation of Neurological Societies Task Force's recommendations in 2010.[46] Similar to migraine, pharmacotherapy for TTH includes the use of abortive and/or

prophylactic medications. Abortive medications include analgesics (such as acetaminophen), NSAIDs (such as ibuprofen, ketoprofen, naproxen, and diclofenac), and their combinations. Prophylactic medications should be considered in frequent ETTH and CTTH, and they include amitriptyline and other antidepressants such as mirtazapine and venlafaxine. Pharmacotherapeutics for migraine, such as triptans and onabotulinum toxin, have not been shown to be effective for TTH. Nonpharmacologic management includes biobehavioral therapies, such as electromyography biofeedback and cognitive behavioral therapy, and other forms of complementary and alternative therapies (such as acupuncture). Comorbidities, such as sleep disorders and psychopathology, should also be identified and managed, along with associated myofascial pain and TMDH.

Trigeminal Autonomic Cephalalgias (ICD-10: G44.0)

TACs are primary headache disorders characterized by unilateral attacks of intense pain associated with ipsilateral autonomic features such as lacrimation, conjunctival injections, nasal congestion, rhinorrhea, and ptosis. This group includes five headaches: cluster headache (CH), paroxysmal hemicrania (PH), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and hemicrania continua (HC).[1]

A fundamental characteristic of all the TACs is that the pain is strictly unilateral. The pain is usually localized in the orbital, supraorbital, or temporal areas (V1), but it can sometimes present in the distribution of the maxillary (V2) and mandibular (V3) branches of the trigeminal nerve and described as "facial pain or toothache."[47] Other characteristic clinical features of the TACs include agitation/restlessness (mainly in CH) and the circadian periodicity of the attacks (also CH). To differentiate the type of TACs, it is very important to consider the differences in duration and frequency of the attacks, and the response to indomethacin.[48]

The pathophysiology of TACs is not well understood yet, but at least three domains are involved: the trigeminovascular system, the autonomic system, and the hypothalamus. The trigeminal autonomic reflex, a connection between the trigeminovascular system and the autonomic system, is responsible for the prominent cranial autonomic symptoms.[49] Several brain imaging studies have shown an activation of the posterior hypothalamus (ipsilateral in some TACs and contralateral in others) in all the TACs.[50] The connection between the hypothalamus and the trigeminovascular system is probably mediated by several neurotransmitters such as orexin.

Although TACs are primary headaches, some intracranial pathologies such as pituitary adenomas, aneurysms, arteriovenous malformations, and hemangiomas may mimic TACs in their clinical presentation. The work-up for all the TACs should include a brain MRI with dedicated views of the cavernous sinus and pituitary gland. An MRA of head and neck and pituitary laboratory exam may also be indicated.[51]

Cluster Headache

CH is a primary neurovascular headache disorder with episodic and chronic subtypes. As the name suggests, CH involves a cluster of headaches, usually occurring over a period of several weeks. The episodic form is characterized by at least two cluster phases lasting seven days to one year, separated by a cluster-free interval of at least three months. The chronic form is characterized by the absence of sustained periods of remission, and can transform from the episodic type, in which the clusters occur more than once a year without remission or the cluster-free interval is shorter than three months.

Epidemiology

CH is a rare disorder compared to migraine, with a prevalence in the general population of 0.1%, but it is the most diagnosed TAC. It is more prevalent in males, with a male:female ratio of 3:1. Age at onset is between 20 and 40 years. When occurring with trigeminal neuralgia, it is known as the cluster-tic syndrome.

Clinical Features

CH is among the most painful of all headache disorders, with the pain usually described as severe and boring or piercing. Patients typically pace the room and are unable to lie down. The attacks can last between 15 and 180 minutes, occurring once every other day to eight times per day. The headache is unilateral and localized in the orbital, supraorbital, and/or temporal areas. At least one ipsilateral autonomic symptom (such as conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, or miosis and/or ptosis) is present with or without restlessness or agitation. Occasionally an ipsilateral Horner's syndrome is present. These autonomic signs are a stark contrast to migraine. A peculiar characteristic of CH is the circannual and circadian presentation. The attacks tend to come at a specific season of the year and occur at one or more predictable times of the day. These cluster periods or bouts are separated by remission periods lasting months or years.

Management

Management of CH includes use of medication to abort the acute attacks as well as preventative treatment.[52] Abortive

medications include the triptans (especially parenteral, considering the short duration of the attacks, such as subcutaneous sumatriptan, and intranasal zolmitriptan and sumatriptan). One limitation of the triptans is the inability to be used multiple times a day. During an active cluster period, headaches occur repeatedly during the day, necessitating additional acute or preventative medications.[53] Oxygen inhalation at a rate of 10 L/min is also effective at aborting a cluster attack. It can be used multiple times a day with minimal side effects.[54] Recently, galcanezumab (a CGRP MAB) was FDA approved for the treatment of episodic cluster.[55–57] The use of intranasal lidocaine, noninvasive vagus nerve stimulation, neuromodulation, and, for refractory patients, a sphenopalatine ganglion stimulator has also been reported.[38,53,58,59]

Preventative medications are gradually titrated during the cluster cycle. After two weeks (in episodic clusters) and one to two months (in chronic clusters) of headache freedom, preventative medications should be discontinued to determine whether remission has occurred. These include verapamil, lithium, oral corticosteroids, melatonin, and galcanezumab.[48] Greater occipital block with anesthetic and steroids is an adjunctive measure.[60] Hypothalamic deep brain stimulation has shown benefit for refractory clusters.[61]

Paroxysmal Hemicrania

Epidemiology

PH is a rare disorder with an estimated prevalence of 0.5 per 100 or less and with a female:male ratio of approximately 2:1. The age of onset is usually the fourth and fifth decades, although a few childhood-onset cases have been described. The ICHD-3 classifies PH into episodic and chronic forms.[1] The episodic form occurs in periods of up to one year, with pain-free or remission periods of at least three months. The chronic form (CPH) occurs for more than one year or with remission periods lasting less than three months. The latter is more prevalent. Like cluster-tic, CPH-tic has also been described.

Clinical Features

PH usually presents as severe unilateral pain in orbital, supraorbital, and temporal areas. The pain is often described as throbbing, aching, or boring, with an abrupt onset and cessation. Similar to other TACs, pain is associated with ipsilateral cranial autonomic symptoms. Photophobia or phonophobia may also be present, but it is lateralized, in contrast to migraine. Compared to CH, the pain attacks of PH have a higher frequency, occurring at least several times a day, and shorter duration, lasting 2–30 minutes. The circadian rhythmicity observed in CH is absent in PH. The most important diagnostic criterion is the dramatic and absolute response to indomethacin.[62]

Management

Due to the short duration of attacks, PH is managed with prophylactic medications. Indomethacin is titrated in divided doses (usually three times a day), with an initial dose of 75 mg/day and increased up to 225mg/day if needed. If a patient is intolerant to the gastrointestinal side effects of indomethacin, a trial of celecoxib or topiramate is indicated. Greater occipital nerve blocks have reportedly been beneficial.

Short-Lasting Unilateral Neuralgiform Headache Attacks

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) are the two forms of short-lasting neuralgiform headaches. Their phenotypes are very similar and the main difference is, as stated in their names, that SUNCT exhibits both conjunctival injection and lacrimation, while SUNA has either one or neither.

Epidemiology

SUNCT and SUNA are rare primary headache disorders, with a reported prevalence between 1 and 100 in 100,000. SUNCT is more prevalent and may be a subtype of SUNA. The age of onset is usually in the fourth to seventh decades, and they are more common in males.[63]

Clinical Features

The pain is unilateral, moderate, or severe in intensity, often described as burning, stabbing, or electric. The distribution is often in the ophthalmic division of the trigeminal nerve. The attacks can occur as a single stab, a group of stabs, or a saw-tooth pattern. These attacks can be repetitive and frequent, and can last minutes or hours despite short-lasting individual attacks.[64]

A unique feature of SUNCT/SUNA, absent in the other TACs, is that pain can be triggered by innocuous cutaneous stimuli such as touching the face, wind, chewing, or brushing the teeth.[65] This feature, combined with the duration and frequency, can sometimes lead to a misdiagnosis of trigeminal neuralgia or occasionally odontogenic pain. Some important distinguishing features include that trigeminal neuralgia lacks cranial autonomic features, affects the maxillary and mandibular of the trigeminal nerve more often than the ophthalmic division, and has a refractory period.[66,67]

Management

The most effective treatment for SUNCT/SUNA is intravenous lidocaine performed by experienced providers.[66] The use of lamotrigine, topiramate, gabapentin, pregabalin, oxcarbazepine, and duloxetine has been described. Greater occipital nerve blocks and occipital nerve stimulation have also been proposed.

Hemicrania Continua

HC is a persistent, constant, strictly unilateral headache associated with ipsilateral autonomic signs and symptoms and/or with restlessness or agitation. Like PH, it responds dramatically to indomethacin.[68] The unremitting subtype, exhibiting continuous pain for at least one year without remission, is more prevalent.

Epidemiology

HC constitutes about 1% of patients with daily or unilateral headaches. The onset is between the third and fifth decades, and it is more common in females.

Clinical Features

The pain, often described as sharp, throbbing, or stabbing, is located unilaterally in the frontal, temporal, and periorbital areas. It is continuous, with episodes of exacerbation. The episodes of exacerbation are associated with autonomic features (usually lacrimation) and migrainous features such as photophobia, phonophobia, nausea, and/or vomiting. The exacerbation period can be triggered by stress, alcohol, poor sleep, and bright lights. Due to the presence of migrainous features in HC, it may be misdiagnosed as chronic migraine. Important distinctions between chronic migraine and HC include that HC is usually side-locked, rarely remits completely, and always responds to a therapeutic dosage of indomethacin.[69,70]

Management

In HC, indomethacin is used at the same dosage as that used for PH. The use of celecoxib, topiramate, gabapentin, and melatonin has also been described. Melatonin, a pineal hormone with a similar chemical structure to indomethacin, can also be used in combination with indomethacin to reduce the dosage of the latter, thereby reducing dyspepsia.[71]

SECONDARY HEADACHES

As described in the ICHD-3, secondary headaches include all headaches caused by an underlying disorder (Table 12-1), even if the headache characteristics resemble primary headaches.[1] The systematic SNNOOP10 is an important and useful screen for secondary headaches (Table 12-2).[3] Management of the underlying disease or condition is key to headache resolution. A selection of secondary headaches is described here.

Headache Attributed to Nontraumatic Subarachnoid Hemorrhage (ICD-10: G44.810)

Also known as the thunderclap headache, the headache attributed to nontraumatic subarachnoid hemorrhage (SAH) is associated with a high mortality of 40–50%. It is classified under the category of headache attributed to cranial or cervical vascular disorder in the ICHD-3.[1] A ruptured aneurysm is the most common cause of SAH, which accounts for about 1% of patients who present with a headache in the emergency department. The headache may be the only symptom of SAH, creating a diagnostic challenge. Up to 25% of SAHs are misdiagnosed.[72] About 20% of aneurysms leak before they rupture, with some patients reporting a severe headache several days or 1–2 weeks prior. This is known as the sentinel, or warning, headache.

The SAH headache is abrupt in onset, peaking within seconds or minutes, often reaching 7 (out of 10) in intensity within 1 minute of onset (therefore known as "thunderclap"). The Ottawa SAH rule recommends investigation for SAH in the presence of one or more of these symptoms: neck pain or stiffness; age 40 years or greater; witnessed loss of consciousness; headache onset during exertion; thunderclap headache; or limited neck flexion on examination.[73] The sudden or thunderclap onset of the "worst headache of my life" is a medical emergency, and aneurysmal SAH must be excluded with a non-contrast-enhanced CT scan (approximately 90% sensitive for SAH), and a lumbar puncture if the CT scan is negative.[74] The fluid-attenuated inversion recovery (FLAIR) MRI has also demonstrated good sensitivity for SAH.[75] Most vascular disorders underlying SAH (such as a ruptured aneurysm) require immediate neurosurgical intervention such as endovascular coiling or surgical clipping. Many patients continue to experience headaches even years after the hemorrhage.[76]

Headache Attributed to Giant Cell Arteritis (ICD-10: G44.812)

Giant cell (previously known as temporal) arteritis (GCA) is an idiopathic large vessel vasculitis preferentially affecting the external carotid artery and the aorta. In the ICHD-3, it is classified under the category of headache attributed to cranial or cervical vascular disorder.[1] GCA is an important differential for sudden-onset and persistent headache in

patients above 60 years of age. The incidence of GCA is 77 per 100,000 individuals and women account for 65% of cases. GCA is associated with a higher risk of ischemic stroke and dementia, and can be comorbid with polymyalgia rheumatica.

The manifestations of GCA include sudden-onset headache and sudden permanent loss of vision. Serologic markers include an elevated erythrocyte sedimentation rate (60–100 mm/h), C-reactive protein, and platelet count.[77] A temporal artery ultrasound (particularly a color-coded duplex sonography) and/or biopsy confirms the diagnosis of GCA.[78] Since vision loss in the second eye may follow within one week of vision loss in one eye (due to anterior ischemic optic neuropathy), prompt administration of intravenous glucocorticoids (or 60–100 mg of oral prednisolone for up to 3 days, followed by a 12–18-month taper) is essential.[79] Tocilizumab, an MAB blocker of IL-6, is approved for the treatment of GCA and has shown sustained disease remission.[80]

Headache Attributed to Idiopathic Intracranial Hypertension (ICD-10: G44.820)

Idiopathic intracranial hypertension (IIH) is classified under the category of headache attributed to nonvascular intracranial disorder in the ICHD-3 and was formerly known as pseudotumor cerebri.[1] IIH is a rare disorder characterized by raised intracranial pressure (greater than 250 mm cerebrospinal fluid [CSF]) of unknown cause.[81] Current theories suggest that there may be increased secretion or decreased absorption of CSF, and/or venous sinus stenosis causing obstruction of the cerebral venous outflow.[82] Associated spontaneous CSF leak has been reported.[83] IIH is more prevalent in young, obese women, although in prepubertal patients there is no association with gender or obesity. The diagnosis of IIH is based on neuroimaging and lumbar puncture.[84]

The headache attributed to IIH presents as a profoundly disabling new headache or a preexisting headache that is significantly worsening in frequency and/or intensity. The accompanying visual impairment, such as blurred vision, due to papilledema (i.e., swelling of the optic disc because of the elevated intracranial pressure) may potentially result in permanent visual loss. Severe increases in intracranial pressure may also result in unilateral or bilateral sixth nerve palsies. Psychiatric comorbidity is highly prevalent and associated with poorer outcome, along with increased risk of death from suicide and overdose.[85–87] While therapeutic lumbar puncture can provide partial and temporary relief, post–lumbar puncture headaches can be an unfortunate sequela.[88] The management also includes weight loss, and the use of acetazolamide and diuretics. Surgical interventions include optic nerve sheath fenestration, CSF diversion with ventriculoperitoneal or lumboperitoneal shunts, and venous sinus stenting.[89] Relapse or recurrence following treatment is not unusual.

Headache Attributed to Intracranial Neoplasm (ICD-10: G44.822)

Headache attributed to intracranial neoplasm is one of numerous nonvascular intracranial disorders. Based on the ICHD-3 diagnostic criteria, the demonstration of a space-occupying intracranial neoplasm and the evidence of causation must be demonstrated.[1] Although approximately 30% of patients with brain tumors report headaches, headache is the isolated presenting symptom in less than 0.2%.[90] Other accompanying symptoms, such as neurologic deficits and seizures, are usually reported.

The clinical features of headache attributed to intracranial neoplasm are varied and there is no pathognomonic symptom. The presentation may sometimes be very similar to a migraine, but the key feature suggestive of intracranial neoplasm relates to the headache progression or deterioration. Tumors should therefore be suspected in progressively severe new "migraine" headaches that are solely unilateral. Vomiting preceding headaches by weeks is highly characteristic of tumors of the posterior cranial fossa.[91]

Sleep Apnea Headache (ICD-10: G44.882)

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by recurrent episodes of partial or complete obstruction of the upper airway during sleep. An Apnea-Hypopnea Index (AHI) of five or more episodes per hour of sleep (where the AHI is the division of the number of apneic events by the total sleep time) indicates the presence of sleep apnea. The consequences of OSA include sleep fragmentation (due to microarousals that occur in an attempt to reestablish upper airway patency), hypoxia, and hypercapnia. Although OSA affects more men than women, the sleep apnea headache affects more women than men. Moreover, in women, self-reported morning headaches are predictive of moderate to severe OSA.[92]

The sleep apnea headache is classified under headache attributed to disorder of homeostasis in the ICHD-3.[1] It is a (usually) bilateral headache present upon awakening that lasts less than four hours. It is described as a "pressing" headache, not accompanied by nausea, photophobia, or phonophobia. The ICHD-3 diagnostic criteria require a causal relation with a diagnosis of OSA to be established, confirmation with an overnight polysomnography, and resolution of the headache with the management of the OSA. The pathophysiology of the sleep apnea headache is

unknown. An important differential for frequent morning headaches is sleep bruxism.[93] This is complicated by the fact that one-third of OSA patients have concomitant sleep bruxism.[94] It is nevertheless noteworthy that maxillary oral appliances for bruxism (i.e., "night guards") may increase the severity of OSA in some patients.[95]

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13

Diseases of the Respiratory Tract

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Given the fact that the oral cavity is contiguous with the trachea and lower airway, it is biologically plausible that conditions within the oral cavity might influence lung function. Respiratory infections are commonly encountered among dental patients. Commonalities between chemotherapeutic options and the anatomic proximity with the oral cavity lead to much interplay between oral and respiratory infections. Recent studies have reported on oral bacteria as causative pathogens in respiratory diseases and conditions associated with significant morbidity and mortality. Furthermore, some respiratory illnesses, such as asthma, may have an effect on orofacial morphology or even on the dentition. This chapter discusses the more common respiratory illnesses and explores the relationship between these conditions and oral health.

UPPER AIRWAY DISEASES

There are several major oral health concerns for patients with upper respiratory infections. These concerns are about infectious matters; for example, the possible transmission of pathogens from patients to health care workers and reinfection with causative pathogens through fomites such as toothbrushes and removable oral acrylic appliances. Furthermore, antibiotic resistance may develop because of the use of similar types of medications for upper respiratory infections and odontogenic infections. Lastly, oral mucosal changes, such as dryness due to decongestants and mouth breathing, and increased susceptibility to oral candidiasis in patients using long-term glucocorticoid inhalers, may be noticed.

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

Viral Upper Respiratory Infections

The most common cause of acute respiratory illness is viral infection, which occurs more commonly in children than in adults. Rhinoviruses account for the majority of upper respiratory infections in adults.[1] These are ribonucleic acid (RNA) viruses, which preferentially infect the respiratory tree. At least 100 antigenically distinct subtypes have been isolated. Rhinoviruses are most commonly transmitted by close person-to-person contact and by respiratory droplets. Shedding can occur from nasopharyngeal secretions for up to 3 weeks, but 7 days or less is more typical. In addition to rhinoviruses, several other viruses, including coronavirus, influenza virus, parainfluenza virus, adenovirus, enterovirus, coxsackievirus, and respiratory syncytial virus (RSV), have also been implicated as causative agents. Infection by these viruses occurs more commonly during the winter months in temperate climates.

Pathophysiology

Viral particles can lodge in either the upper or lower respiratory tract. The particles invade the respiratory epithelium, and viral replication ensues shortly thereafter. The typical incubation period for rhinovirus is 2 days, with a symptom duration of 7 to 14 days.[2] During this time, active and specific immune responses are triggered, and mechanisms for viral clearance are enhanced. The period of communicability tends to correlate with the duration of clinical symptoms.

Clinical and Laboratory Findings

Signs and symptoms of upper respiratory tract infections are somewhat variable and are dependent on the sites of inoculation.[3] Common symptoms include rhinorrhea, nasal congestion, and oropharyngeal irritation. Nasal secretions can be serous or purulent. Other symptoms that may be present include cough, fever, malaise, fatigue, headache, and myalgia.[2] A complete blood count (CBC) with differential may demonstrate an increase in mononuclear cells, lymphocytes, and monocytes ("right shift"). Laboratory tests are typically not required in the diagnosis of upper respiratory infections. Viruses can be isolated by culture or determined by rapid diagnostic assays. However, these tests are rarely clinically warranted.

Diagnosis

A diagnosis is made on the basis of medical history as well as confirmatory physical findings. Diagnoses that should be excluded include acute bacterial rhinosinusitis, allergic rhinitis, and group A streptococcal pharyngitis.

Management

The treatment of upper respiratory infections is symptomatic as most are self-limited. Analgesics can be used for sore throat and myalgias. Antipyretics can be used in febrile patients, and anticholinergic agents may be helpful in reducing rhinorrhea. Oral or topical decongestants, such as phenylephrine and pseudoephedrine, may be effective in terms of decreasing subjective nasal congestion.[4] Adequate hydration is also important in homeostasis, especially during febrile illnesses.

Antimicrobial agents have no role in the treatment of acute viral upper respiratory infections. Presumptive treatment with antibiotics to prevent bacterial superinfection is not recommended.[2] Any excessive use of antibiotics can result in the development of drug-resistant bacteria.[3]

Antiviral compounds have not been found to provide significant benefit for viral upper respiratory infections.[5]

Prognosis

As most patients recover in 5 to 10 days, the prognosis is excellent. However, upper respiratory infections can put patients at risk for exacerbations of asthma, acute bacterial sinusitis, and otitis media; this is especially so in predisposed patients, such as children and patients with an incompetent immune system.

Oral Health Considerations

The most common oral manifestation of upper respiratory viral infections is the presence of small round erythematous macular lesions on the soft palate. These lesions may be caused directly by the viral infection, or they may represent a response of lymphoid tissue. Individuals with excessive lingual tonsillar tissue also experience enlargement of these foci of lymphoid tissue, particularly at the lateral borders at the base of the tongue.

Treatment of upper respiratory infections with decongestants may cause decreased salivary flow, and patients may experience oral dryness (see Chapter 9 "Salivary Gland Diseases" for a discussion of the treatment of oral dryness).

Although there has been discussion in regards to a relationship between dentofacial morphology, malocclusion, and nasal obstruction, there is currently no clear causal relationship.[6]

Allergic Rhinitis and Conjunctivitis and Nonallergic Rhinitis

Allergic rhinitis is a chronic recurrent inflammatory disorder of the nasal mucosa. Similarly, allergic conjunctivitis is an inflammatory disorder involving the conjunctiva. When both conditions occur, the term *allergic rhinoconjunctivitis* is used. The basis of the inflammation is an allergic hypersensitivity (type I) to environmental triggers. Allergic rhinoconjunctivitis can be seasonal or perennial. Typical seasonal triggers include grass, tree, and weed pollens. Common perennial triggers include dust mites, cockroach, animal dander, and mold spores.

Allergic rhinitis is one of the most prevalent chronic medical conditions in the United States (US). It affects up to 58 million people in the US.[7] Allergic rhinitis is associated with a significant economic burden with a total of more than $11.2 billion (US) in direct costs due to this condition in 2005.[8] It is estimated that allergic rhinitis accounts for 3.5 million lost work days and 2 million missed school days each year.[9]

When nasal congestion, postnasal drainage and rhinorrhea are present perennially and, in the absence of significant sneezing or itching, this may be indicative of an entity called nonallergic rhinitis (NAR). NAR typically presents at a later age. The most common triggers for NAR include smoke, strong odors or fragrances, and changes in temperature or barometric pressure. When NAR occurs in conjunction with allergic rhinitis, this is termed mixed rhinitis and is the most common form of rhinitis in adults.[10]

Pathophysiology

Patients with allergic rhinoconjunctivitis have a genetically predetermined susceptibility to allergic hypersensitivity reactions, known as atopy. Prior to the allergic response, an initial phase of sensitization is required. This sensitization phase is dependent on exposure to a specific allergen and on recognition of the allergen by the immune system. The end result of the sensitization phase is the production of specific immunoglobulin E (IgE) antibody and the binding of this specific IgE to the surface of tissue mast cells and blood basophils. Upon re-exposure to the allergen, an interaction between surface IgE and the allergen takes place, which results in IgE crosslinking. The crosslinking of surface IgE triggers degranulation of the mast cell and basophils causing the release of preformed mediators. This is the early-phase allergic reaction. Histamine is the primary preformed mediator released by mast cells, and it contributes to the clinical symptoms of sneezing, pruritus, and rhinorrhea. Mast cells also release cytokines that permit amplification and feedback of the allergic response. These cytokines cause an influx of other inflammatory cells, including eosinophils, resulting in the late-phase allergic reaction. Eosinophils produce many proinflammatory mediators that contribute to chronic allergic inflammation and to the symptom of nasal congestion.

NAR includes two main subtypes. Vasomotor rhinitis is sometimes erroneously used synonymously with NAR. It is thought that neural or glandular pathways are involved in causing symptoms of congestion and rhinorrhea in response to nonspecific environmental irritants such as temperature changes (e.g., cold or dry air) or pollutants. Another subtype of NAR termed gustatory rhinitis involves significant rhinorrhea within a few hours after eating (hot and spicy food are the most common triggers) and is thought to be due to stimulation of the vagus nerve.[11]

Clinical and Laboratory Findings

The symptoms of allergic rhinoconjunctivitis can vary from patient to patient and depend on the specific allergens to which the patient is sensitized. Conjunctival symptoms may include pruritus, lacrimation, crusting, and burning. Nasal symptoms may include sneezing, pruritus, clear rhinorrhea, and nasal congestion. Other symptoms can occur, such as postnasal drainage with throat irritation, pruritus of the palate and ear canals, and fatigue.

The clinical signs of allergic rhinoconjunctivitis include injection of the conjunctiva with or without cobblestoning; prominent infraorbital creases/folds (Dennie–Morgan lines), swelling, and darkening ("allergic shiners"); a transverse nasal crease; and frequent upward rubbing of the tip of the nose (the allergic "salute"). Direct examination of the nasal mucosa reveals significant edema and a pale blue coloration of the turbinates. A copious clear rhinorrhea is often present. Nasal polyps may also be visible. Postnasal drainage or oropharyngeal cobblestoning might be identified upon examination of the oropharynx. A high-arched palate, protrusion of the tongue, and overbite may be seen.

Laboratory investigations are usually kept to a minimum. Patients with allergic rhinitis might have elevated levels of serum IgE and an elevated total eosinophil count. These findings are not, however, sensitive or specific indicators of atopy. Microscopic examination of nasal secretions often demonstrates significant numbers of eosinophils. Blood tests, such as the traditional radioallergosorbent test (RAST), is a method of testing for specific allergic sensitivities that is based on circulating levels of specific IgE. Specific IgE levels are determined by using serum samples and are quantified by using radioactive markers. Although bloodwork is somewhat less reliable than skin testing (see below), it is a useful test in certain situations, such as pregnancy or severe chronic skin disorders, including atopic dermatitis.

Classification

There is no universal classification system for allergic rhinoconjunctivitis. Many authors make the distinction between perennial and seasonal illness, with the former being caused mainly by indoor allergens (e.g., house dust mites, cockroaches, pets) and the latter being triggered primarily by outdoor allergens (e.g., trees, grasses, weeds). Perennial allergic rhinitis sufferers might benefit more from specific environmental control measures than would seasonal allergic rhinitis sufferers.

Diagnosis

The diagnosis of allergic rhinoconjunctivitis is usually apparent, based on history and physical examination. Patients present with a history suggestive of allergic sensitivity, recurrent symptoms with specific exposures, or predictable exacerbations during certain times of the year.

Symptoms that have recurred for 2 or more years during the same season are very suggestive of seasonal allergic disease. Alternatively, the history might indicate a pattern of worsening symptoms while the patient is at home, with improvement while the patient is at work or on vacation; this pattern is highly suggestive of perennial allergic disease with indoor triggers. The presence of the characteristic physical findings described above would confirm the presence of allergic rhinoconjunctivitis.

The preferred method of testing for allergic sensitivities is skin testing, which is performed with epicutaneous (prick/scratch) tests and this can be followed by intradermal testing if needed. Prick skin testing is the type most widely used. With prick testing, a small amount of purified allergen is inoculated through the epidermis only (i.e., epicutaneously) with a pricking device. Positive (histamine) and negative (saline) controls are used for comparison (Figures 13-1A and 13-1B). Reactions are measured at 15 minutes, and positive reactions (wheal and flare reactions) indicate prior allergen sensitization. Tests that yield negative results may be repeated intradermally to increase the sensitivity of the testing. All tests with positive results need to be interpreted carefully in the context of the patient's history and physical findings.

NAR is a diagnosis of exclusion. Therefore, other etiologies of rhinitis such as allergic, pharmacologic, infectious, and structural, and so on, must be excluded.[10]

Management

Three general treatment modalities are used in the therapy of allergic rhinoconjunctivitis: allergen avoidance, pharmacotherapy (medication), and immunotherapy (i.e., allergy injections). The best treatment is avoidance of the offending allergen. This requires the accurate identification of the allergens implicated and a thorough knowledge of effective interventions that can minimize or eliminate the exposure. Complete avoidance is rarely possible.

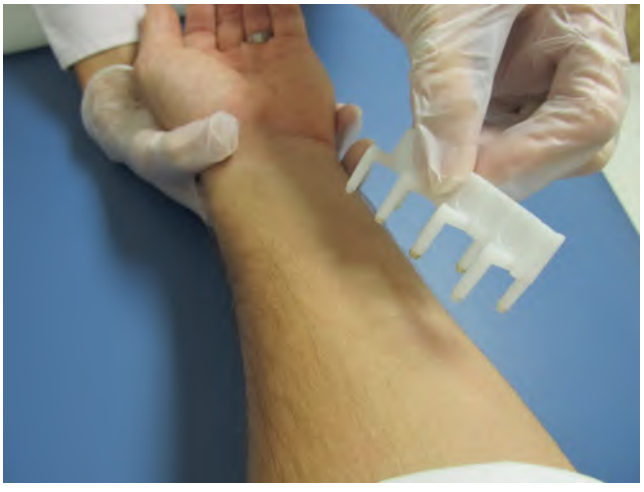

Figure 13-1A Skin prick allergy testing about to be applied to the forearm of patient to a panel of allergens.

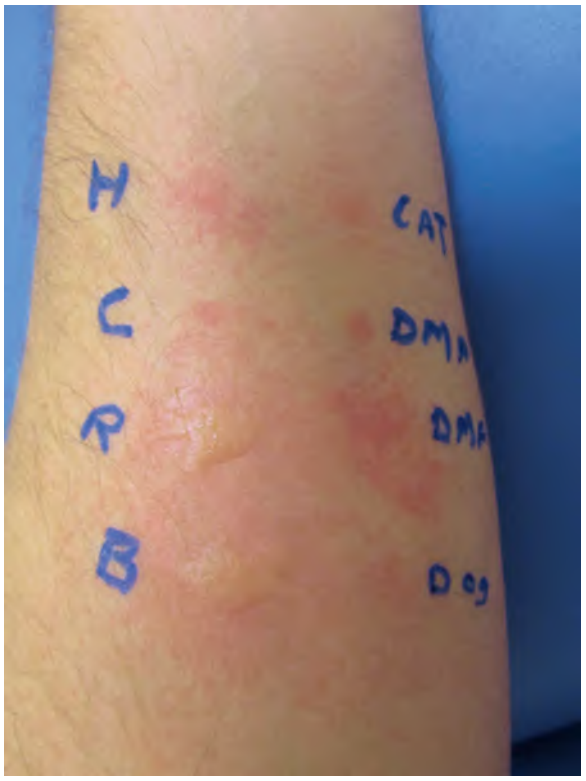

Figure 13-1B Positive sensitivities to multiple allergens from previous panel placed. Note the large wheals (bubble) and flare (redness) to Ragweed and Birch tree. Note: H=histamine, C=Control, R=Ragweed, B=Birch, DM=Dust mite.

Pharmacotherapy is often recommended for patients with incomplete responses to allergen avoidance and for patients who are unable to avoid allergen exposures. Many treatment options are available. For patients with prominent sneezing, pruritus, or rhinorrhea, antihistamines are an excellent treatment option. Second-generation antihistamines such as cetirizine, loratadine, and fexofenadine are now widely available. These medications deliver excellent antihistaminic activity with few side effects.[12] Oral decongestants can be added to oral antihistamines to relieve nasal congestion and obstruction. Combination medications are available in once-daily and twice-daily dosage forms for ease of administration. Leukotriene receptor antagonists may have additional benefit as well. Some studies have demonstrated that therapy with a leukotriene receptor antagonist plus antihistamine may have a greater effect than either agent administered alone.[12,13] For patients with daily nasal symptoms or severe symptoms that are not relieved with antihistamine-decongestants, topical anti-inflammatory agents for the nasal mucosa are available. These medications include corticosteroid, antihistamine, and cromolyn sodium nasal sprays.

The benefits of topical corticosteroids include relief of the total symptom complex and once daily dosing.

Immunotherapy is an effective means of treatment for patients with allergic rhinoconjunctivitis. Numerous studies have shown the efficacy of long-term allergen immunotherapy in inducing prolonged clinical and immunologic tolerance.[14] Immunotherapy is available for a variety of airborne allergens, including grass, tree, and weed pollens; dust mites; animal dander; and mold spores. Formulations include subcutaneous injections, sublingual drops, and sublingual tablets. Excellent candidates for immunotherapy include those patients who are unable to avoid exposures, patients with suboptimal responses to pharmacotherapy, patients who prefer to avoid the long-term use of medications, and women who are contemplating pregnancy.

First-line treatment of NAR is either an intranasal glucocorticoid and/or an intranasal antihistamine such as azelastine. There are no head-to-head studies comparing these two treatment options. Combination therapy is often used if monotherapy is not sufficient. For patients with gustatory rhinitis or significant rhinorrhea, ipratropium nasal spray may be helpful. Adjunctive therapies include nasal saline sprays and nasal irrigations, oral antihistamines, and short-term oral or nasal decongestants. Antileukotriene and intranasal chromone efficacy are less well established in NAR.[15]

Prognosis

Although allergic rhinoconjunctivitis is not a life-threatening disorder, it does have a significant impact on the patient's quality of life. With proper allergy care, most patients can lead normal lives, with an excellent quality of life.

Oral Health Considerations

The use of decongestants and first-generation antihistamines may be associated with oral dryness. There may also be an increased incidence of oral candidiasis in long-term users of topical corticosteroid-containing sprays.

It has been reported that dental personal are at risk for allergic respiratory hypersensitivity from exposure to dental materials such as methacrylates and natural rubber latex.[16] These allergenic materials, however, have been eased out of the dental workplace due to the widespread understanding of their allergic/irritant potential.

Otitis Media

Otitis media is inflammation of the middle ear space and tissues. It is the most common illness occurring in children who are 8 years of age or younger. Approximately 70% of children experience at least one episode of otitis media by age 3 years; of these, approximately one third experience three or more episodes in this same time interval.[17]

Otitis media can be subdivided into acute otitis media, recurrent otitis media, otitis media with effusion, and chronic suppurative otitis media. The underlying problem in all types of otitis media is dysfunction of the Eustachian tube. A poorly functioning Eustachian tube does not ventilate the middle ear space sufficiently. This lack of proper ventilation results in pressure changes in the middle ear and subsequent fluid accumulation. The fluid frequently becomes infected, resulting in acute otitis media. The most common infectious causes are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and viruses. In chronic infections, *Staphylococcus aureus* and anaerobic organisms may be causative pathogens while in young infants Gram-negative bacilli may be isolated.[18]

Pathophysiology

There are several factors that influence the pathogenesis of otitis media. Nasopharyngeal colonization with large numbers of bacteria such as *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis* and pathogenic viruses can increase the risk of otitis media. The likelihood of aspiration of these nasopharyngeal pathogens can be increased by nasal congestion or obstruction, negative pressure in the middle ear space, acute viral upper respiratory infections, and exposure to tobacco smoke.[19] For infants, breastfeeding can decrease the risk of otitis media, whereas impaired immune responsiveness can increase this risk.

Under normal circumstances, the Eustachian tube acts to ventilate the tympanomastoid air cell system during the act of swallowing. Any process that impairs normal Eustachian tube function can lead to negative pressure in the middle-ear space. Transient impairments of Eustachian tube function are seen in conditions that cause nasopharyngeal mucosal edema and obstruction of the Eustachian tube orifice, such as allergic rhinitis and viral upper respiratory infections. Chronic Eustachian tube obstruction can be seen with several conditions, including cleft palate and nasopharyngeal masses, such as enlarged adenoids. Aspiration of nasopharyngeal pathogens can then occur due to negative pressure in the middle ear space, with subsequent infection by these pathogens. This leads to the clinical manifestations of otitis media.

Clinical And Laboratory Findings

The most common symptoms in acute otitis media are fever and otalgia. Other symptoms include irritability, anorexia, and vomiting. Parents may note their child pulling or tugging at one or both ears. Symptoms of a viral upper respiratory infection might also be present, preceding the development of otitis media. On physical examination, the tympanic membrane may appear erythematous and bulging, suggesting inflammation of the middle ear. Other otoscopic

findings include a loss of landmarks and decreased mobility of the tympanic membrane as seen by pneumatic otoscopy.[18]

In otitis media with effusion, patients often complain of "clogged" ears and "popping." Otoscopic examination reveals serous middle-ear fluid, and air-fluid levels may be present. The mobility of the tympanic membrane is usually diminished, and mild to moderate conductive hearing loss may be demonstrated. In chronic suppurative otitis media, otorrhea is present and can be visualized either from a tympanic membrane perforation or from surgically placed tympanostomy tubes.

Investigations that can aid in the diagnosis or management of otitis media include tympanometry and myringotomy with aspiration. Tympanometry is a technique that measures the compliance of the tympanic membrane by using an electroacoustic impedance bridge. Decreased compliance of the tympanic membrane indicates a middle-ear effusion. Myringotomy with aspiration can be useful in situations when culture of the middle ear fluid is needed, such as with immunocompromised hosts or with patients who have persistent effusions despite medical management.

Classification

Acute otitis media is defined as middle-ear inflammation with an infectious etiology and a rapid onset of signs and symptoms. Otitis media with effusion is defined as a middle ear effusion (often asymptomatic) that can be either residual (3 to 16 weeks following acute otitis media) or persistent (lasting more than 16 weeks). Recurrent otitis media is defined as three or more new episodes of acute otitis media in 6 months' time or four or more new episodes in a 12-month period. Chronic suppurative otitis media is defined as persistent otorrhea lasting longer than 6 weeks.

Diagnosis

The diagnosis of otitis media is made on the basis of the history and physical examination. The most useful tool for diagnosing otitis media is pneumatic otoscopy, which allows the clinician not only to visualize the tympanic membrane but also to assess its mobility. As stated above, an immobile tympanic membrane probably represents the presence of middle ear fluid, and (in the context of a confirmatory medical history) the diagnosis of otitis media is made in such a case.

Management

Recent practice guidelines in the management of otitis media without significant signs and symptoms, have suggested that observation with close follow-up is justified.[20] There is evidence that suggests that antibiotics may be more beneficial in certain children, specifically those aged less than 2 years with bilateral acute otitis media and in those with both acute otitis media and otorrhea.[21,22] If antibiotics are indicated, initial antibiotic therapy is directed toward the most common middle-ear pathogens. Common choices include amoxicillin, azithromycin, and trimethoprim-sulfamethoxazole. In recalcitrant cases, treatment is directed toward β-lactamase-producing organisms and antibiotic-resistant strains of *S. pneumoniae*. Common choices for this situation include high-dose amoxicillin, amoxicillin-clavulanate, second- or third-generation cephalosporins, and clindamycin. The duration of therapy varies from 3 to 14 days.[20]

Multiple surgical modalities currently are used for the management of otitis media, including myringotomy with or without tympanostomy tube insertion, tympanocentesis, and adenoidectomy. Insertion of tympanostomy tubes is indicated when a patient experiences more than six acute otitis media episodes during a 6-month period or has recurrent otitis media in addition to otitis media with effusion or persistent bilateral effusions for longer than 3 months. A trial of antibiotic prophylaxis is commonly carried out prior to surgical consultation.[20]

Antihistamines and decongestants are ineffective for otitis media with effusion and are not recommended for treatment.[23] The management of chronic suppurative otitis media often includes parenteral antibiotics to cover infection by *Pseudomonas* species and anaerobic bacteria.

Prognosis

The prognosis for acute otitis media is excellent. Studies show that over 80% of children in the United States who were treated symptomatically for acute otitis media without antibiotics had complete resolution of otitis without suppurative complications.[24] However, complications can occur, more commonly in patients younger than 1 year of age. The most common complication is conductive hearing loss related to persistent effusions. Serious complications, including mastoiditis, cholesteatoma, labyrinthitis, extradural or subdural abscesses, meningitis, brain abscess, and lateral sinus thrombosis, are uncommon.[25]

Oral Health Considerations

Many children with recurrent otitis media are treated frequently (and sometimes for extensive periods) with various antibiotics. Included in the antibiotic armamentarium are medications that are also used for odontogenic infections. Oral health care providers need to be aware of what type of antibiotics the patient has taken within the previous 4 to 6 months, to avoid giving the patient an antibiotic to which resistance has already developed. It has been demonstrated that antibiotic regimens used for the treatment of otitis media promote the emergence of antibiotic-resistant bacteria.[26] Furthermore, the extended use of antibiotics may result in the development of oral candidiasis.

Sinusitis

Sinusitis is defined as an inflammation of the epithelial lining of the paranasal sinuses. The inflammation of these tissues causes mucosal edema and an increase in mucosal secretions. The most common trigger is an acute upper respiratory infection, although other causes, such as exacerbations of allergic rhinitis, dental infections or manipulations, and direct trauma can be implicated. If blockage of sinus drainage occurs, retained secretions can promote bacterial growth and subsequent acute bacterial sinusitis.

Acute sinusitis is a very common disorder, affecting about 31 million Americans per year.[27] Sinusitis accounts for about $5.8 billion (US) in costs with about 73 million days of restricted activity per year.[28]

Pathophysiology

The paranasal sinuses are air-filled cavities that are lined with pseudostratified columnar respiratory epithelium. The epithelium is ciliated, which facilitates the clearance of mucosal secretions. The frontal, maxillary, and ethmoid sinuses drain into an area known as the ostiomeatal complex. Rhythmic ciliary movement and the clearance of secretions can be impaired by several factors, including viral upper respiratory infections, allergic inflammation, and exposure to tobacco smoke and other irritants. In addition, foreign bodies (accidental or surgical) or a severely deviated nasal septum can cause obstruction. If blockage of the sinus ostia or obstruction of the ostiomeatal complex occurs, stasis of sinus secretions will allow pooling in the sinus cavities, which facilitates bacterial growth.

The most common organisms found in acute bacterial sinusitis are *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Organisms that are commonly associated with chronic sinusitis are *Staphylococcus aureus* and anaerobic bacteria such as *Bacteroides* spp and *Fusobacterium* spp. Sinusitis due to a fungal infection rarely occurs, usually in immunocompromised patients and in patients who are unresponsive to antibiotics.[29]

Clinical and Laboratory Findings

The symptoms of acute sinusitis include facial pain, tenderness, and headache localized to the affected region. Sinusitis affecting the sphenoid sinuses or posterior ethmoid sinuses can cause headache or pain in the occipital region. Other symptoms that are commonly described include purulent nasal discharge, fever, malaise, and postnasal drainage with fetid breath. Occasionally, there may be toothache or pain with mastication. Patients with chronic sinusitis often present with other symptoms that are often vague and poorly localized. Chronic rhinorrhea, postnasal drainage, nasal congestion, sore throat, facial "fullness," and anosmia are common complaints.

Physical examination reveals sinus tenderness and purulent nasal drainage. On occasion, erythema and swelling of the overlying skin may be evident. The nasal mucosa can appear edematous and erythematous, and nasal polyps might also be visible.

In routine cases of suspected acute bacterial sinusitis, imaging studies are not required. When there are more persistent symptoms as in chronic sinusitis or an incomplete response to initial management, imaging studies may become appropriate. Plain-film radiography is not helpful for establishing ostiomeatal complex disease. Computed tomography (CT) is the study of choice for documenting chronic sinusitis with underlying disease of the ostiomeatal complex and is superior to magnetic resonance imaging (MRI) for the identification of bony abnormalities. CT can also accurately assess polyps, reactive osteitis, mucosal thickening, and fungal sinusitis.[29]

Classification

Sinusitis is classified as either acute, subacute, or chronic, based on the duration of the inflammation and underlying infection. Acute sinusitis is defined as inflammation of less than 4 weeks, subacute as 4 to 8 weeks, and chronic as either longer than 8 to 12 weeks in duration.[30]

Diagnosis

The diagnosis of acute sinusitis is made on the basis of history and physical examination. As previously noted, radiologic evaluations may be helpful in certain situations. Patients with recurrent disease need to be evaluated for underlying factors that can predispose patients to sinusitis. Allergy evaluation for allergic rhinitis is often helpful. Chronic sinusitis may be the presentation of an underlying systemic disease, such as granulomatosis with polyangiitis (formerly known as Wegener's) or eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss). Other predisposing factors, such as tobacco smoke exposure, immunodeficiency, cystic fibrosis, primary ciliary dyskinesia, and septal deviation, should be considered.[29,30]

CT usually aids the diagnosis of chronic sinusitis. Evaluation of the ostiomeatal complex is crucial in the management of these patients. In addition, rhinoscopy may be helpful for direct visualization of sinus ostia.

Management

Initial medical treatment consists of antibiotics to cover the suspected pathogens, along with topical or oral decongestants to facilitate sinus drainage. First-line antibiotics such as amoxicillin are often effective, although second-generation cephalosporins, azithromycin, and amoxicillin-clavulanate can be helpful in resistant cases. Comprehensive treatment of bacterial sinusitis may also include adequate hydration,

sinus rinses, steam inhalation, and pharmacologic measures intended to treat underlying disease, such as rhinitis, and to restore ostial patency. Nasal glucocorticoids are thought to be potentially effective adjuncts to antibiotic therapy, but available objective data have not unequivocally demonstrated effectiveness.[31] Acute frontal or sphenoid sinusitis can be serious because of the potential for intracranial complications. Intravenous antibiotics are indicated, and surgical intervention is considered, based on the condition's response to medical management.[29]

The management of chronic sinusitis involves antibiotics of a broader spectrum, and a prolonged treatment course may be required. Topical corticosteroids or short courses of oral corticosteroids may help reduce the swelling and/or obstruction of the ostiomeatal complex.[29] Avoidance of exacerbating factors such as allergens or tobacco smoke should be emphasized. Patients with histories suggestive of allergy should undergo a thorough allergy evaluation. Dupilumab is currently approved for the treatment of refractory chronic rhinosinusitis with nasal polyps in adults. Several of the other biologic agents currently approved for the treatment of moderate-to-severe persistent asthma are actively being studied as treatment options as well (see section Asthma).[32]

Patients who have chronic sinusitis with evidence of disease of the ostiomeatal complex who fail medical management often require surgical intervention. Functional endoscopic sinus surgery (FESS) involves the removal of the ostiomeatal obstruction through an intranasal approach. This procedure can be performed with either local or general anesthesia and without an external incision. The recovery time from this procedure is short, and morbidity is generally low.

Prognosis

Patients treated for acute sinusitis usually recover without sequelae. Children with sinusitis, particularly ethmoid and maxillary sinusitis, are at risk for periorbital or orbital cellulitis. Periorbital cellulitis is most often treated on an outpatient basis with broad-spectrum antibiotics and rarely leads to complications. Orbital cellulitis, on the other hand, requires hospital admission with broad-spectrum intravenous antibiotics. Further treatment is tailored on a case-by-case basis and may entail surgical or endoscopic drainage of the infection.[33]

Frontal sinusitis can extend through the anterior wall and present as Pott's puffy tumor. Sinusitis can also spread intracranially and result in abscess or meningitis. These complications, although uncommon, are more likely to occur in male adolescent patients.

Patients with chronic sinusitis are more likely to require a prolonged recovery period, with a resultant decrease in quality of life. Chronic medication use can lead to side effects or other complications, such as rhinitis medicamentosa from prolonged use of topical decongestants. Surgical intervention and underlying-factor assessment will often reverse the chronic process, leading to an improvement in quality of life.

Oral Health Considerations

Patients with sinus infections who present with a complaint of a toothache are commonly encountered in a dental office. The oral health care professional evaluating the patient must be able to differentiate between an odontogenic infection and sinus pain. On history, sinus infections usually present with pain involving more than one tooth in the same maxillary quadrant, whereas a toothache usually involves only a single tooth. Ruling out odontogenic infections by a dental examination and appropriate periapical radiography strengthens a diagnosis. Additional testing,[34] including pulp testing of teeth with large restorations as well as limited field cone beam CT of potential sources of infection may rule in an odontogenic origin of both sinus-localized pain as well as maxillary sinusitis of endodontic origin.[34,35]

Chronic sinus infections are often accompanied by mouth breathing. This condition is associated with oral dryness and (in long-time sufferers) increased susceptibility to oral conditions such as gingivitis.[36]

As with other conditions for which the prolonged use of antibiotics is prescribed, the potential development of bacterial resistance needs to be considered. Switching to a different class of antibiotics to treat an odontogenic infection is preferable to increasing the dosage of an antibiotic that the patient has recently taken for another condition.

The use of decongestants may be associated with oral dryness, which may need to be addressed.

Laryngitis and Laryngotracheobronchitis

The upper airway is the site of infection and inflammation during the course of a common cold, but respiratory viruses can affect any portion of the respiratory tree. Laryngitis is defined as an inflammation of the larynx, usually because of a viral infection. Laryngotracheobronchitis (also termed viral croup) involves inflammation of the larynx, trachea, and large bronchi. Although these illnesses have distinct presenting features, both result from a similar infectious process and the reactive inflammation that follows. Laryngitis can present at any age, although it is more common in the adult population.[37] In contrast, laryngotracheobronchitis is an illness seen primarily in young children and has a peak incidence in the second and third years of life. These infections are most common during the fall and

winter months, when respiratory viruses are more prevalent.

The viruses most commonly implicated in laryngitis are parainfluenza virus, coxsackieviruses, adenoviruses, and herpes simplex virus. The viruses most commonly associated with laryngotracheobronchitis are parainfluenza virus, RSV, influenza virus, and adenovirus.[38]

Acute laryngitis can also result from excessive or unusual use of the vocal cords, gastroesophageal reflux, or irritation due to tobacco smoking.

Pathophysiology

The underlying infectious process is quite similar to that seen in viral infections of the upper respiratory tract (see above). After infection of the respiratory epithelium occurs, an inflammatory response consisting of mononuclear cells and polymorphonuclear leukocytes is mounted. As a result, vascular congestion and edema develop. Denudation of areas of respiratory epithelium can result. In addition to edema, spasm of laryngeal muscles can occur. Because the inflammatory process is triggered by a viral infection, the disease processes are usually self-limited.

Clinical and Laboratory Findings

Patients with laryngitis usually have an antecedent viral upper respiratory infection. Complaints of fever and sore throat are common. The most common manifestation of laryngitis is hoarseness, with weak or faint speech.[37] Cough is somewhat variable in presentation and is more likely when the lower respiratory tract is involved.

Children presenting with viral croup commonly have an antecedent upper respiratory tract infection, which may include fever. Shortly thereafter, a barking cough and intermittent stridor develop. Stridor at rest, retractions, and cyanosis can occur in children with severe inflammation. Neck radiography will demonstrate subglottic narrowing (a finding termed "steeple sign") on an anteroposterior view.

Classification

There is no universal classification system for these illnesses. The anatomic site most affected describes these diseases.

Diagnosis

The diagnosis of laryngitis is based on the suggestive history. There are no specific findings on physical examination or laboratory tests, although the presence of hoarseness is suggestive. The differential diagnosis includes other causes of laryngeal edema, including obstruction of venous or lymphatic drainage from masses or other lesions, decreased plasma oncotic pressure from protein loss or malnutrition, increased capillary permeability, myxedema of hypothyroidism, and hereditary angioedema. Carcinoma of the larynx can also present with hoarseness.

The diagnosis of laryngotracheobronchitis is usually apparent and is based on a suggestive history. Radiologic evaluation may or may not aid physicians in the diagnosis. Only 50% of patients with laryngotracheobronchitis show the classic steeple sign on plain neck radiography (Figure 13-2).[38] With children, it is important to rule out other causes of stridor, including foreign-body aspiration, acute bacterial epiglottitis, and retropharyngeal abscess.[39]

Management

Most cases of laryngitis are mild and self-limited, so only supportive care need be prescribed. The use of oral corticosteroids in severe or prolonged cases can be considered, although their routine use is controversial.[39]

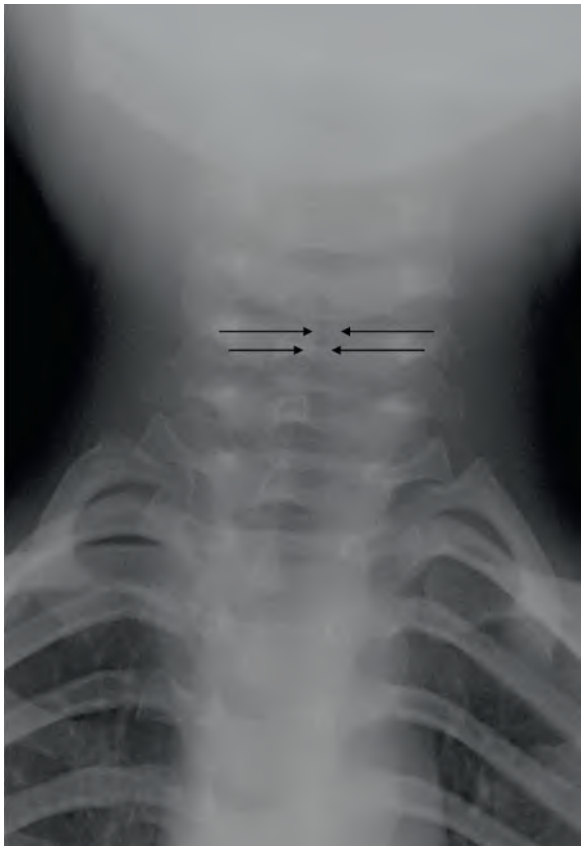

Figure 13-2 Anteroposterior radiograph of the neck show narrowing of the upper trachea that is most evident on the anteroposterior view (black arrows). This type of narrowing is typically present in croup and is known as the steeple sign on the anteroposterior radiograph given its similarity to a church steeple.

The most important aspect in the management of laryngotracheobronchitis is airway maintenance. The standard therapy includes mist therapy, corticosteroids, and racemic epinephrine. Any child with evidence of respiratory distress should be considered a candidate for steroid treatment. Less frequently, hospitalization and intubation or tracheotomy are necessary.[38]

Prognosis

As with viral upper respiratory infections, most cases of laryngitis and laryngotracheobronchitis are self-limited and require minimal medical intervention. Recovery within a few days to a week is expected. In some cases, laryngotracheobronchitis can recur, although the factors influencing this are not well understood.

Pharyngitis and Tonsillitis

Inflammation of the tonsils and pharynx is almost always associated with infection, either viral or bacterial. The vast majority of cases are caused by viral infections. These infections can be associated with fever, rhinorrhea, and cough. The major viral etiologies include rhinovirus, coronavirus, adenovirus, Epstein-Barr, para-influenza, herpes simplex virus (HSV), and influenza.[40]

The most common bacterial cause of acute tonsillopharyngitis is group A β-hemolytic *Streptococcus* (GABHS) infection, specifically *Streptococcus pyogenes* infection. Proper diagnosis and treatment of this infection are extremely important in order to prevent disease sequelae, namely, acute rheumatic fever and glomerulonephritis. Less common bacterial causes include *Corynebacterium diphtheriae*, *Neisseria gonorrhoeae*, *Chlamydia*, and *Mycoplasma pneumoniae*.

Chronic mouth breathing, chronic postnasal drainage, and inflammation due to irritant exposure can also cause pharyngitis and tonsillitis.

Pathophysiology

Streptococcal infections are spread through direct contact with respiratory secretions. Transmission is often facilitated in areas where close contact occurs, such as schools and daycare centers. The incubation period is 2 to 5 days.

Clinical and Laboratory Findings

Sore throat is the predominant symptom. Associated clinical findings are based on the infectious etiology. Patients with Epstein-Barr virus infections develop infectious mononucleosis, a disease characterized by exudative tonsillopharyngitis, lymphadenopathy, fever, and fatigue. Physical examination can reveal hepatosplenomegaly. Common laboratory findings include leukocytosis, with more than 20% atypical lymphocytes on blood smear. Blood chemistries may reveal elevated liver enzymes.

Infection with coxsackievirus can cause several distinct illnesses, each associated with tonsillopharyngitis. Herpangina is a disease that is characterized by small ulcers that are 2 to 3 mm in size and located on the anterior tonsillar pillars and possibly the uvula and soft palate. Hand-foot-and-mouth disease is characterized by ulcers on the tongue and oral mucosa, in association with vesicles found on the palms and/or soles. Small yellow-white nodules on the anterior tonsillar pillars characterize lymphonodular pharyngitis; these nodules do not ulcerate.

Pharyngoconjunctival fever is a disorder characterized by exudative tonsillopharyngitis, conjunctivitis, and fever. Infection is due to adenovirus.

Measles is a disease with a prodromal phase that is characterized by symptoms of upper respiratory infection, tonsillopharyngitis, and small white lesions with erythematous bases on the buccal mucosa and inner aspect of the lower lip (Koplik's spots). These lesions are pathognomonic of early measles infection.

Streptococcal pharyngitis is characterized by exudative tonsillitis and fever. Physical examination often reveals a beefy red uvula, cervical adenitis, and oral petechiae. Laboratory evaluation should include testing for group A *Streptococcus*.[41]

Classification

Pharyngotonsillitis is classified on the basis of etiology and clinical presentation (see above).

Diagnosis

Diagnosis is based on a history of sore throat and is established by appropriate physical findings and results of testing. A rapid antigen detection test is available for diagnosing streptococcal pharyngitis. The test has a high specificity (95+%) and slightly lower sensitivity (80–90%).[41] The importance of confirmatory cultures is still controversial, with some studies concluding that culture confirmation of negative rapid antigen detection tests may not be necessary in all circumstances.[42]

Antistreptococcal antibody titers reflect past and not present immunologic events and are of no value in the diagnosis of acute GABHS pharyngitis. They are valuable for confirmation of prior GABHS infections in patients suspected of having acute rheumatic fever or post-streptococcal acute glomerulonephritis.

Management

The viral causes of tonsillopharyngitis are treated symptomatically. Gargle solutions, analgesics, and antipyretics are often helpful. The course is self-limited.

Acute streptococcal pharyngitis is treated with oral penicillin V, cephalosporins, macrolides, clindamycin, or an intramuscular injection of benzathine penicillin G. Failure rates for penicillin vary from 6 to 23%, so an additional antibiotic course may be necessary.[41] GABHS carriers appear unlikely to spread the organism to close contacts and are at a low risk of developing complications. Antimicrobial therapy is generally not indicated for the majority of GABHS carriers.[43]

Prognosis

The prognosis for viral tonsillopharyngitis is very good as the infections are self-limited. Late sequelae from group A streptococcal tonsillitis can be avoided by prompt diagnosis and treatment.[43] Other complications due to streptococcal tonsillitis are uncommon but include cervical adenitis, peritonsillar abscesses, otitis media, cellulitis, and septicemia.

Oral Health Considerations

The association between GABHS infection and the development of severe complications, such as rheumatic fever and its associated heart condition, is well known. Although failure to successfully treat GABHS infections was more common in the pre-penicillin era, there are some concerns today regarding reinfection in cases in which penicillin is unable to eradicate the organism. One study found a significant association between the persistence of GABHS on toothbrushes and removable orthodontic appliances and the recovery of GABHS in the oropharynx of symptomatic patients after 10 days of treatment with penicillin.[44] Interestingly, when toothbrushes were rinsed with sterile water, organisms could not be cultured beyond 3 days, whereas nonrinsed toothbrushes harbored GABHS for up to 15 days. Thus, patients with GABHS infections should be instructed to thoroughly clean their toothbrushes and removable acrylic appliances daily. It is also advisable to change to a new toothbrush after the acute stage of any oropharyngeal infection.

LOWER AIRWAY DISEASES

The association between oral health and respiratory diseases has received renewed attention. Several articles have suggested that dental plaque may be a reservoir for respiratory pathogens involved in pneumonia and chronic obstructive pulmonary disease (COPD).[45,46,47,48] Although this may not be a critical problem for ambulatory healthy individuals, deteriorating oral health may be a major factor for both morbidity and mortality among institutionalized elderly persons, as well as for patients in critical care units.

Acute Bronchitis

Acute bronchitis is an acute respiratory infection involving the large airways (trachea and bronchi) that is manifested predominantly by cough with or without phlegm production that lasts up to 3 weeks. In patients who are otherwise healthy and without underlying pulmonary disease, bronchitis is commonly caused by a viral infection.[49] The viruses most commonly implicated are influenza, parainfluenza, and RSV. Viruses that are predominantly associated with upper respiratory tract infections, including coronavirus, rhinovirus, and adenovirus, have also been implicated as causes of acute bronchitis.[50] Acute bronchitis due to bacterial infection is less common. Atypical bacteria including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis* are often important causes of bronchitis.[51] *Staphylococcus* and Gram-negative bacteria are common causes of bronchitis among hospitalized individuals.

Pathophysiology

The pathophysiology of acute bronchitis is similar to that of other respiratory tract infections. Following infection of the mucosal cells, congestion of the respiratory mucosa develops. Inflammation causes an increase in secretory activity, resulting in increased sputum production. Polymorphonuclear leukocytes infiltrate the bronchial walls and lumen. Desquamation of the ciliated epithelium may occur, and spasm of bronchial smooth muscle is common.

Clinical and Laboratory Findings

Acute viral bronchitis usually presents with sudden onset of cough, with or without sputum expectoration and without evidence of pneumonia, the common cold, acute asthma, or an acute exacerbation of chronic bronchitis.[50] Chest discomfort may occur; this usually worsens with persistent coughing bouts.[52] Other symptoms, such as dyspnea and respiratory distress, are variably present. Physical examination may reveal wheezing. The presentation may closely resemble an acute asthma exacerbation. Symptoms gradually resolve over a period of 1 to 2 weeks. Patients with underlying chronic lung disease might also experience respiratory compromise, with a significant impairment in pulmonary function.

The presentation of acute bacterial bronchitis is very similar to that of bacterial pneumonia (see below). Symptoms may include fever, dyspnea, productive cough with purulent sputum, and chest pain. Bacterial bronchitis can be differentiated from pneumonia by the lack of significant findings on chest radiography.

Classification

Although there is no universal classification scheme, acute bronchitis can be differentiated on the basis of etiology. Viral

bronchitis presents differently from bacterial bronchitis, as described above.

Diagnosis

Diagnosis of acute bronchitis is based on a suggestive history and a physical examination. Neither blood cell counts nor sputum analyses are particularly diagnostic in otherwise healthy patients. Routine testing for viruses is generally not obtained for bronchitis.[53] Chest radiography may be helpful in distinguishing bacterial bronchitis from pneumonia. Patients with recurrent bouts of acute bronchitis should be evaluated for possible asthma. This evaluation should include pulmonary function testing.

Patients with persistent symptoms in the course of presumed viral bronchitis should be evaluated to determine possible underlying etiologies. Sputum cultures might prove useful in these circumstances but are not performed routinely.[52]

Management

Viral bronchitis can be managed with supportive care only as most individuals who are otherwise healthy recover without specific treatment. If significant airway obstruction or hyperreactivity is present, inhaled bronchodilators, such as albuterol, may be useful. Cough suppressants, such as codeine, can also be considered for patients whose coughing interferes with sleep.

The treatment of bacterial bronchitis may include amoxicillin, amoxicillin-clavulanate, macrolides, or cephalosporins. For suspected or confirmed pertussis infection, treatment with a macrolide or trimethoprim-sulfamethoxazole is appropriate to decrease disease transmission. Although commonly used, inhaled β_2-agonist bronchodilators and mucokinetic agents, like expectorants, are not recommended for routine use in patients with acute bronchitis.[50]

Prognosis

Acute bronchitis carries an excellent prognosis for patients who are without underlying pulmonary disease, and recovery without sequelae is the norm. However, for patients with chronic lung disease and respiratory compromise, bronchitis can be quite serious and may often lead to hospitalization and respiratory failure. In other high-risk individuals, such as those with human immunodeficiency virus (HIV) infection or other immunodeficiencies, acute bronchitis may lead to the development of bronchiectasis.

Oral Health Considerations

Resistance to antibiotics may develop rapidly and last for 10 to 14 days.[52] Thus, patients who are taking amoxicillin for acute bronchitis should be prescribed another type of antibiotic (such as clindamycin or a cephalosporin) when an antibiotic is needed to treat an odontogenic infection.

Pneumonia

Pneumonia is defined pathologically as an infection and a subsequent inflammation involving the lung parenchyma. Both viruses and bacteria are causes, and the presentation is dependent on the causative organism. Pneumonias can be broadly classified as either nosocomial or community-acquired. Nosocomial infections are infections that are acquired in a hospital or health care facility and often affect debilitated or chronically ill individuals. Community-acquired infections can affect all persons but are more commonly seen in otherwise healthy individuals. In the US, there were 52,000 deaths from community-acquired pneumonia in 2007 with 4.2 million ambulatory care visits for this condition in 2006.[54]

Formerly, bacterial pneumonia was categorized into several subtypes; community-acquired pneumonia, aspiration pneumonia, hospital-acquired (nosocomial) pneumonia, ventilator associated pneumonia, and nursing home associated pneumonia. In all cases, connections have been made with oral health status. However, in 2005 a new category was created called health care-associated pneumonia or HCAP.[55] Health care-associated pneumonia was defined as pneumonia occurring in a diverse group of patients, including those undergoing home-infusion therapy or wound care, chronic dialysis, recently hospitalized patients, or nursing home residents. Patients in these settings are often at high risk for pneumonia caused by multidrug resistant organisms such as methicillin-resistant *Staphylococcus aureus* or resistant Gram-negative bacilli. Thus, treatment guidelines for HCAP include broad-spectrum antibiotic therapy.

The most common bacterial cause of community-acquired pneumonia is *S. pneumoniae*, followed by *H. influenzae*. The organisms responsible for HCAP include aerobic Gram-negative bacilli, such as *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species. Infections due to Gram-positive cocci, such as *S. aureus*, particularly methicillin-resistant *S. aureus* (MRSA), have been rapidly emerging in the United States as well.[56] A related condition is aspiration pneumonia, which is typically caused by anaerobic organisms most often originating from the gingival crevice.[57] Aspiration pneumonia often occurs in patients with dysphagia, depressed consciousness, or others at risk for aspiration of oral contents into the lung, including alcoholics. Aspiration pneumonia occurs both in the community and in institutional settings.

Atypical organisms commonly associated with pneumonia include *M. pneumoniae*, *Legionella*, and *Chlamydia*.[58] The atypical organisms may cause a pneumonia that differs in clinical presentation from that caused by the aforementioned bacteria (see below). Pneumonia can be caused by viruses, such as influenza, parainfluenza, adenovirus, and RSV, as well as fungi such as *Candida*, *Histoplasma*, *Cryptococcus*, and *Aspergillus*. Pneumonia may also be caused by other organisms including *Pneumocystis jiroveci (carinii)*, seen in immunocompromised hosts, *Nocardia*, and *Mycobacterium tuberculosis*. Infection with these organisms can often be differentiated by chest radiography.

Pathophysiology

The pathophysiology of pneumonia is dependent on the causative infectious organism. In bacterial pneumonia caused by *S. pneumoniae*, for example, the bacteria first enter the alveolar spaces after inhalation. Once inside the alveoli, the bacteria rapidly multiply, and extensive edema develops. The bacteria cause a vigorous inflammatory response, which includes an influx of polymorphonuclear leukocytes. In addition, capillary leakage is pronounced. As the inflammatory process continues, the polymorphonuclear leukocytes are replaced by macrophages. Subsequent deposition of fibrin ensues as the infection is controlled, and the inflammatory response resolves.[58]

Other infections of the lung (i.e., viral, atypical, etc.) are interstitial processes. The organisms are first inhaled into the alveolar spaces. The organisms then infect the type I pneumocytes directly. As these pneumocytes lose their structural integrity and necrosis ensues, alveolar edema begins. Type II pneumocytes proliferate and line the alveoli, and an exudative cellular debris accumulates. An interstitial inflammatory response is mounted, primarily by mononuclear leukocytes. This process can occasionally progress to interstitial fibrosis, although resolution is the norm.

Clinical and Laboratory Findings

Pneumonia due to community-acquired bacterial infection typically presents acutely, with a rapid onset of symptoms. A prodrome similar to that seen with acute infections of the upper respiratory tract is unusual. Common symptoms include fever, pleuritic chest pain, and coughing that produces purulent sputum.[52] Chills and rigors are also common. Pneumonia due to *H. influenzae*, which is seen more commonly in patients with COPD or alcoholism, presents with fever, cough, and malaise. Chest pain and rigors are less common.

Nosocomial pneumonia with *Staphylococcus* secondary to aspiration presents with fever, dyspnea, cough, and purulent sputum. In cases acquired hematogenously, signs and symptoms related to the underlying endovascular infection predominate. Otherwise, respiratory tract symptoms are mild or absent despite radiographic evidence of multiple pulmonary infiltrates. The classic clinical features of nonbacteremic *Enterobacteriaceae* or *Pseudomonas* pneumonia are abrupt onset of dyspnea, fever, chills, and cough in an older patient who is either hospitalized or chronically ill.[59]

Physical examination demonstrates crackles (rales) in the affected lung fields. Decreased breath sounds and dullness to percussion might also be noted. Signs of respiratory distress may be present in severely affected individuals, including retractions, use of accessory muscles, and cyanosis.

With atypical pneumonia, symptoms usually develop over 3 to 4 days and initially consist of low-grade fevers, malaise, a nonproductive cough, and headache. Often systemic complaints are more prominent than the respiratory complaints. Sputum production, if present, is usually minimal. Findings on physical examination of the chest are usually unremarkable, with only scattered rhonchi. Infection due to *Mycoplasma* is common among younger patients. Pneumonias due to viral causes have a similar presentation but can have a more rapid onset.

Infection with *Legionella* spp (Legionnaires' disease) begins with a prodrome consisting of fever and malaise and progresses rapidly to an acute phase of high fever, rigors, pleuritic chest pain, gastrointestinal complaints, and confusion. The cough is typically nonproductive and is only variably present. Elevated liver enzymes and proteinuria indicate renal and hepatic involvement. Hypoxia can also develop and progress rapidly. Legionnaires' disease was first described at an American Legion convention in Philadelphia in 1976. The causative organisms have a predilection for moist areas such as air-conditioning ducts and cooling towers. The infection tends to occur more commonly among middle-aged men with a history of tobacco smoking.

Classification

Pneumonia is initially classified on clinical presentation as either viral, bacterial, or atypical. Different classifications based on radiologic or pathologic manifestations are less commonly used.

Diagnosis

When a patient with probable pneumonia is being evaluated, the possible causative organism will be suggested by: (1) the clinical presentation and course of the illness; (2) the degree of immunocompetency of the patient; (3) the presence or absence of underlying lung disease; and (4) the place of acquisition (hospital or community). Ultimately, the goal

is rapid diagnosis to establish an etiology so that appropriate antimicrobial therapy can be initiated. With community-acquired pneumonia, the diagnosis should be based on a clinical history and physical examination findings. Chest radiography, laboratory studies, and blood cultures may be considered.[60]

In nosocomial infection, the presence of pneumonia is defined by new lung infiltrate on radiography plus clinical evidence that the infiltrate is of an infectious origin. The presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38 °C, leukocytosis or leukopenia, and purulent secretions) represents the most accurate combination of criteria for starting empiric antibiotic therapy.[56] For diagnosis of ventilator associated pneumonia, quantitative microbiological cultures from bronchoalveolar lavage (BAL) samples are often employed, with pathogenic bacteria $\geq 10^4$cfu/mL of BAL indicative of an infection.[61]

Sputum analysis is the traditional tool used for diagnosis and management. Spontaneously coughed or induced sputum is analyzed by Gram stain and allows for the identification of a select group of pathogens and thus a more directed antibiotic therapy. For example, Gram-positive cocci in pairs (diplococci) are suggestive of pneumococcal infection. Gram-positive cocci in grape-like clusters suggest infection with *S. aureus*. Gram-negative pleomorphic rods are typical of *H. influenzae*, whereas *Klebsiella* is identified by its short, plump Gram-negative rod appearance. Numerous polymorphonuclear leukocytes are also often seen. This method, however, is limited since very often sputum contains bacteria of the normal flora that may be confused with pathogens.

Quantitative cultures for hospital-acquired infections can be performed on endotracheal aspirates or samples collected either bronchoscopically or nonbronchoscopically. These techniques may aid in diagnosis and management as well. Routine culture can identify *S. pneumoniae*, *H. influenzae*, *S. aureus*, and Gram-negative rods. Specialized culturing techniques are needed to identify *Legionella*, *Mycobacterium*, *Nocardia*, *Mycoplasma*, and fungi. Tissue cultures are used to identify viruses and *Chlamydia*. In patients with nosocomial pneumonia, a lower respiratory tract culture should be collected before antibiotic therapy, but collection of cultures should not delay the initiation of therapy in critically ill patients.[56]

Chest radiography can be a valuable tool in the evaluation of the patient with pneumonia. The radiologic presentation is dependent on the infectious etiology and the underlying medical condition of the patient. A pattern of lobar consolidation and air bronchograms is seen most commonly in cases of pneumococcal pneumonia (Figure 13-3). The lower lobes and right middle lobe are most commonly involved. A pattern of patchy nonhomogeneous infiltrates, pleural effusion, and cavitary lesions is common with staphylococcal pneumonia. *Klebsiella* pneumonia typically involves multiple lobes and can also be associated with effusion and cavitation. Viral or atypical organisms usually present with an interstitial infiltrative pattern or patchy segmental infiltrates. Organisms such as *Nocardia*, *Mycobacterium*, and fungi often cause nodular or cavitary lesions, which are demonstrable on chest radiography. Rapid accumulation of pleural fluid or empyema is seen most often with bacterial infection.

The presence of cold agglutinins is suggestive of *Mycoplasma* infection. Cold agglutinins are antibodies (produced in response to *Mycoplasma* infection) that agglutinate red blood cells upon cold exposure. Titers reach maximal levels in 3 to 4 weeks but can be detected 1 week after the onset of disease. These antibodies can be found in 60–70% of patients with *Mycoplasma* pneumonia but are not specific to this disease.

Legionella pneumonia can be diagnosed by a urine antigen assay and by culture of the organism, using specialized media, or by direct fluorescent antibody staining of sputum.

Management

Empiric treatment is started immediately upon diagnosis of pneumonia. Treatment options for outpatients with community-acquired pneumonia include β-lactams (e.g., amoxicillin-clavulanate), macrolides, and doxycycline. Patients who have received antimicrobial therapy within the previous 3 months are at increased risk for infection with antimicrobial-resistant *S. pneumoniae* and may require starting with a fluoroquinolone or a combination of antibiotics (e.g., β-lactam and macrolide).[62]

In the case of nosocomial pneumonia, patients with low risk of infection by an antibiotic-resistant organism should

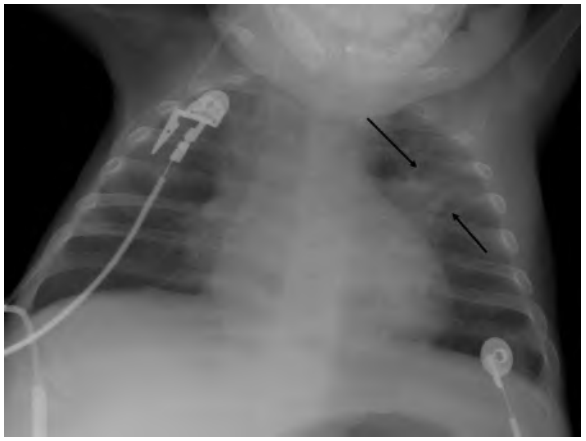

Figure 13-3 Anteroposterior radiograph of the chest in an infant shows an infiltrate in the left upper lobe (black arrows). Blood cultures obtained on this infant were positive for *Pneumoccous*.

be treated with empiric therapy, such as a third-generation cephalosporin or fluoroquinolone. However, more aggressive broad-spectrum therapy (such as an antipseudomonal cephalosporin, carbapenem, or fluoroquinolone, along with linezolid or vancomycin for MRSA), is required for high-risk patients, such as those with a prolonged duration of hospitalization (5 days or more), admission from a health care-related facility, or recent prolonged antibiotic therapy.[56]

Nonspecific treatment for patients with pneumonia includes aggressive hydration to aid in sputum clearance. Chest physiotherapy is advocated by many clinicians, although evidence of efficacy is lacking. If hypoxia is present, supplemental oxygen is given.[62]

A pneumococcal vaccine is available for active immunization against pneumococcal disease. The vaccine is effective for preventing disease from of the most common pneumococcal serotypes. It is effective for adults and for children older than 2 years of age and is recommended for all individuals over the age of 65 years and selected high-risk patients with certain medical conditions.[62] A conjugate pneumococcal vaccine has been part of the US childhood immunization schedule since 2000 and has led to a sustained reduction in hospitalizations for childhood pneumonia.[63]

Prognosis

Mortality due to community-acquired pneumonia is low. The risk of mortality is higher for older patients, patients with underlying pulmonary disease, patients with immunodeficiency (e.g., asplenia), and patients with positive blood cultures. Most deaths occur within 5 days of the onset of disease.

Mortality due to staphylococcal pneumonia is high, and patients who do recover often have residual pulmonary abnormalities. Mortality due to atypical pneumonia is low, with the exception of *Legionella* pneumonia, which has a 15% mortality rate if left untreated.

Oral Health Considerations

The aspiration of salivary secretions containing oral bacteria into the lower respiratory tract can cause aspiration pneumonia. Numerous periodontally associated oral anaerobes and facultative species have been isolated from infected pulmonary fluids.[64] Although most reports suggest increased susceptibility to the development of nosocomial pneumonia from periodontal pathogens, other oral bacteria (such as *Streptococcus viridans*) have been implicated in community-acquired pneumonia.[53]

The connection of oral health to pneumonia involves aspiration of a pathogen from a proximal site; for example, the oral-pharyngeal cavity, into the lower airway. The teeth or dentures have nonshedding surfaces upon which oral biofilms, that is, dental plaque, form, which are susceptible to colonization by respiratory pathogens. Indeed, intensive care subjects were found to harbor greater levels of dental plaque than nonhospitalized control patients, and bacterial pathogens known to cause pneumonia were found to be prevalent in the dental plaque from the intensive care subjects.[46] In some cases, up to 100% of the aerobic flora was found to be *S. aureus*, *P, aeruginosa*, or several enteric species. In contrast, the control dental patients were only rarely colonized by respiratory pathogens. Poor oral hygiene therefore may predispose high-risk patients to oral colonization by respiratory pathogens and therefore increase the risk for lung infection. In addition, the host response to oral biofilms results in inflammation of the periodontal tissues.[65] Thus, inflammatory products from the gingival tissues as well as pathogenic bacteria shed from oral biofilms into the secretions can be aspirated into the lower airway to promote lung infection.[64]

Elderly individuals residing in nursing homes also have an increased prevalence of poor oral health, including increased plaque retention.[66] Studies have evaluated the occurrence of pneumonia in cohorts of elderly individuals who were receiving and not receiving oral care. In one such study, the relative risk of developing pneumonia increased 67% in the group without access to oral health interventions compared with individuals who had access to oral care.[67] These data support the benefit of increased awareness and increased oral health interventions in hospitalized and institutionalized individuals. More intervention studies are needed to assess the impact of oral pathogens on the incidence of pneumonia, but, at present, there is ample evidence that poor oral health status is a risk indicator for the development of pneumonia.

These and other studies support the notion that institutionalized subjects, especially those in hospital intensive care and nursing home settings, have a greater risk for dental plaque colonization by respiratory pathogens than do community-dwelling subjects. This suggests that oral intervention to reduce or control dental plaque may serve as a simple, cost-effective method to reduce pathogen colonization in high-risk populations. Several systematic reviews of the literature have examined the evidence for oral interventions to reduce the risk of pneumonia in hospital and nursing home patients. The weight of the evidence supports the notion that interventions that improve oral hygiene significantly reduce the incidence of pulmonary infection; however, mortality seems unaffected.[68,69,70]

Interventions tested to date include topical disinfections using chlorhexidine[71] and supervised mechanical plaque control augmented with topical agents.[72] Taken together, the available evidence suggests that there is a relationship

between poor oral hygiene and bacterial pneumonia in special care populations, including those in hospital and nursing home settings. Interventions designed to improve oral hygiene may reduce the risk of pneumonia in these populations. This raises the question "what is the present status of oral hygiene practice in hospitals and nursing homes?" A recent paper described clinical practice guidelines for oral hygiene in critically ill patients based upon a systematic literature review followed by prospective consideration of the evidence at a consensus development conference.[73] From this, several recommendations were offered to guide clinicians in the care of vulnerable patients. These recommendations were that provision of effective oral care is an important strategy in reducing nosocomial pneumonia. The remaining recommendation can be found in the selected reading (Liu et al. and Gomes-Filho et al.).

Other measures for consideration for intubated patients may include removal of all dental appliances upon admissions to the critical care unit, periodic repositioning the tube, or deflation of the cuff. Removing hard deposits (e.g., tartar/calculus) from the teeth should be considered, if possible, prior to admission (for example in the case of elective surgery). Placement the patient's head to the side or place in semi-fowlers (semi-reclined body position) will also minimize inadvertent aspiration.

Bronchiolitis

Bronchiolitis is a disease that affects children under the age of 2 years; it is most common among infants aged 2 to 12 months. It is characterized by infection of the lower respiratory tract, with the bronchioles being most affected. The inflammatory response can be caused by various pathogens, including RSV, human metapneumovirus, parainfluenza virus, influenza virus, adenovirus, and *M. pneumoniae*.[74,75]

Pathophysiology

Infection of the bronchioles leads to a marked inflammatory response with a prominent mononuclear cell infiltrate. This inflammatory response results in edema and necrosis of epithelial cells lining small airways, mucosal thickening and mucus hypersecretion, plugging, and bronchospasm.[74] Bronchiolar spasm is an occasional feature. Due to these changes, the lumina of the bronchioles are critically narrowed, leading to areas of micro-atelectasis and emphysema. Respiratory compromise is common, with decreased blood oxygen saturation, hypercarbia, respiratory acidosis, and, in severe cases, respiratory failure.

Clinical and Laboratory Findings

Infants first develop signs and symptoms of an infection of the upper respiratory tract, with low-grade fever, profuse clear rhinorrhea, and cough. Signs of infection in the lower respiratory tract soon follow, including tachypnea, retractions, wheezing, nasal flaring, and, on occasion, cyanosis. Crackles can be audible, and thoracic hyper-resonance can be noted on percussion. Associated findings can include conjunctivitis, otitis media, and pharyngitis. Pulse oximetry can be used to determine oxygen saturation levels.

Chest radiography may show peribronchial cuffing, flattening of the diaphragms, hyperinflation, increased lung markings or areas of atelectasis.

Laboratory studies reveal a mild leukocytosis with a prominence of polymorphonuclear leukocytes ("left shift").

Classification

Bronchiolitis can be classified by the causative agent, as is the case with acute bronchitis.

Diagnosis

The diagnosis is clinical, based on the history and physical examination. Laboratory and radiologic studies for diagnosis are not generally required. The etiology can be determined (and the diagnosis confirmed) by performing a nasopharyngeal culture for RSV and other respiratory viruses. Rapid viral diagnostic assays are also available.

The differential diagnosis includes many other causes of wheezing and respiratory distress in this age group, such as asthma, congenital heart disease, and cystic fibrosis.

Management

Clinical treatment of these infants is generally limited to supportive care. Infants may be placed in cool-mist oxygen tents, where continuous oxygen administration can be given. Due to an increase in insensible water losses, hydration must be ensured. Aerosolized bronchodilators should not be used routinely in the management of bronchiolitis, although a carefully monitored trial may be attempted if there is a documented positive clinical response. Corticosteroid medications are generally not indicated.[76]

Antiviral therapy with ribavirin is rarely used, although it may be considered for use in highly selected situations involving documented RSV bronchiolitis with severe disease or in those who are at risk for severe disease (e.g., immunocompromised and/or hemodynamically significant cardiopulmonary disease).[74] Ribavirin was traditionally administered by aerosolization but now there are intravenous and oral formulations.[77]

Mechanical ventilation is required in the infant with respiratory failure. Very young infants (less than 1 month of age) are at risk for apnea due to RSV infection, so close observation is required.

An intramuscular monoclonal antibody to the RSV F protein, palivizumab, is effective in preventing severe RSV

disease in high-risk infants when given before and during the RSV season. This prophylaxis is currently recommended only for high-risk patient populations, such as those with chronic lung disease, a history of prematurity, or congenital heart disease.[78]

Prognosis

Although mortality due to bronchiolitis is not uncommon, most patients recover without sequelae. Epidemiologic studies with a several-year follow-up of index and control children show a higher incidence of wheezing and asthma in children with a history of bronchiolitis, unexplained by family history or other atopic syndromes. It is unclear whether bronchiolitis incites an immune response that manifests as asthma later or whether those infants have an inherent predilection for asthma that is merely unmasked by their episode of RSV.[78]

Asthma

Asthma is a chronic inflammatory disorder of the airways. It is characterized by recurrent and often reversible airflow limitation due to an underlying inflammatory process. The etiology of asthma is unknown, but allergic sensitivity is seen in most patients with asthma.[5] There is a significant hereditary contribution, but no single gene or combination of genes has yet been identified as causative. Multiple risk factors for the development of asthma have been identified, including family history of asthma, atopy, respiratory infections, inhaled pollutants in indoor and outdoor air and in the workplace, allergens, food sensitivities, and other exposures, such as tobacco smoke.[79]

In the US, asthma affects about 19 million adults and over 6 million children.[80] In addition, asthma represents a significant economic and social burden with about $56 billion (US) spent on medical costs, lost school/work days, and early deaths.[81] It accounted for 3400 deaths in the US in 2010. Overall, trends do not appear to be declining despite advances in our understanding of asthma and newer pharmacologic modalities.

Pathophysiology

The clinical features of asthma are due to the underlying chronic inflammatory process. Although the etiology is not known, certain histopathologic features provide insights into the chronic process. Infiltration of the airway by inflammatory cells such as activated lymphocytes and eosinophils, denudation of the epithelium, deposition of collagen in the sub-basement membrane area, and mast cell degranulation are often features of mild or moderate persistent asthma. Other features seen, include mucus hypersecretion, smooth muscle hypertrophy, and angiogenesis.[82]

Airway inflammation contributes significantly to many of the hallmark features of asthma, including airflow obstruction, bronchial hyper-responsiveness, and the initiation of the injury-repair process (remodeling) found in some patients. Bronchial smooth muscle spasm is instrumental in the excessive airway reactivity. Resident airway cells, including mast cells, alveolar macrophages, and airway epithelium, as well as migrating inflammatory cells, secrete a variety of mediators that directly contract the bronchial smooth muscle. These same mediators, such as histamine, cysteinyl leukotrienes, and bradykinin, increase capillary membrane permeability to cause mucosal edema of the airways.[83]

Atopy is the strongest risk factor associated with the development of asthma. Persistent exposure to relevant allergens in a sensitized individual can lead to chronic allergic inflammation of the airways. Although atopy is seen more commonly in childhood-onset asthma, it can also play an important role in asthma in adults.

Clinical and Laboratory Findings

The hallmark clinical features of asthma are recurrent reversible airflow limitation and airway hyper-responsiveness. These factors lead to the development of the signs and symptoms of asthma, which include intermittent wheezing, coughing, dyspnea, and chest tightness. Symptoms of asthma tend to worsen at night and in the early morning hours. In addition, well-defined triggers may precipitate asthma symptoms. These triggers include allergens, gastroesophageal reflux, exercise, cold air, respiratory irritants, nonsteroidal anti-inflammatory drugs, emotional extremes, and infections, particularly viral infections. Symptoms can progress slowly over time, or they may develop abruptly.[2,84,85,86]

Historical points that suggest the diagnosis of asthma include chronic coughing with nocturnal awakenings, dyspnea or chest tightness with exertion, recurrent "croup" or "bronchitis" associated with infections of the upper respiratory tract, and wheezing that occurs on a seasonal basis. Physical examination of patients with mild disease often shows no abnormalities. However, common findings in patients with more severe disease include an increased anteroposterior chest diameter, a prolonged expiratory phase, wheezing, and diminished breath sounds. Digital clubbing is rarely seen. Concurrent allergic disease such as allergic rhinitis may be present. During acute exacerbations, patients may show signs of respiratory distress, with tachypnea, intercostal retractions, nasal flaring, and cyanosis.

Pulmonary function testing or spirometry is recommended in the initial assessment of most patients with suspected asthma. These tools can often be useful to monitor the course of asthma and a patient's response to therapy. The technique involves a maximal forced expiration following a maximal inspiration (see Figure 13-4). The key measurements are the forced vital capacity (FVC), which is the amount of air expired during the forced expiration, and the forced

expiratory volume in 1 second (FEV_1), which is the volume of air expired during the first second of expiration; FEV_1 is a measure of the rate at which air can be exhaled. Given the FEV_1 and the FEV_1/FVC ratio, an objective determination of airflow limitation is possible. Reversibility can be demonstrated after administration of a short-acting bronchodilator, such as albuterol, and repeating spirometry to demonstrate significant improvement in the FEV_1. In patients with normal baseline spirometry values, a demonstration of bronchial hyper-responsiveness is useful. This is performed by bronchoprovocation, using nonspecific triggers such as histamine or methacholine. When delivered by aerosol, these agents allow the determination of bronchial hyper-reactivity by triggering a decrease in the FEV_1 immediately following inhalation. Subsequent measurements of peak expiratory flow rate (PEFR) at home may also be helpful to assess symptoms, to alert to worsening of airflow obstruction, and to monitor therapeutic responses.[87] The PEFR is easy to determine, and durable metering devices are available at little cost. Newer diagnostic tests, like exhaled nitric oxide levels (FE_{NO}), are becoming useful in detecting eosinophilic airway inflammation.[88]

Allergen skin testing is another valuable tool. This testing allows the accurate identification of allergic triggers, which can translate into more specific therapies, such as allergen avoidance and immunotherapy (see section Allergic rhinitis and conjunctivitis, above). Chest radiography may be useful, especially as a means of excluding other diseases from the diagnosis.

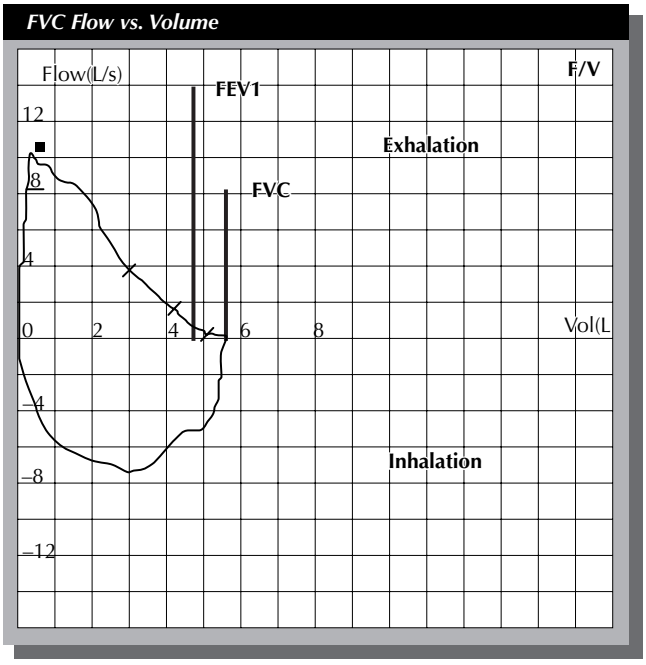

Figure 13-4 Spirometric Flow–Volume curve demonstrating FEV_1 and FVC along with exhalation and inhalation phases.

Classification

Asthma is classified according to its severity taking into consideration impairment and risk. Although there is no universal classification scheme, the guidelines set forth by the National Asthma Education and Prevention Program (NAEPP) in 2007, updated in December 2020, and the Global Initiative for Asthma (GINA), updated in 2019, are widely used in the United States.[82,89,90] Asthma patients are classified as having intermittent, mild-persistent, moderate-persistent, or severe-persistent disease. The categories are defined by both subjective (historical) and objective (spirometric) points. Follow up visits determine asthma is control thus classification can change over time. Asthma may also be classified by the underlying trigger (e.g., exercise-induced asthma and occupational asthma).

Diagnosis

The diagnosis of asthma is made on the basis of a suggestive history, confirmatory physical findings, and the demonstration of reversible airflow limitation. This can be documented during hospitalizations, by outpatient use of spirometry or PEFR determinations, or by clinical assessment after therapeutic trials.

The differential diagnosis of asthma includes other causes of chronic coughing and wheezing. The diseases that are usually considered are chronic rhinitis or sinusitis, cystic fibrosis, gastroesophageal reflux disease, airway narrowing due to compression (i.e., masses), and COPD (chronic bronchitis). Factors favoring the diagnosis of asthma include intermittent symptoms with asymptomatic periods, complete or nearly complete reversibility with bronchodilators, the absence of digital clubbing, and a history of atopy.

Management

The goals of asthma management include the patient having little or no chronic symptoms, few or no exacerbations requiring oral steroids, no hospitalizations, and minimal or no activity limitation. This is to be achieved using the least amount of medication. Ideal control would include no need for short-acting bronchodilators, normal PEFRs, no PEFR variability, and no adverse effects from controller medications. All patients with asthma, regardless of its severity, should have an asthma control plan to aid in understanding the underlying process and treatment options and to effectively treat asthma exacerbations. Regular monitoring of asthma is important; spirometry, PEFR measurement, FE_{NO} levels, and validated questionnaires may be useful tools for this purpose. Avoidance control measures are regularly emphasized, focusing on allergen and irritant triggers. Treatment for concomitant diseases that may exacerbate asthma (such as allergic rhinitis, gastroesophageal reflux disease, and chronic sinusitis) should be instituted.[91]

Pharmacotherapy of asthma is based on the severity of disease. The NAEPP guidelines provide a stepwise approach (steps 1-6) for increasing and decreasing medications based on a patient's asthma severity, and its 2020 Asthma Guideline Update provides new evidence-based recommendations (Figure 13-5).[82]

Patients with **mild-intermittent asthma** usually require a short-acting β2-agonist (SABA) on an as-needed basis (Step 1). These medications (such as albuterol) are preferably administered by inhalation. In addition to relaxing airway smooth muscle, β-agonists enhance mucociliary clearance and decrease vascular permeability.[91]

Patients with **mild-persistent asthma** usually require routine therapy for control of underlying airway (Step 2). The original NAEPP guidelines recommend a daily, low-dose inhaled corticosteroid (ICS) with as-needed (SABA). The NAEPP's 2020 Asthma Guideline Update provides another option: as-needed concomitant ICS and SABA treatment.[82] Inhaled corticosteroids are the most widely used and most effective asthma anti-inflammatory agents.[91] Inhaled corticosteroids are the most potent and consistently effective long-term control medication for asthma.[77] Patients with mild to moderate persistent asthma treated with inhaled steroids have improved symptom scores, decreased exacerbations, less β_2-agonist use, fewer oral steroid courses and fewer hospitalizations.[91] Inhaled corticosteroids have an excellent safety profile at conventional doses, although high-dose therapy can put patients at risk for corticosteroid side

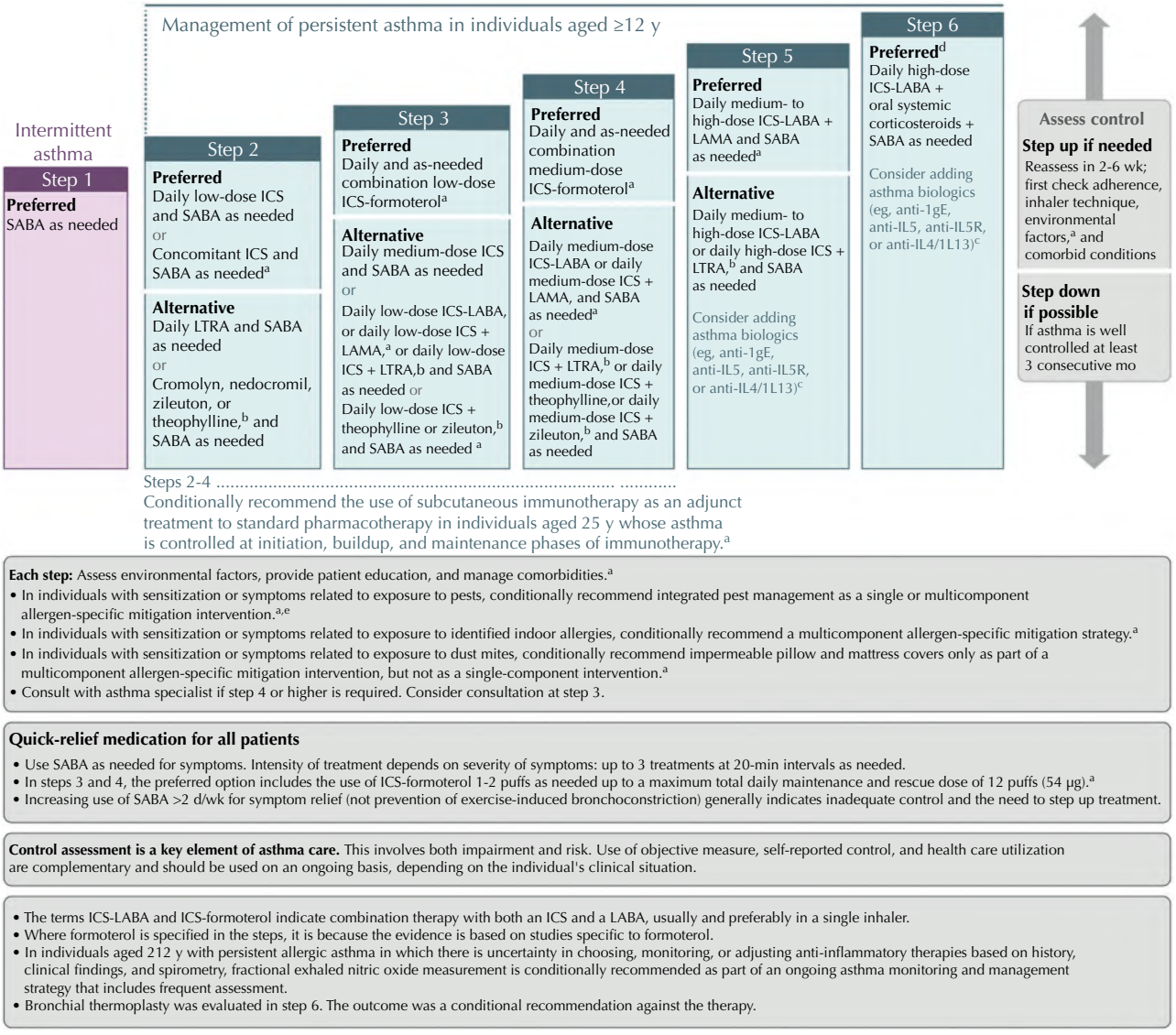

Figure 13-5 Stepwise approach for treating asthma in adults and children ⩾ 12 years. *Source:* From National Heart, Lung and Blood Institute; National Institutes of Health; U.S. Department of Health and Human.

effects. These medications have been used for decades in both children and adults without significant long-term side effects in most patients. Although there is the potential for a decreased growth-velocity effect, evidence suggests that the use of inhaled corticosteroids at recommended doses does not have long-term, clinically significant, or irreversible effects.[82] Alternative medications include the nonsteroidal anti-inflammatory agents nedocromil and cromolyn, leukotriene receptor antagonists (LTRAs), or sustained-release theophylline.

Patients with **moderate-persistent asthma** (Steps 3 or 4) and **severe-persistent asthma** (Steps 5 or 6) require more intensive therapy. Long-acting bronchodilators such as salmeterol and formoterol have been shown to have an additive effect when used with inhaled corticosteroids and are useful additions to inhaled corticosteroid therapy.[92] For steps 3 and 4, the NAEPP's 2020 Asthma Guideline Update now prefers a single maintenance and reliever treatment (SMART), i.e., daily as well as as-needed combination low-dose ICS-formoterol for adults and children ≥ 12 years. Formoterol was the LABA studied in SMART, hence the recommendation is specific to formoterol therapy. Formoterol also has a fast onset of action, and its dose range permits more than twice daily use. The older NAEPP recommendation of using a daily medium-dose ICS with as-needed SABA remains an alternative for step 3.[82]

Tiotropium, an inhaled long-acting muscarinic antagonist (LAMA) that has been widely used in chronic obstructive pulmonary disease (COPD), has been approved as maintenance treatment for asthma. Patients who have persistent symptoms and frequent exacerbations despite ICS/LABA combination therapy may benefit from a LAMA.[90,93] Step 5 in the NAEPP's 2020 Asthma Guideline Update now prefers adding on a LAMA as a controller in patients whose asthma is not sufficiently controlled by a medium- to high-dose ICS/LABA. Step 6 remains unchanged. The use of SMART was not addressed for steps 5 and 6 in this update.[82]

A minority of patients might require long-term corticosteroids; these patients are difficult to manage, but adequate symptom control while minimizing the dose is of paramount importance.[91]

Patients who continue to have uncontrolled asthma despite high dose ICS/LABA therapy or are oral glucocorticoid dependent may be candidates for a biologic agent (Table 13-1). Currently, there are five biologic agents that are FDA-approved for uncontrolled moderate- and/or severe-persistent asthma. Omalizumab, a subcutaneous recombinant humanized monoclonal anti-IgE antibody indicated for

Table 13-1 Biologic agents approved for the treatment of moderate to severe persistent asthma.

Biologic Agent	Target	FDA Approved Age	Labs Required	Route	Dose & Interval	Adverse Effects	Also Approved For
omalizumab (Xolair ©)	IgE	6+ years	IgE 30-700 IU/mL Sensitivity to perennial allergen	SC	Based on weight and IgE level (maximum dose: 375mg every 2 weeks)	Local site reaction Anaphylaxis	CIU
mepolizumab (Nucala ©)	IL-5	6+ years	AEC ≥ 150	SC	100mg every 4 weeks (40mg every 4 weeks for ages 6-11 years)	Local site reaction Herpes Zoster	EGPA
benralizumab (Fasenra ©)	IL-5 Rα	12+ years	AEC ≥ 300	SC	30mg every 4 weeks for the first 3 doses; then every 8 weeks	Headache, fever Local site reaction	
reslizumab (Cinqair ©)	IL-5	18+	AEC ≥ 400	IV	3mg/kg every 4 weeks	Anaphylaxis 0.3% (Black Box warning) Transient increase in CPK	
dupilumab (Dupixent ©)	IL-4Rα	12+ years	None in studies	SC	2 doses: 200mg or 300mg every 2 weeks	Transient eosinophilia Local site reaction Keratitis Conjunctivitis	Atopic dermatitis CRSwNP

AEC: absolute eosinophil count; CIU: chronic idiopathic urticaria; CPK: creatine phosphokinase; CRSwNP: chronic rhinosinusitis with nasal polyps; EGPA: eosinophilic granulomatosis with polyangiitis; IgE: total serum immunoglobulin E; IL-4Rα: interleukin-4 receptor alpha; IL-5: interleukin-5; IL-5Rα: interleukin-5 receptor alpha; IV: intravenous infusion; mg/kg: milligram per kilogram; SC: subcutaneous injection

perennial atopic patients with moderate to severe asthma in patients age 6 and above, has been shown to improve asthma symptom scores, decrease exacerbations, and decrease inhaled corticosteroid doses.[94] Interleukin (IL)-5 mediates eosinophilic inflammation in the airways. There are three monoclonal antibodies that target the IL-5 pathway that have been approved as add-on, maintenance treatment in patients with severe-persistent asthma with an eosinophilic phenotype. Mepolizumab, is a subcutaneous formulation approved in patients aged 6 or older with peripheral eosinophil count of 150/microliter or greater and is administered every 4 weeks. Reslizumab, an IV formulation dosed based on weight, is approved for patients aged 18 and up with a peripheral eosinophil count of 400/microliter or greater. Benralizumab is a monoclonal antibody directed against the IL-5 receptor alpha subunit that decreases IL-5 signaling and also depletes eosinophils through enhanced antibody-dependent cell-mediated cytotoxicity. It has been approved as add-on maintenance therapy in patients aged 12 and up with severe eosinophilic asthma with a peripheral eosinophil count ≥ 300 cells/microliter. These biologics that target the eosinophilic pathway of asthma have all show improved quality of life and a reduction in exacerbation rates.[95,96] Lastly, dupilumab is a humanized monoclonal antibody that targets the alpha subunit of the IL-4 receptor. By binding to this subunit, dupilumab inhibits the activity of cytokines IL-4 and IL-13, integral players in asthma and allergy pathophysiology. Dupilumab is administered subcutaneously and is indicated for the treatment of moderate- to severe-persistent asthma in patients aged 12 and up. Dupilumab has been shown to decrease oral glucocorticoid, reduce exacerbations, and improve lung function.[97]

Other therapies that are also currently under investigation include an antithymic stromal lymphopoietin (TSLP) biologic agent called tezepelumab, a novel glucocorticoid receptor agonist, and a prostaglandin D2 receptor antagonist called fevipiprant.[98,99,100]

Bronchial thermoplasty involves administering thermal energy during bronchoscopy to decrease smooth muscle mass. It has been shown to decrease exacerbations, emergency room visits, and days missed from school/work in patients with severe-persistent asthma.[101] Patients with allergic triggers may benefit from allergen immunotherapy. Many studies have now documented improvement from following a 3- to 5-year course of specific immunotherapy.[102] This is an excellent means of minimizing medications while maintaining control for many patients.

Prognosis

Although asthma is not a curable disease, it is a controllable disease. Asthma education programs are extremely important in making early diagnosis and interventions possible. Despite an increase in our knowledge of the underlying pathophysiology, asthma mortality rates have not declined. With early diagnosis and a comprehensive management plan, patients with asthma can experience a normal life expectancy with good quality of life.

Oral Health Considerations

The main concern when treating any medically complex patient is to avoid exacerbation of the underlying condition. Several protocols suggesting appropriate procedures for dental treatment of asthmatic patients have been put forth.[103,104,87,105] However, few studies assessing the respiratory response of patients to dental care have been performed. One study indicated that although 15% of asthmatic pediatric patients will have a clinically significant decrease in lung function, no clinical parameter or historical data pertaining to asthma can predict this phenomenon.[106]

However, numerous dental products and materials, including toothpaste, fissure sealants, tooth enamel dust, and methylmethacrylate, have been associated with the exacerbation of asthma, whereas other items (such as fluoride trays and cotton rolls) have been suggested as being so associated.[105,106,107,108,109,110,111]

There is still no consensus regarding the association between asthma and dentofacial morphology.[112,113] Although nasal respiratory obstruction resulting in mouth breathing has been implicated in the development of a long and tapered facial form, an increased lower facial height, and a narrow maxillary arch, this relationship has never been substantiated with unequivocal evidence.

Oral manifestations include candidiasis, decreased salivary flow, increased calculus, increased gingivitis, increased periodontal disease, and possible increased incidence of caries.[114,115,116] It is possible that prolonged use of β_2-agonists may cause reduced salivary flow, with a resulting increase in cariogenic bacteria and caries and an increased incidence of candidiasis.[117,118]

Dental treatment for asthmatic patients needs to address the oral manifestations of this condition, as well as its potential underlying systemic complications. Elective dental procedures should be avoided in all but those whose asthma is well controlled. The type and frequency of asthmatic attacks, as well as the type of medications used by the patient, indicate the severity of the disease.

The following are considerations and recommendations for administering dental care to patients who have asthma:

1) Caries risk assessment and fluoride supplements as warranted should be instituted for all asthmatic patients, particular those taking β_2-agonists.
2) The patient should be instructed to rinse his or her mouth with water after using inhalers.

3) Oral hygiene should be reinforced to reduce the incidence of gingivitis and periodontitis.
4) Antifungal medications should be administered as needed, particularly in patients who are taking inhaled corticosteroids.
5) Evaluate potential risks in patients taking long-term systemic corticosteroids associated with major surgical procedures (see Chapter 20 "Transplantation Medicine").
6) Use stress-reducing techniques. Conscious sedation should be performed with agents that are not associated with bronchoconstriction, such as hydroxyzine. Barbiturates and narcotics should be avoided due to their potential to cause bronchospasm and reduce respiratory functions. Nitrous oxide can be used for all but patients with severe asthma as it may irritate the airways.[103]
7) Avoid dental materials that may precipitate an attack. Acrylic appliances should be cured prior to insertion. Dental materials without methylmethacrylate should be considered.
8) Schedule these patients' appointments for late morning or later in the day to minimize the risk of an asthmatic attack.[119]
9) Have oxygen and bronchodilators available in case of an exacerbation of asthma.
10) There are no contraindications to the use of local anesthetics containing epinephrine, but preservatives such as sodium metabisulfite may contribute to asthma exacerbation in susceptible patients.[120] Nevertheless, interactions between epinephrine and R_2-agonists may result in a synergistic effect, producing increased blood pressure and arrhythmias.
11) Judicious use of rubber dams will prevent reduced breathing capability.
12) Care should be used in the positioning of suction tips as they may elicit a cough reflex.
13) About 7–14% of adult asthmatic patients have an allergy to aspirin and other nonsteroidal anti-inflammatory agents.[121] A careful history concerning the use of these types of drugs needs to be elicited. Although the use of acetaminophen has been proposed as an alternative to the use of aspirin, recent data suggest caution because these types of drugs have also been associated with more severe asthma.[122]
14) Drug interactions with theophylline are common. Macrolide antibiotics may increase the level of theophylline, whereas phenobarbitals may reduce the level. Furthermore, drugs such as tetracycline have been associated with more accentuated side effects when given together with theophylline.
15) During an acute asthmatic attack, discontinue the dental procedure, remove all intraoral devices, place the patient in a comfortable position, make sure the airway is opened, and administer a β_2-agonist and oxygen. If no improvement is noted, administer epinephrine subcutaneously (1:1000 concentration, 0.01 mg/kg of body weight, up to a maximum of 0.3 mg) and alert emergency medical assistance.

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a disease state characterized by airflow limitation. The airflow is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[123] COPD includes emphysema, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a clinically defined condition with chronic cough and phlegm; and small airways disease, a condition in which small bronchioles are narrowed. COPD is present only if chronic airflow obstruction occurs; chronic bronchitis without chronic airflow obstruction is not included within COPD.

The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposures to risk factors and the aging population. The diagnosis should be considered in any patient with symptoms of cough, sputum production or dyspnea, and/or a history of exposure to risk factors for the disease.[123]

Risk factors for the disease can include environmental exposures and host factors, such as a rare hereditary deficiency in the enzyme α_1-antitrypsin. This enzyme is responsible for inhibiting the activity of trypsin and other proteases in the serum and tissues. The characteristic panlobular emphysematous changes that are seen in α_1-antitrypsin deficiency are related to the loss of alveolar walls. More commonly, risk factors for the disease include environmental exposure to tobacco smoke, heavy exposure to occupational dusts and chemicals (vapors, irritants, fumes), and indoor/outdoor pollution.[123]

The clinical course of patients with COPD is quite varied. Most patients display some degree of progressive dyspnea, exercise intolerance, and fatigue. In addition, patients are susceptible to frequent exacerbations, usually caused by infections of the upper or lower respiratory tract. Most patients with COPD have little respiratory reserve. Therefore, any process that causes airway inflammation can lead to clinical deterioration.

Pathophysiology

Three processes are thought to be important in the pathogenesis of COPD: chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature; oxidative stress; and an imbalance of proteases and antiproteases in the lung. These pathologic changes lead to the physiologic changes characteristic of the disease, including mucus hypersecretion, ciliary dysfunction, airflow limitation,

pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale.[123]

Expiratory airflow limitation is the primary physiologic change in COPD. Airflow limitation results from fixed airway obstruction mainly. Patients with COPD may also have airway hyperresponsiveness overlapping with asthma.[124] Mucous hypersecretion and ciliary dysfunction lead to chronic cough and sputum production. In advanced COPD, peripheral airway obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, leading to hypoxemia and hypercapnia.[123]

Many toxins in tobacco smoke can cause a vigorous inflammatory response. In humans, chronic exposure to tobacco smoke results in an increase in the number of goblet cells because of hyperplasia and metaplasia. Acrolein, for example, causes both impairment of both ciliary and macrophage activities, as well as increases mucin hypersecretion.[125] Nitrogen dioxide causes direct toxic damage to the respiratory epithelium. Hydrogen cyanide is responsible for the functional impairment of enzymes that are required for respiratory metabolism. Carbon monoxide causes a decrease in the oxygen-carrying capacity of red blood cells by associating with hemoglobin to form carboxyhemoglobin. Lastly, polycyclic hydrocarbons have been implicated as carcinogens.

Hypoxemia is the result of the ventilation-perfusion mismatch that accompanies airway obstruction and emphysema. Portions of the lung that are not aerated due to obstruction cannot oxygenate the blood. This causes a decrease in overall oxygen concentrations. In addition, emphysema causes a decreased diffusion capacity because of a loss of air-space capillary units. Hypercarbia also develops and is often progressive and asymptomatic. Pulmonary hypertension can result from chronic hypoxia due to vasoconstriction of pulmonary vessels.

Patients with emphysema alone have less ventilation-perfusion mismatching early in the course of the disease; this is due to the loss of both air space and supplying blood vessels. Severe hypoxia, pulmonary hypertension, and cor pulmonale are generally not seen until late in the disease process. Emphysema manifests as loss of the elastic recoil of the lungs, making the lungs more compliant. The work of breathing is therefore not significantly increased. However, the decrease in recoil allows the easy collapse of the peripheral airways, leading to further airway obstruction and airflow limitation.[126]

Clinical and Laboratory Findings

Patients with COPD have symptoms of dyspnea, cough, and sputum production. An increase in the production of purulent sputum is a sign of exacerbation due to respiratory infection. Physical findings include diffuse wheezing, possibly associated with signs of respiratory distress, including the use of accessory muscles of respiration (retractions) and tachypnea.[124] Liver enlargement due to congestion, ascites, and peripheral edema can develop as the disease progresses to pulmonary hypertension and cor pulmonale. This leads to the characteristic clinical patient presentation termed the *blue bloater*.

Patients with emphysema present primarily with dyspnea. Patients can be adequately oxygenated in the early stages of the disease and thus can have fewer signs of hypoxia; the term *pink puffer* has been used to describe these patients. Physical findings include an increase in chest wall size. Wheezing is present to varying degrees.

Chest radiography may show evidence of an increase in lung compliance, with flattened diaphragms, hyper-expansion, and an increase in anteroposterior diameter (Figure 13-6). Spirometry will show evidence of airflow limitation. A post bronchodilator FEV_1/FVC ratio of < 0.7 confirms the presence of airflow limitation that is not fully reversible.[127] Complete pulmonary function studies will also indicate an increase in residual volume and total lung capacity.[124] Pulmonary diffusion capacity will be decreased due to a loss of gas-exchanging units.

Classification

COPD is now classified into five stages: at risk, mild, moderate, severe, and very severe. The at-risk stage is defined by normal spirometry, but patients have chronic symptoms of cough and sputum production. Mild, moderate, and severe COPD have evidence of increasing airway obstruction on spirometry in each progressive stage. Finally, very severe COPD is defined by severe airway obstruction with chronic respiratory failure. Patients with severe COPD are at more risk for other systemic diseases including cardiovascular disease, osteoporosis, lung cancer, and depression.[128]

Diagnosis

The diagnosis is suggested by the history and physical findings. Patients often have cough, dyspnea, and sputum production and/or a history of exposure to risk factors. Alternative diagnoses, such as asthma, CF, and congestive heart failure, should be considered. Complete pulmonary function tests are a valuable means of assessing airflow limitation and any reversibility. For patients with more severe disease, assessment of oxygen status with pulse oximetry is a valuable office procedure. A determination of arterial blood gases is important for patients who are clinically deteriorating and for the management of hospitalized patients.[124] Chest radiography can be helpful to exclude alternative diagnoses but is rarely diagnostic in COPD.

Management

There are no curative treatments for chronic bronchitis and emphysema. Smoking cessation is the single most important intervention to stop the progression of COPD. Reduction of

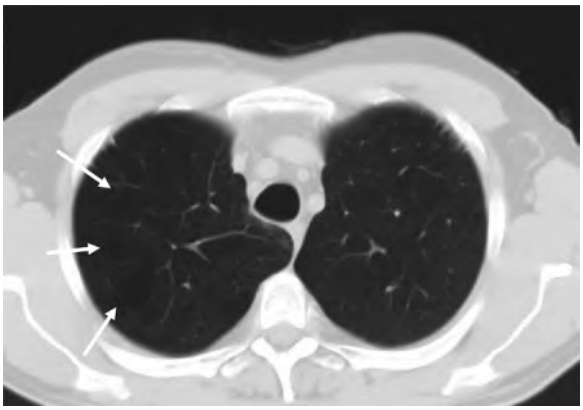

Figure 13-6 Axial computed tomography image of the upper chest demonstrates decreased attenuation of the lung tissue bilaterally, especially on the right (white arrows) where there is evidence of centrilobular emphysema.

exposures to occupational dusts and chemicals and indoor/outdoor pollution can also decrease the progression of disease.[123] Influenza and pneumococcal vaccines are recommended.

Management focuses on reducing symptoms and exacerbations. The most recent Global Initiative for Obstructive Disease guidelines gives management recommendations after patients have been assessed combining symptom scores, airflow limitations, and exacerbations (Figure 13-7). Maintenance therapy includes trials of inhaled bronchodilators such as β-agonists and ipratropium bromide. Long-acting bronchodilators, such as formoterol or salmeterol, may be added as well as mucolytics. Theophylline products have also been used with some efficacy as well as phosphodiesterase-4 inhibitors. Long-term monotherapy with oral or inhaled corticosteroids is not recommended as inhaled steroids with long acting β-agonists are more effective.[123]

Chest physiotherapy has not been proven to be of value in the management of COPD.

The long-term administration of oxygen therapy to patients with chronic respiratory failure increases survival. Additionally, during exacerbations, oxygen therapy is often required. Caution must be used when administering oxygen to patients with COPD as their ventilatory drive will often be diminished. This is the result of chronic retention of carbon dioxide and subsequent insensitivity to hypercarbia. As a result, patients with COPD are sensitive to increases in oxygen tension, which provides the major stimulus for respiratory drive. Oxygen therapy during sleep can also be a useful means of limiting hypoxemia and subsequent pulmonary hypertension. An option for some patients involves lung-volume reduction which removes severely emphysematous tissue from the both upper lobes allowing the remaining tissue to expand and function more effectively.[128]

Antibiotics are often used during exacerbations of COPD. The presence of purulent sputum during an exacerbation generally requires treatment with 7 to 10 days of an oral antibiotic chosen based on local bacterial resistant patterns. The primary pathogens in COPD exacerbations include *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

Prognosis

The prognosis is poor for patients who are frequently symptomatic due to COPD. The need for hospital admission for an exacerbation, especially if intensive care is required, is an ominous prognostic sign in COPD as about half of such patients admitted to the intensive care unit do not survive a year after admission.[129]

Oral Health Considerations

The association, if any, between oral disease and lung disease was analyzed by the National Health and Nutrition Examination Survey I (NHANES I).[130] Of 23,808 individuals, 386 reported a suspected respiratory condition (as assessed by a physician) categorized as a confirmed chronic respiratory disease (chronic bronchitis or emphysema) or acute respiratory disease (influenza, pneumonia, acute bronchitis), or not to have a respiratory disease.

Significant differences were noted between subjects having no disease and those having a chronic respiratory disease confirmed by a physician. Individuals with a confirmed chronic respiratory disease had a significantly greater oral hygiene index than subjects without a respiratory disease. Logistic regression analysis was performed to simultaneously control for multiple variables, including gender, age, race, oral hygiene index (OHI), and smoking status. The results of this analysis suggest that for patients having the highest OHI values, the odds ratio for chronic respiratory disease was 4.5.

Another study of elderly subjects (aged 70 to 79) found that, after controlling for smoking status, age, race, and gender, there was a significant association between periodontal health and airway obstruction in former smokers,[131] and an additional study suggested that cigarette smoking may be a cofactor in the relationship between periodontal disease and COPD.[132] A recent systematic review and meta-analysis further confirmed an association between periodontitis and COPD;[133] however, further longitudinal epidemiologic studies and clinical trials are necessary to determine the role of oral health status in COPD.

These results were supported by a subsequent study that measured associations between poor oral health and chronic lung disease, and this study was able to carefully control for a number of potentially confounding variables. Data from NHANES III, which documented the general health and nutritional status of randomly selected United States subjects from 1988 to 1994, were analyzed.[130] This cross-sectional, retrospective study of the NHANES III database included a study population of 13,792 subjects

COMMONLY USED MAINTENANCE MEDICATIONS IN COPD*

Generic Drug Name	Inhaler Type	DELIVERY OPTIONS: *Nebulizer*	*Oral*	*Injection*	Duration Of Action
BETA$_2$-AGONISTS					
SHORT-ACTING (SABA)					
Fenoterol	MDI	√	pill, syrup		4-6 hours
Levalbuterol	MDI	√			6-8 hours
Salbutamol (albuterol)	MDI & DPI	√	pill, syrup, extended release tablet	√	4-6 hours 12 hours (ext. release)
Terbutaline	DPI		pill	√	4-6 hours
LONG-ACTING (LABA)					
Arformoterol		√			12 hours
Formoterol	DPI	√			12 hours
Indacaterol	DPI				24 hours
Olodaterol	SMI				24 hours
Salmeterol	MDI & DPI				12 hours
ANTICHOLINERGICS					
SHORT-ACTING (SAMA)					
Ipratropium bromide	MDI	√			6-8 hours
Oxitropium bromide	MDI				7-9 hours
LONG-ACTING (LAMA)					
Aclidinium bromide	DPI, MDI				12 hours
Glycopyrronium bromide	DPI		solution	√	12-24 hours
Tiotropium	DPI, SMI, MDI				24 hours
Umeclidinium	DPI				24 hours
Glycopyrrolate		√			12 hours
Revefenacin		√			24 hours
COMBINATION SHORT-ACTING BETA$_2$-AGONIST PLUS ANTICHOLINERGIC IN ONE DEVICE (SABA/SAMA)					
Fenoterol/ipratropium	SMI	√			6-8 hours
Salbutamol/ipratropium	SMI, MDI	√			6-8 hours
COMBINATION LONG-ACTING BETA$_2$-AGONIST PLUS ANTICHOLINERGIC IN ONE DEVICE (LABA/LAMA)					
Formoterol/aclidinium	DPI				12 hours
Formoterol/glycopyrronium	MDI				12 hours
Indacaterol/glycopyrronium	DPI				12-24 hours
Vilanterol/umeclidinium	DPI				24 hours
Olodaterol/tiotropium	SMI				24 hours
METHYLXANTHINES					
Aminophylline			solution	√	Variable, up to 24 hours
Theophylline (SR)			pill	√	Variable, up to 24 hours
COMBINATION OF LONG-ACTING BETA$_2$-AGONIST PLUS CORTICOSTEROID IN ONE DEVICE (LABA/ICS)					
Formoterol/beclometasone	MDI, DPI				12 hours
Formoterol/budesonide	MDI, DPI				12 hours
Formoterol/mometasone	MDI				12 hours
Salmeterol/fluticasone propionate	MDI, DPI				12 hours
Vilanterol/fluticasone furoate	DPI				24 hours
TRIPLE COMBINATION IN ONE DEVICE (LABA/LAMA/ICS)					
Fluticasone/umeclidinium/vilanterol	DPI				24 hours
Beclometasone/formoterol/glycopyrronium	MDI				12 hours
Budesonide/formoterol/glycopyrrolate	MDI				12 hours
PHOSPHODIESTERASE-4 INHIBITORS					
Roflumilast			pill		24 hours
MUCOLYTIC AGENTS					
Erdosteine			pill		12 hours
Carbocysteine†			pill		
N-acetylcysteine†			pill		

**Not all formulations are available in all countries. In some countries other formulations and dosages may be available. † Dosing regimens are under discussion. MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.*

Figure 13-7 Therapeutic options for patients with COPD based on assessment. *Source:* Based on the Global Initiative for Obstruction Lung Disease (GOLD); Global Strategy for the Diagnosis Management, and Prevention of Chronic Obstructive Pulmonary Disease (2021 report). https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf.

20 years of age and older having at least six natural teeth. A history of bronchitis and/or emphysema was recorded from the medical questionnaire. Lung function was estimated by calculation of the ratio of forced expiratory volume after 1 sec (FEV_1)/forced vital capacity (FVC). Oral health status was deduced from the Decayed Missing Filled System (DMFS/T) index, gingival bleeding, gingival recession, gingival pocket depth, and periodontal attachment level. Subjects with COPD had, on average, more periodontal attachment loss (CAL 1.48 ± 1.35- mean ± SD) than those without COPD (mean CAL 1.17 ± 1.09). The risk for COPD appeared to be significantly elevated when mean attachment loss (MAL) was found to be severe (mean attachment loss; MAL ≥ 2.0 mm) compared with periodontal health (< 2.0 mm MAL: odds ratio 1.35, 95% CI: 1.07–1.71). Furthermore, the odds ratio was 1.45 (95% CI: 1.02– 2.05) for those who had ≥ 3.0 mm MAL. A trend was also noted in that lung function appeared to diminish as the amount of attachment loss increased. No such trend was apparent when gingival bleeding was considered.

Another study examined the relation between airway obstruction and periodontal disease in a cohort of 860 community dwelling elders enrolled in the Health, Aging, and Body Composition Study (Health ABC).[134] Results showed that, after stratification by smoking status and adjustment for age, race, gender, center, and number of pack-years, those with normal pulmonary function had significantly better gingival index (P .036) and loss of attachment (P .0003) scores than those with airway obstruction. Thus, a significant association between periodontal disease and airway obstruction was noted, especially in former smokers.

A recent meta-analysis explored the relationship between periodontal disease and COPD.[135] Fourteen observational studies including 3,988 COPD patients were included in the analysis. A significant association between PD and COPD was identified.[136] There is thus great need for randomized controlled trails to determine if periodontal interventions prevent the initiation and/or progression of COPD.

Apart from the periodontal pathogens mentioned above, *Streptococci* have been shown to be the causative pathogen of exacerbation in 4% of individuals with COPD.[137] One prospective study suggested that oral colonization with respiratory pathogens in patients residing in a chronic care facility was significantly associated with COPD.[138] The relationship between oral pathogens and exacerbations of COPD clearly deserves serious consideration. It is essential that elderly individuals (particularly institutionalized patients) receive adequate oral hygiene in order to minimize respiratory complications.

Drug interactions with theophylline may arise (see above), and an evaluation of medications by the oral health care provider including intermittent antibiotic use is appropriate.

As mentioned above, increased oxygen tension may diminish respiratory function in patients with COPD. Extreme caution must be exercised when administering supplemental oxygen in emergencies.

Cystic Fibrosis (CF)

CF is a multisystem genetic disorder that is characterized chiefly by chronic airway obstruction and infection and by exocrine pancreatic insufficiency, with its effects on gastrointestinal function, nutrition, growth, and maturation.[139]

The disorder is caused by numerous mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) that helps regulate ion flux at epithelial surfaces. The disease is characterized by hyperviscous secretions in multiple organ systems. Thickened secretions affect the pancreas and intestinal tract, causing malabsorption and intestinal obstruction. In the lungs, viscid mucous causes airway obstruction, infection, and bronchiectasis. Pulmonary complications are the major factors affecting life expectancy in patients with CF. This section focuses on the pulmonary manifestations of CF.

CF is an autosomal recessive trait resulting from mutations at a single gene locus on the long arm of chromosome 7. The incidence of CF among Caucasians is approximately 1 in 3200 births; the incidence is lower among those of other races.[140]

Pathophysiology

The primary defect in the *CFTR* gene results in a defective chloride transport system in exocrine glands. As a result, mucous production occurs without sufficient water transport into the lumen. The resultant mucus is dry, thick, and tenacious and leads to inspissation in the affected glands and organs. In the airways, the viscid secretions impair mucociliary clearance and promote airway obstruction and bacterial colonization. Most airway injury in CF is believed to be mediated by neutrophil products, including proteases and oxidants, liberated by the abundance of neutrophils in the CF airway at almost all ages.[141] Bacterial superinfection is common and can lead to respiratory compromise.

Clinical and Laboratory Findings

Patients with CF may present in infancy with extrapulmonary manifestations such as meconium ileus or failure to thrive. Pulmonary manifestations include cough, recurrent infections of the lower respiratory tract, refractory lung infiltrates, and bronchospasm. Tachypnea and crackles can be found on physical examination. As the disease progresses, digital clubbing and bronchiectasis (Figure 13-8) may become apparent. Most of the nonpulmonary pathology in CF occurs in the gastrointestinal tract and related organs.

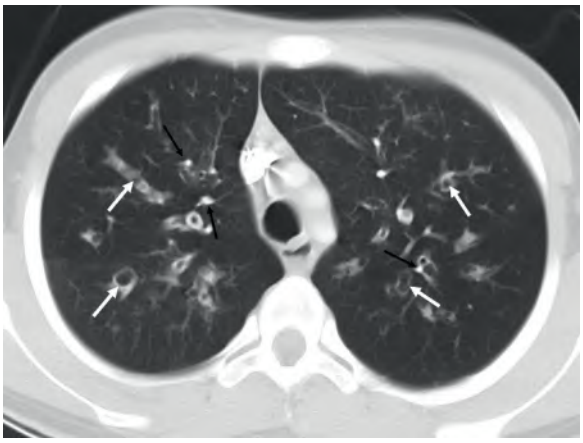

Figure 13-8 Axial computed tomography scan shows thickening of the bronchial walls in the upper lobes and bronchiectasis (dilation of the bronchi) bilaterally (white arrows). The bronchi should be approximately the same size as its associated pulmonary artery (black arrows).

Spirometry and pulmonary function testing are useful tools for documenting and monitoring airflow limitation. Airway obstruction tends to worsen with disease progression, although some patients with CF have mild pulmonary disease. CT analysis of the remarkable lung structural changes may be another potential outcome measure to monitor disease progression.

Classification

There is no universally accepted classification system for CF.

Diagnosis

The diagnosis of CF is based on the presence of pulmonary or extrapulmonary symptoms, as described above. A sweat test can be performed to confirm the diagnosis. The procedure involves the collection of sweat after stimulation with pilocarpine. Samples containing > 60 mEq/L chloride are considered positive. Patients with indeterminate values (40 to 60 mEq/L) can be further assessed by using deoxyribonucleic acid (DNA) mutation analysis. Characteristic nasal epithelial bioelectric abnormalities can also serve as laboratory evidence of CFTR dysfunction and be used to diagnose CF when phenotypic clinical features are present.[139] Due to the importance of early diagnosis, all states have now implemented newborn screening for CF.

Management

Treatment of CF includes antibiotics, bronchodilators, anti-inflammatory agents, chest physiotherapy with postural drainage, and mucolytic agents. In addition to oral and parenteral antibiotics, inhaled antibiotics such as tobramycin are used to help minimize systemic effects.[142] Long-term macrolide antibiotics have been used to effectively treat diffuse panbronchiolitis as well.[139] The use of anti-inflammatory agents in young patients with mild disease may help slow the decline of lung function.[143] Recombinant enzyme deoxyribonuclease therapy has also been shown to offer benefit to some patients with purulent airway secretions.[144] Finally, proper nutrition and exercise are essential. Approximately 90% of patients with CF require mealtime pancreatic enzymes,[129] and vitamin and caloric supplementation is essential as well. Exercise is generally considered beneficial for patients with CF and should be encouraged, except for those with the most severe lung disease and hypoxemia.[145]

Prognosis

Although the mortality rate is high, the most recent statistics from the Cystic Fibrosis Foundation indicate that 50% of patients can now be expected to survive beyond the age of 37 years.[139] The severity of lung disease often determines long-term survival. Lung transplantation has become an accepted treatment for respiratory failure secondary to CF.[146] New treatment modalities that are being investigated to help prolong survival include pharmacologic interventions targeted to improving CFTR functioning (potentiators) and trafficking (correctors).[147]

Oral Health Considerations

It has been suggested that patients with CF may have the same type of dentofacial morphology as other mouth-breathing patients.[148] However, larger prospective studies are needed to confirm this.

Several studies have reported that the number of decayed, missing, and filled teeth and plaque, calculus, and gingival bleeding of CF patients is lower than that of non-CF control subjects, but additional studies cite increased risk.[149] These contradictions may be due age related differences in populations studied[150] and more antibiotic use by CF patients.

It has also been reported that the same bacterial clone of *P. aeruginosa*, an important bacterial pathogen for CF patients, can be found in subgingival plaque and saliva, serving as a reservoir of colonization.[151] This suggests that oral hygiene strategies may help reduce the level of these pathogens in the mouth and thus reduce potential lung infection.

As with other patients with chronic lower respiratory infections, improved oral hygiene including toothbrush hygiene[152] may minimize exacerbation of the underlying condition.

Of note, patients with cystic fibrosis may ultimately receive a lung transplant, so precautions appropriate for post-transplant patients should be followed (Chapter 20 "Transplantation Medicine")

Pulmonary Embolism

Pulmonary embolism (PE) is a result of an exogenous or endogenous material traveling to the lung and causing blockage of a pulmonary arterial vessel. The embolus may

originate anywhere, but it is usually due to a thrombosis in the lower extremities.[153] Other substances, such as septic emboli, venous gas, fat emboli, and intravascular foreign bodies are potential causes of pulmonary emboli.[154] Risk factors for PE include prolonged immobilization (such as in a postoperative state), lower extremity trauma, a history of deep venous thromboses, and the use of estrogen-containing oral contraceptives (especially in association with tobacco smoking).[155] The most common reversible risk factor for PE is obesity, an increasing problem in the US.[156]

Pathophysiology

PE causes occlusion of pulmonary arterial vessels, which results in a ventilation-perfusion mismatch. Massive PE causes right-sided heart failure and is rapidly progressive. Local bronchoconstriction may occur due to factors released by platelets and mast cells at the sites of occlusion. Pulmonary hypertension due to vessel occlusion and arterial vasospasm is a common finding.

Clinical And Laboratory Findings

Patients usually present with dyspnea. Other features that are variably present include chest pain, fever, diaphoresis, cough, hemoptysis, and syncope. Physical findings can include evidence of a lower extremity deep venous thrombosis, tachypnea, crackles or rub on lung auscultation, and heart murmur.

Hypoxemia is common in acute PE. Measurements of arterial blood gases are helpful as patients may demonstrate a decrease in partial pressure of arterial oxygen (PaO_2) and partial pressure of arterial carbon dioxide ($PaCO_2$), with an increase in hydrogen ion concentration (pH). However, normal arterial blood gases do not rule out the possibility of PE.

Diagnosis

The diagnosis is made on the basis of history and physical findings. The diagnostic utility of plasma measurements of circulating D-dimer (a specific derivative of crosslinked fibrin) has been found to have a high negative predictive value of 99.5%.[157] However, in patients with a high clinical probability of a PE, a D-dimer test should not be used since the negative predictive value of this test is low.[158]

Chest radiography is often not helpful but may reveal suggestive signs such as elevated hemidiaphragm, pleural effusions, and pulmonary artery dilatation. Troponin levels may be elevated, the echocardiogram may be abnormal with increased right ventricular volume, and electrocardiography may help establish or exclude alternative diagnoses, such as acute myocardial infarction.

Although the ventilation-perfusion scan has historically been the most common diagnostic test used when PE is suspected, spiral (helical) CT scanning has replaced it at many centers. The use of pulmonary angiography has declined and is typically reserved for cases in which catheter based treatment would be an option.[158]

Management

Heparin, both unfractionated and low molecular weight, remains the mainstay of therapy. For most patients with PE, systemic thrombolytic therapy (such as streptokinase, urokinase, and tissue-type plasminogen activator) is not required unless the patient is hemodynamically unstable. Pulmonary embolectomy may be indicated in select patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy.[159] Oxygen is administered as necessary, and the need for intubation and mechanical ventilation in massive PE is considered. Patients with recurrent disease may be candidates for vena caval interruption by placement of an inferior vena cava filter.

Prognosis

Although many patients with PE die before medical attention is received, the rate of mortality due to PE once adequate anticoagulation therapy is initiated is less than 5%.

Oral Health Considerations

The main concern in the provision of dental care for individuals with PE is the patient who is being managed with oral anticoagulants. As a general rule, dental care (including simple extractions) can safely be provided for patients with an international normalized ratio of 2.5. However, it is recommended that any dental care for these patients be coordinated with their primary medical care provider.

Pulmonary Neoplasm

Lung cancer is the leading cause of cancer deaths in both men and women. About 149,000 people in the United States died from lung cancer in 2016.[160] Cigarette smoking remains the primary risk factor for development of lung cancer, with risks now almost identical for both men and women compared with never smokers.[161] Non-small cell types of lung cancers account for about 85% of lung cancers and these include squamous cell, adenocarcinomas, and large cell.[162]

Squamous cell carcinomas account for about one fourth of lung cancers. The neoplasm derives from bronchial epithelial cells that have undergone squamous metaplasia. This is a slow-growing neoplasm that invades the bronchi and leads to airway obstruction.

Adenocarcinomas are the most common type of lung cancer accounting for about 40%. These neoplasms are of glandular origin and develop in a peripheral distribution. They grow more rapidly than squamous cell carcinomas

and tend to invade the pleura. This cancer is not associated with exposure to tobacco smoke.[163]

Large cell carcinomas account for about 10% of lung cancers. They are poorly differentiated tumors that resemble neither squamous cell carcinomas nor adenocarcinomas. They can grow and spread quickly.

Small cell carcinomas account for approximately 15% of all lung cancers. This type of lung cancer has the highest association with smoking, almost never arising in the absence of a smoking history. These derive from neuroendocrine cells in the airways and metastasize rapidly. Most small cell tumors have metastasized prior to diagnosis.[163]

Pathophysiology

Metaplasia of the respiratory epithelium occurs in response to injury, such as that induced by tobacco smoking. With continued injury, the cells become dysplastic, with the loss of differentiating features. Neoplastic change first occurs locally; invasive carcinoma usually follows shortly thereafter.[164]

Clinical and Laboratory Findings

A chronic nonproductive cough is the most common symptom. Sputum production may occur, usually associated with obstructive lesions. Hemoptysis and dyspnea are variably present.[164] Facial edema, cyanosis, and orthopnea indicate the possibility of superior vena cava syndrome, caused by compression of the superior vena cava by tumor. The acute onset of hoarseness may signal tumor compression of the recurrent laryngeal nerve. Shoulder and forearm pain might suggest the presence of Pancoast's tumor, which is found in the apical region of the lungs below the pleura.

Metastatic and paraneoplastic effects are also common. The symptoms of metastasis depend on the sites involved and on the size of the tumor. The bones, the brain, and the liver are common sites of metastasis. Paraneoplastic effects include endocrine abnormalities that are due to tumors that secrete hormones such as antidiuretic hormone, adrenocorticotropic hormone, and parathyroid hormone-related peptides.[165]

Classification

The World Health Organization has differentiated pulmonary neoplasms into histologic types. The major clinical distinction is between small cell types and nonsmall cell types; each type has different therapeutic implications. The above mentioned four major pathologic categories are squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma

Diagnosis

Diagnosis is suggested by the history and physical examination. The method of diagnosis of suspected lung cancer depends on the type of lung cancer (i.e., small cell lung cancer or nonsmall cell lung cancer), the size and location of the primary tumor, the presence of metastasis, and the overall clinical status of the patient. CT scanning is the anatomic imaging modality of choice and is performed in virtually all patients with suspected or known lung cancer (Figure 13-9). Other diagnostic modalities include sputum or pleural fluid cytology, excisional biopsy, transthoracic needle aspiration, and bronchoscopy.[166] In recent years, low-dose helical computed tomography (LDCT) for lung cancer screening has been shown to decrease lung cancer and all-cause mortality. The US Preventive Services Task Force currently recommends annual low-dose CT scans for high risk individuals (ages 55 to 80 years who have a 30 pack-year smoking history and

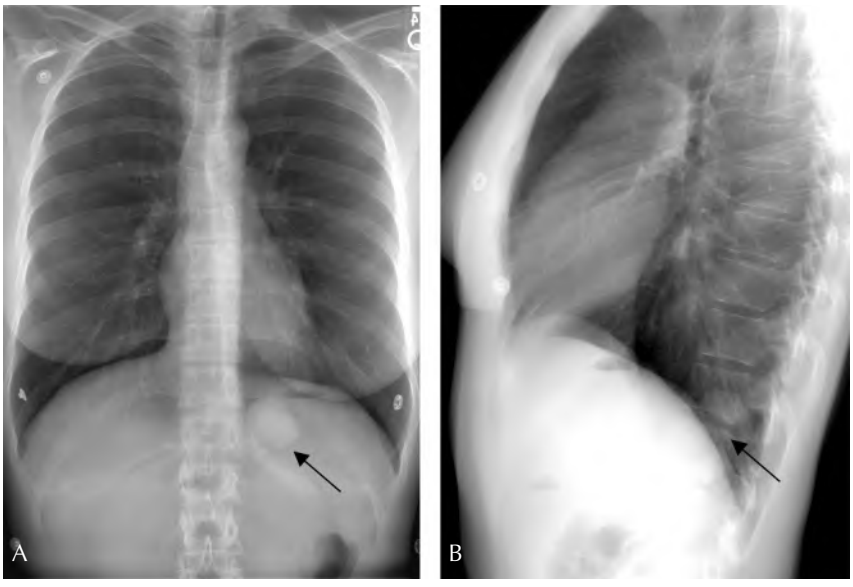

Figure 13-9 Anteroposterior (A) and lateral (B) chest radiographs demonstrate a rounded mass in the medial left costophrenic angle (black arrows) that is seen to be located in the posterior portion of the left lower lobe. This is best seen on the lateral view.

currently smoke or have quit within the past 15 years). Screening can be discontinued once the individual has not smoked for 15 years or there is a limited life expectancy.[167,168]

Management

Complete surgical resection of localized lung cancer offers patients the best chance for cure. However, treatment is based on the stage of the disease and the patient's clinical status. In general, early-stage disease is surgically managed, locally advanced disease is managed with chemotherapy and radiotherapy, and advanced disease is managed with chemotherapy with supportive care or supportive care alone. Radiation therapy is an important palliative measure, especially for patients with superior vena cava syndrome, brain metastases, or bone lesions.

Prognosis

Despite the presence of developed modalities for treatment, the prognosis for patients with lung cancer has remained poor, with the overall 5-year survival being approximately 23%. There is about a 60% 5-year survival when the lung cancer detected is localized. Unfortunately, most pulmonary cancers are found too late for a cure; only about 20% of patients undergo a radical surgical procedure, which is the only curative treatment.[169,170]

Oral Health Considerations

As many lung cancers are associated with smoking, it is important to be vigilant regarding any oral mucosal changes in a patient who has been diagnosed with lung cancer. In addition, with the advent of immunotherapy for various types of lung cancer, it is important to be aware of the type of chemotherapy the patient is receiving and consider these patients as potentially immune compromised (see Chapter 19 "Immunological Diseases").

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14

Diseases of the Cardiovascular System

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Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

Cardiovascular disease (CVD) is the leading cause of mortality in the world. In 2017, CVD caused an estimated 17.8 million deaths worldwide, representing ~32% of all deaths and 360 million disability-adjusted life years (DALYs) lost.[1] These numbers have climbed steadily both in absolute numbers and relative proportion since 2010. While the global mortality rate from CVD has increased in the past 30 years, the rates of CVD death in high-income countries has decreased and therefore reflects a significant increase in CVD death in low- and middle-income countries. CVD now accounts for the most deaths in all low- and middle-income regions (except in Sub-Saharan Africa where it is the leading cause of death in those >45 years and causes four to five times as many deaths as in high-income countries.[2] As of 2016, CVD remained the leading cause of death in the United States, accounting for ~840,000 deaths. The annual total cost of CVD in 2014–2015 was estimated at $351 billion. It is estimated that in 2019, ~1.1 million Americans will have suffered a new coronary event and ~800,000 will have had a new stroke. This amounts to a coronary event and stroke every 40 seconds. There has been an overall decrease in CVD deaths over the past 30 years in the United States, though gender, socioeconomic, and racial disparities do exist. In particular, it has been estimated that the avoidable CVD death rate in black people is nearly twice as high as in white people.[3]

CVD includes hypertension, coronary artery disease (CAD), valvular heart disease (VHD), congenital cardiovascular defects, congestive heart failure (CHF), congenital cardiovascular defects, heart valve disorders, venous thromboembolic disease, and stroke (Table 14-1).[3] Although these diseases are associated with a high mortality, the associated morbidity and detrimental effect on the quality of life of affected individuals are perhaps even more pronounced, since they affect nearly all populations. This chapter considers common cardiovascular conditions and their implications for the practice of dentistry.

What follows is an overview of the demographics, diagnosis, medical management, and dental management considerations for the more common cardiovascular conditions seen in dental offices.

Table 14-1 Percentage breakdown of deaths attributable to cardiovascular disease in the United States in 2016.

Coronary heart disease	43%
Stroke	17%
Hypertension	10%
Heart failure	9%
Diseases of the arteries	3%
Other	18%

Source: Adapted from Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56–e528.

GENERAL CONSIDERATIONS FOR THE DENTAL MANAGEMENT OF THE CARDIAC PATIENT

The high prevalence of cardiac disease in the general population suggests frequent dental management considerations in dental practice. Advances in cardiac surgery and medical management of patients with congenital heart disease (CHD), for example, have resulted in large numbers of adults with a variety of cardiac conditions that may be of concern with regard to stressful, prolonged, or invasive dental procedures. It is therefore important for dentists caring for these patients to understand their cardiac condition as well as medical history.

Multiple longstanding uncertainties and controversies exist concerning the dental management of patients with cardiovascular diseases and conditions. There are, however, multiple guidelines and scientific papers to help dental practitioners with assessment and management issues for specific cardiac patient populations.[4] Additional studies are needed, however, as many of these guidelines are based on small studies and expert opinion.[5] The lack of systematic reviews and formal guidelines does not release the dental healthcare provider from the responsibility to use good clinical judgment in accordance with the provider's training, knowledge base, and experience.

Importance of the Medical History

The patient's medical history should be documented in the patient's chart. Important aspects of the medical history screening include (1) current medications; (2) history of chest pain, arrythmia, or cardiac surgery; (3) indications for antibiotic prophylaxis prior to dental procedures; and (4) primary care physician's and/or cardiologist's name and contact information. For many of these patients, consultation with their primary care physician or cardiologist may be desirable for questions concerning elements in the patient's history that are unclear, the severity of active problems, and potential risks from invasive or stressful dental procedures.

The medical history for patients with cardiac disease or conditions may reveal other medical problems of importance. For example, diabetes mellitus has a direct impact on the progression of CAD and therefore increases the risk of invasive or stressful procedures.[6] The finding of uncontrolled hypertension is of particular concern for patients undergoing dental procedures, and protocols have been proposed to evaluate these patients and carry out dental procedures in the safest manner.[7]

Oral healthcare providers should be aware of medications they prescribe that may have systemic side effects and interact with the patient's medications (e.g., analgesics with anticoagulant properties). Likewise, some cardiovascular medications have side effects that may cause intraoral changes (e.g., oral dryness, gingival overgrowth). Other cardiac medications may have significant implications for dental procedures (e.g., anticoagulants, both antiplatelet therapy and vitamin K antagonists).

Some aspects of dental management are generic to several of the patient populations in this chapter.[8] For example, acquiring blood pressures (BPs) has become standard in many dental practices and it is particularly important for cardiac populations. Additionally, the determination of vital signs prior to dental procedures is an important preventive measure. There is a high prevalence of hypertension in the general population and therefore in dental practices. Although hypertensive crises are extremely rare in the dental office setting, the increased risks associated with painful or stressful procedures support the practice of taking a BP on all new patients and those with significant cardiovascular disease. Many patients will not be aware that they have hypertension and it is important that they be referred to their primary care physician for evaluation.

Given the nature of this patient population, it is desirable for oral healthcare professionals treating patients with cardiovascular disease to be certified in American Heart Association (AHA) basic life support or advanced cardiac life support.[9]

Importance of Preventive Dentistry

Although there may be a weak association between periodontal disease and atherosclerosis, independent of known risk factors (e.g., smoking), a causal link has not been established. Nevertheless, pain and stress from an acute pulpitis or abscess could potentially trigger angina, stroke, or myocardial infarction (MI). Poor oral hygiene is associated with more frequent bacteremia from routine daily activities (e.g., tooth brushing) and this clearly puts some cardiac patients at risk for infective endocarditis.[10,11]

Stress

An overriding focus for dental care is to reduce the risks from long, painful, or stressful dental procedures that increase catecholamine release and induce hemodynamic changes before, during, and following a procedure, to include increased heart rate and BP, and decreased myocardial output. Examples include patients with a history of hypertension, coronary artery bypass grafts (CABG), coronary stents, arrhythmia, and some cardiac medications. Studies have reported that the sound of a dental handpiece alone is enough to increase stress and anxiety.[12] Multiple short appointments may be preferable and premedication with antianxiety agents is commonly used for this purpose. Nitrous oxide/oxygen analgesia can be used for most cardiac patients, though given the mild negative inotropic effect, use in patients with severe left ventricular dysfunction or pulmonary hypertension should be avoided.

Use of Vasoconstrictors for Dental Procedures

Risks from local anesthetics containing epinephrine as a vasoconstrictor are controversial and may be of concern with some cardiac conditions.[13] The benefits of vasoconstrictors (e.g., hemostasis and more profound and prolonged anesthetic effect) likely outweigh the risk of systemic effects from stress-related endogenous epinephrine (e.g., increased heart rate and BP).[14] In the vast majority of stable outpatients with cardiovascular disease, local anesthetics with epinephrine can be used safely. In patients with a very recent MI (within the past month) or history of ventricular arrhythmias (particularly Brugada syndrome if using procaine), it would be reasonable to consult with the patient's cardiologist.[15,16]

Concentrations of epinephrine greater than 1:100,000 are felt to be unnecessary and may carry a higher risk.[17] Clearly, it is important to restrict the total volume of local anesthetics, and especially epinephrine. A small dose of low-concentration epinephrine should not have a significant systemic effect.[14] When using epinephrine, it is important to aspirate, but due to the small diameter of dental anesthetic needles, a negative aspiration does not insure that intravascular injection will not occur.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective oral analgesics and anti-inflammatory agents. Their use has been associated, however, with a small but significant increased risk of cardiovascular events. This association is present among all NSAIDs, including both traditional NSAIDs such as diclofenac, ibuprofen, and naproxen as well as selective cyclooxygenase-2 inhibitors such as celecoxib.[18] The risk may be lower with ibuprofen (total daily dose <1200 mg/day) and naproxen (<500 mg/day). The risk appears to be related to duration and dose, though the increased risk can be seen with 8 days.[18] In addition to the risk of cardiovascular events, it is also important to appreciate that use of NSAIDs in patients on antithrombotic medications, including aspirin, clopidogrel, and the direct oral anticoagulants, may also increase the risk of gastrointestinal bleeding.[19] Based on these observations, it is generally recommended that in patients with existing cardiovascular disease, use of nonpharmacologic therapy and acetaminophen be prioritized. There is no adverse cardiovascular risk associated with

use of acetaminophen and the hepatic risk is also extremely low provided the total daily dose is 3–4 g in the absence of significant alcohol intake. If acetaminophen use is not effective, risk–benefit assessment would favor a short course of NSAID use. In patients who are on multiple thrombotic agents, consultation with the treating cardiologist/internist will be important if use is expected to exceed 1 week.

Oral Manifestations of Cardiac Medications

Side effects from cardiac drugs may cause oral mucosal changes. For example, gingival overgrowth can occur with calcium-channel blockers and xerostomia often results from antihypertensive drugs. Altered taste (e.g., metallic) has also been reported with antihypertensives (e.g., an angiotensin-converting enzyme inhibitor, ACEi), and they may be associated with lichenoid reactions. If the side effects are severe enough, a change in antihypertensive medication may avoid the necessity for topical steroids.

HYPERTENSION

Definition, Classification, and Epidemiology

There has been wide variation in the definition of hypertension. The most recent guidelines put forth by the AHA, American College of Cardiology (ACC), and American Society of Hypertension define hypertension as a systolic BP >130 mm Hg or diastolic BP >80 mm Hg.[20] This is in contrast to European Society of Cardiology (ESC) guidelines that have a higher threshold for hypertension definition, with a systolic BP >140 mm Hg or a diastolic BP >90 mm Hg (Table 14-2).[21] Regardless of the precise cut point for defining hypertension, it remains a significant cause of morbidity and mortality worldwide.

Hypertension is classified as primary and secondary. Primary or essential hypertension accounts for ~90%. The precise etiology of primary hypertension is complex and is likely multifactorial, with contributions from genetic factors, age, dietary intake (particularly sodium and potassium), physical inactivity, obesity, and alcohol use. In ~10% of cases, a specific treatable cause of hypertension can be identified; these entities are termed secondary hypertension. The most common causes of secondary hypertension include drug-related causes (in particular NSAIDs, oral contraceptives, and corticosteroids, to name a few), primary renal disease, obstructive sleep apnea, renovascular disease (such as fibromuscular dysplasia), and endocrinologic causes such as a primary hyperaldosteronism (see Table 14-3).

The global prevalence of hypertension was estimated to be ~1.1 billion in 2015 and is estimated to reach 1.5 billion by 2025. From 2013–2016, it was estimated to be present in ~116 million Americans and in 2015, ~150 million across central and eastern Europe. Worldwide, it is estimated to be present in ~30–45% of adults. The high prevalence is consistent across low-, middle-, and high-income countries. The prevalence increases with age, with a prevalence of >60% in those >60 years. Around 35% of patients with hypertension are completely unaware of their diagnosis. The prevalence of hypertension among African Americans is among the highest in the world, with an age-adjusted prevalence of 57.6% in men and 53.2% in women between 2011 and 2016.[20]

Table 14-2 Major guideline definitions for hypertension.

	SBP (mm Hg)		DBP (mm Hg)
ACC/AHA Guidelines			
Normal	<120	and	<80
Elevated	120–129	and	<80
Stage 1 Hypertension	130–139	or	80–89
Stage 2 Hypertension	≥140	or	≥90
ESC Guidelines			
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

ACC, American College of Cardiology; AHA, American Heart Association; DBP, diastolic blood pressure; ESC, European Society of Cardiology; SBP, systolic blood pressure.

Cardiovascular Risk Association

In 2015, hypertension was the leading global contributor to premature death, accounting for ~10 million deaths and over 200 million DALYs. In addition, despite advances in diagnosis and treatment, the DALYs attributable to hypertension have increased by 40% since 1990. Hypertension has a clear independent and continuous relationship with the incidence of stroke (both hemorrhagic and ischemic), MI, sudden cardiac death, heart failure, peripheral arterial disease, and renal disease. There is also increasing evidence linking hypertension with atrial fibrillation, as well as cognitive decline and dementia. Increases in both systolic and diastolic BP have been associated with adverse cardiovascular events, though elevated systolic BP is more predictive in older patients (>50 years) as opposed to elevated diastolic BP, which is more predictive in younger patients (<50 years). Many adult patients

Table 14-3 Causes of secondary hypertension.

Medication-related
• Alcohol
• Angiogenesis inhibitors (e.g., bevacizumab)
• Amphetamines
• Antidepressants (e.g., monoamine oxidase inhibitors, selective norepinephrine reuptake inhibitors, tricyclic antidepressants)
• Atypical antipsychotics (e.g., clozapine, olanzapine)
• Caffeine
• Cocaine
• Corticosteroids (systemic)
• Decongestants (e.g., phenylephrine and pseudoephedrine)
• Herbal supplements (e.g., Ma Huang, St. John's wort)
• Immunosuppressants (e.g., cyclosporine)
• Nonsteroidal anti-inflammatory drugs
• Oral contraceptives
• Tyrosine kinase inhibitors (e.g., sunitinib, sorafenib)
Renal parenchymal disease
Renovascular disease
• Fibromuscular dysplasia (more common in younger patients)
• Atherosclerotic disease
Obstructive sleep apnea
Endocrinologic causes
• Primary hyperaldosteronism
• Thyroid dysfunction
• Pheochromocytoma
• Cushing's syndrome
• Primary hyperparathyroidism
• Congenital adrenal hyperplasia
• Mineralocorticoid excess syndromes other than primary aldosteronism
• Acromegaly
Aortic coarctation

with hypertension have other CVD risk factors (see Table 14-4). Among patients with hypertension in the United States in 2009–2012, 63% had hypercholesterolemia, 50% were obese, 27% had diabetes, 16% were current smokers, and 16% had chronic kidney disease (CKD).

Diagnostic Evaluation

Diagnosis

Most patients with hypertension are asymptomatic and the sequelae of hypertension are typically seen years after sustained exposure. Because of this, early and accurate diagnosis is critical. BP assessment in the office setting is relatively easy, but often results in misleading assessments. To accurately assess BP in the office, careful attention needs to be paid to appropriate patient preparation, patient positioning, measurement technique, and documentation (see Table 14-5). Before a diagnosis is made, multiple measurements should be taken,

Table 14-4 Cardiovascular risk factors common in patients with hypertension.

Modifiable Risk Factors	Relatively Fixed Risk Factors
• Cigarette smoking	• Chronic kidney disease
• Diabetes	• Family history
• Dyslipidemia/ hypercholesterolemia	• Increased age
• Obesity	• Low socioeconomic and/or educational status
• Physical inactivity	• Male sex
• Poor diet	• Obstructive sleep apnea
	• Psychosocial stressors

Source: Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):e127–e248.

Table 14-5 Appropriate steps to accurate in-office blood pressure (BP) measurements. Proper technique is key to an accurate BP assessment. Improper technique has been well demonstrated to lead to inaccurate BP measurements.

Key Steps for Proper BP Measurements	Specific Instructions
Step 1: Properly prepare the patient	1) Have the patient relax, sitting in a chair (feet on floor, back supported) for > 5 min 2) The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement 3) Ensure patient has emptied his/her bladder 4) Neither the patient nor the observer should talk during the rest period or during the measurement 5) Remove all clothing covering the location of cuff placement 6) Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria
Step 2: Use proper technique for BP measurements	• Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically • Support the patient's arm (e.g., resting on a desk) • Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum) • Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger or smaller than normal cuff size is used • Either the stethoscope diaphragm or bell may be used for auscultatory readings

(*Continued*)

Table 14-5 (Continued)

Step 3: Take the proper measurements needed for diagnosis and treatment of elevated BP/hypertension	• At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings • Separate repeated measurements by 1–2 min • For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20–30 mm Hg above this level for an auscultatory determination of the BP level • For auscultatory readings, deflate the cuff pressure 2 mm Hg per second, and listen for Korotkoff sounds
Step 4: Properly document accurate BP readings	• Record SBP and DBP. If using the auscultatory technique, record SBP and DBP at onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number • Note the time of most recent BP medication taken before measurements
Step 5: Average the readings	Use an average of ≥ 2 readings obtained on ≥ 2 occasions to estimate the individual's level of BP
Step 6: Provide BP readings to patient	Provide patients the SBP/DBP readings both verbally and in writing

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

both at the same visit and averaged over several visits ideally. Since the ideal conditions for in-office measurement are often practically challenging, the use of ambulatory blood pressure monitoring (ABPM) can also be helpful. These monitors are typically programmed to obtain readings every 15–30 minutes throughout the day and every 15–60 minutes in the evening. Testing occurs over a 24-hour period and occurs while patients participate in their normal daily activities. ABPM is particularly helpful in identifying both white-coat hypertension (defined as hypertension in the office setting but no hypertension while at home) as well as masked hypertension (defined as no hypertension in the office but hypertension while at home). While data surrounding the impact of white-coat hypertension on CVD are conflicting (though the majority suggest no increased risk), the risk of masked hypertension is similar to that seen with sustained hypertension.

Clinical Evaluation

The three main goals of the medical evaluation of patients with hypertension are to (1) identify treatable (secondary) or curable causes; (2) assess the impact of persistently elevated BP on target organs; and (3) estimate the patient's overall risk profile for the development of CVD. A routine history and physical examination should be performed, though it is important to note that making a diagnosis of hypertension is beyond the scope of practice of dentistry. The history should focus on the duration of the hypertension and any prior treatment. Asking the patient about the duration of their high BP may be misleading, as in many cases the patient will not have had a BP measurement for many years prior to the discovery of hypertension. Symptoms of organ dysfunction, lifestyle habits, diet, and psychosocial factors should be included. The main goals of the physical examination are to accurately confirm the diagnosis of hypertension, identify signs of end-organ involvement, and evaluate potential causes of secondary hypertension (see Table 14-3). These types of examinations should only be performed by trained and experienced healthcare providers. Once the diagnosis of hypertension is made, it is recommended that patients undergo laboratory testing with measurement of fasting blood glucose, complete blood count, lipid prolife, serum creatinine, sodium, potassium, calcium, thyroid-stimulating hormone, and urinalysis.[20] Electrocardiogram is also recommended and may show signs of left atrial enlargement, left axis deviation, and abnormalities suggestive of left ventricular hypertrophy. Cardiac arrhythmias such as atrial fibrillation may also be seen. Transthoracic echocardiography can be considered in patients with a diagnosis of hypertension. In addition to providing a more sensitive assessment of left ventricular hypertrophy (LVH) and left atrial dilation, it also provides information on left ventricular systolic and diastolic function, valvular function, estimates on pulmonary artery pressures, and can serve as a screening for the presence of aortic coarctation, another potential secondary cause of upper extremity hypertension. The identification of LVH is important as it is an independent predictor of mortality in patients with hypertension. Hypertrophy of the ventricle initially results in the impairment of left ventricular relaxation (diastolic function) and can ultimately progress to weakening of the myocardial pumping function (systolic dysfunction). Impairment in both diastolic and systolic function can result in clinical signs of CHF.

Management

Management should start with lifestyle modifications, including weight reduction, adoption of the DASH (Dietary Approaches to Stop Hypertension) diet, sodium restriction, increased potassium intake, regular physical activity, and reduction in or cessation of alcohol consumption (Table 14-6). Careful attention should be paid to the patient's current medication list during history-taking and concerted efforts should be made to reduce the use of potentially

Table 14-6 Nonpharmacologic management of hypertension.

	Intervention	Recommendation	Approximate Decrease in SBP in Hypertensive Patients
Weight loss	Weight/body fat	Best goal ideal body weight, but aim for 1 kg reduction for overweight adults. Expected about 1 mm Hg reduction for every 1 kg in weight loss	5 mm Hg
Healthy diet	DASH dietary pattern	Consume diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced content of saturated and total fat	11 mm Hg
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1500 mg/d, but aim for at least 1000 mg/d reduction	5–6 mm Hg
Enhanced intake of dietary potassium	Dietary potassium	Goal 3500–5000 mg/dL, ideally through consumption of a diet rich in potassium	4–5 mm Hg
Physical activity	Aerobic	90–150 min/week	5–8 mm Hg
	Dynamic resistance	90–150 min/week	4 mm Hg
	Isometric resistance	3 sessions/week	5 mm Hg
Moderation in alcohol intake	Alcohol consumption	Reduce alcohol intake (men ≤2, women ≤1 drink(s) daily)	4 mm Hg

DASH, Dietary Approaches to Stop Hypertension; SBP, systolic blood pressure
Source: Adapted from Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):e127–e248.

offending medications if clinically possible. Adoption of these changes can be challenging for patients practically. Importantly, even with 100% adherence to these changes, many patients will still require pharmacologic therapy.[20]

There are several classes of antihypertensive medications. The results of an increasing number of trials suggest that at the same level of BP control, most antihypertensive drugs provide similar degrees of cardiovascular protection. In those with uncomplicated hypertension, beginning with a low dose of a thiazide diuretic (e.g., 12.5–25 mg of hydrochlorothiazide or 25–50 mg of chlorthalidone) has the advantages of very low cost and low risk of metabolic complications such as hypokalemia, lipid abnormalities, and hyperuricemia. Use of an ACEi, angiotensin receptor blocker (ARB), or a calcium-channel blocker can also be considered as first-line agents. In patients whose BPs are markedly elevated at first diagnosis (systolic BP >20 mm Hg above target or diastolic BP >10 mm Hg), initiation of a two-drug approach is very reasonable. If the patient remains hypertensive on a thiazide diuretic, ACEi/ARB, and calcium-channel blocker, use of an aldosterone antagonist (such as spironolactone or eplerenone) or a beta-blocker, particularly one with some degree of alpha blockade (such as a carvedilol), can be added as second-line options. It is important to note that certain factors will affect clinical decision-making in the pharmacologic management of hypertension, including ischemic heart disease, heart failure, CKD, diabetes, atrial fibrillation, and race/ethnicity (Table 14-7).[20]

The role of education and the importance of patient contact are paramount in successfully treating hypertension. Self-recorded measurements and ambulatory BP monitoring aid in the physician's titration of medications and monitoring of the 24-hour duration of action of antihypertensive agents. The monitoring of BP by oral healthcare providers will therefore support the overall medical care of their hypertensive patients.

Dental Management Considerations for Patients with Hypertension

Patients with elevated BP are potentially at increased risk for adverse events in a dental office setting, particularly if their BP is poorly controlled or if there is target organ disease involvement (heart, brain, kidney, peripheral arteries).[7] However, the absence of target organ disease does not mitigate a careful evaluation and treatment of patients within safe and appropriate parameters of care. The primary concern for these patients is precipitating a hypertensive crisis, stroke, or MI. Poor compliance with antihypertensive medications and diet is a common problem, and dentists can help by reinforcing the importance of following medical advice and guidelines (Tables 14-4 and 14-5). Dental management guidelines have been proposed based on the medical model for assessment, risk stratification, and treatment of patients with hypertension.[22–24]

Side effects of antihypertensive medications vary and can include orthostatic hypotension, synergistic activity with

Table 14-7 Pharmacologic management of hypertension in specific patient groups.

	Antihypertensive Preference
Ischemic heart disease	• Beta-blockers favored • Dihydropyridines (amlodipine and nifedipine) can also be used to treat anginal symptoms
Heart failure with reduced ejection fraction	• Beta-blockers including metoprolol, carvedilol, and bisoprolol • ACEis or ARBs • Aldosterone antagonists such as spironolactone or eplerenone • Sacubitril-valsartan • Loop diuretics more useful at managing volume status • Non-dihydropyridine calcium-channel blockers (verapamil and diltiazem) should be avoided
Chronic kidney disease	• ACEis or ARBs
Diabetes	• ACEis or ARBs
Atrial fibrillation	• Beta-blockers to provide concomitant rate control • Non-dihydropyridine calcium-channel blockers (verapamil and diltiazem) to provide concomitant rate control • ARBs may be associated with reduction in atrial fibrillation recurrence
African American	• Thiazide diuretics and/or dihydropyridine calcium-channel blockers should be first-line therapy • Multidrug regimens are often necessary
Pregnant women or those contemplating pregnancy	• Use of methyldopa, labetalol, and nifedipine is safe and well-studied in this population • ACEis and ARBs should not be used

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

narcotics, and potassium depletion. Although safe limits for invasive dental procedures cannot be strictly defined, and they are largely based on an individual patient's overall medical condition, there arc general guidelines depending on whether patients have prehypertension, stage one or stage two hypertension, and target organ disease (Table 14-2). Elective treatment should be avoided if the BP is significantly above the patient's baseline or if it is >180 mm Hg systolic or >100 mm Hg diastolic. If patients have any symptoms potentially related to hypertension, such as chest pain, headache, or focal neurologic symptoms, elective procedures should be canceled. For patients who have an urgent dental problem, it may be desirable to remove the source (e.g., abscessed tooth) if the patient has mildly elevated BP, but if significantly elevated, oral pain and infection can usually be well managed pharmacologically until the BP is brought under control. Patients may have somewhat elevated BP from pain and/or anxiety and they may have some lowering of their BP after local anesthesia, but this is unpredictable.

CORONARY ARTERY DISEASE

Definition and Epidemiology

CAD accounts for approximately 30%–50% of all cases of CVD in the United States. Almost 7% of or ~18 million Americans >20 years of age have CAD (7.4% in males and 6.2% in females). In 2016, CAD-related mortality was ~360,000 individuals, with mortality directly due to an MI ~110,000. It is estimated that each year 730,000 Americans will have a new coronary attack, and 355,000 will have recurrent attacks. While CAD remains a major cause of morbidity and mortality, gains have been made, with a reduction in relative and absolute rates of CAD-related deaths by ~32% and 15%, respectively.[3]

Pathophysiology of Stable Coronary Artery Disease versus Acute Coronary Syndromes

CAD is characterized by progressive obstruction of the epicardial coronary arteries. Atherosclerosis is the pathophysiologic process responsible for the development of these obstructions and begins as a fatty streak in early adolescence. The lesions progress over decades and develop into frank atherosclerotic plaques. This plaque is characterized by disruption of the vascular endothelium, extracellular lipid accumulation, smooth muscle cell migration/proliferation, and inflammation.[25] Atherosclerosis may affect any vascular bed, including the coronary, cerebral, renal, mesenteric, and peripheral vascular systems. In the coronary circulation, progressions in these plaques can result in two distinct clinical entities: stable CAD and an acute coronary syndrome (ACS). In stable CAD, there is gradual progression of plaque growth leading to arterial luminal obstruction over years. Clinically, this manifests as progressive exertional angina due to the mismatch in myocardial oxygen demand and supply with exertion. ACSs, in contrast, are the result of plaque instability. In ACS, the unstable plaque (either obstructive or nonobstructive) ruptures and acute thrombosis occurs, leading to an abrupt decrease in myocardial oxygen delivery. If blood flow is not restored (either spontaneously, pharmacologically, or mechanically), this can result in myocardial injury, termed a myocardial infarction.[26] While these two entities are the clinical result of coronary atherosclerosis, their management differs greatly, thereby making the clinical distinction critical in practice.

Risk Factors

The development of coronary atherosclerosis is influenced by several risk factors, including dyslipidemia, systemic hypertension, diabetes, cigarette smoking, diet, physical activity, obesity, family history, and inflammation. The impact of each of these factors upon CAD risk, however, differs among different subgroups. For example, diabetes and a low high-density lipoprotein (HDL) cholesterol/total cholesterol ratio have a greater impact in women, cigarette smoking has more of an impact in men, and systolic BP and isolated systolic hypertension are major risk factors independent of age or sex. Risk factor assessment is useful as a guide to therapy for dyslipidemia, hypertension, and diabetes; multivariable prediction rules can be used to help estimate risks for subsequent coronary disease events. Current guidelines recommend using the 10-year risk of cardiovascular events as a basis for initiating risk factor–modifying therapy for lipid abnormalities.[27] Based on the increased risk conferred by the various CAD risk factors, concepts of "normal" have continued to evolve from "usual" or "average" to more biologically optimal values associated with long-term freedom from disease. As a result, optimal BP, blood glucose, and lipid values have been continually revised downward in the past 20 years.

Lipids

The total cholesterol concentration in serum is a major and clear-cut risk factor for CAD. In the Multiple Risk Factor Intervention Trial (MRFIT) of more than 350,000 middle-aged American men, the risk of CAD progressively increased with higher values of serum total cholesterol.[28] In addition to total cholesterol, data from the Framingham Heart Study demonstrated that HDL is strongly inversely associated with CAD risk, low-density lipoprotein (LDL) is strongly directly associated with CAD risk, and triglycerides are mildly associated with CAD risk.[29] In the nearly 35 years since the initial observations in the MRFIT trial, it has become clear that there is a linear relationship between LDL reduction and adverse event reduction, such as for every 38 mg/dL reduction in LDL there is ~23% reduction in major cardiovascular events.[30] In the highest-risk population of patients who have suffered multiple cardiac events already, dramatic LDL reductions to as low as 30 and 50 mg/dL have confirmed that this relatively linear relationship holds true even after very low LDL levels.[31–33]

Based on these studies, there has been a paradigm shift away from a single appropriate cut point for lipid therapy, toward tailoring therapy based on overall risk. The most recent guidelines have recommended assessing the overall cardiovascular risk using the Atherosclerotic Cardiovascular Disease (ASCVD) algorithm.[27] In patients who have clinical atherosclerotic cardiovascular disease, including established CAD, stroke, or peripheral vascular disease, use of a high-intensity statin (atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily) is recommended. Diabetes is considered an ASCVD equivalent and in those patients use of at least a moderate-intensity statin is strongly recommended. In those patients who have an elevated 10-year risk (>7.5%) of an ASCVD event as predicted by the ASCVD risk calculator, use of a high-intensity statin is recommended. For all others, if the LDL is >190 mg/dL, treatment with a high-intensity statin is recommended. For intermediate-risk patients (5–7.5% 10-year risk), treatment with a moderate-intensity statin is recommended. For low-risk patients (<5% risk), the therapy should be tailored through a shared decision-making process (Figure 14-1).

Hypertension

As previously discussed, hypertension and LVH are well-established risk factors for CAD morbidity and mortality. In patients with established CAD, careful management of hypertension is key to preventing recurrent ischemic events.

Glucose Intolerance and Diabetes Mellitus

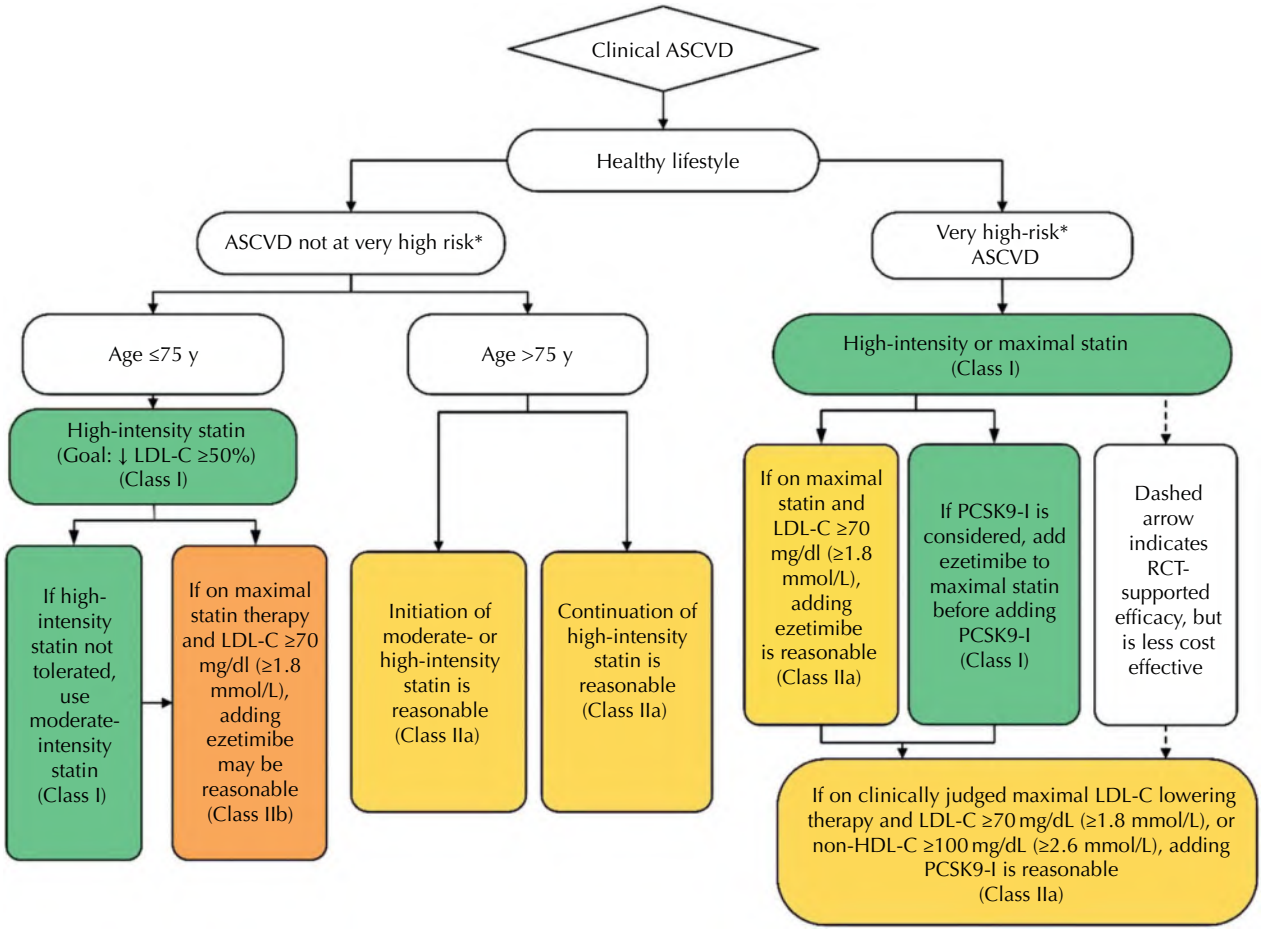
Insulin resistance, hyperinsulinemia, and glucose intolerance all appear to promote atherosclerosis. As diabetic individuals have a greater number of additional atherogenic risk factors (including hypertension, hypertriglyceridemia, increased cholesterol-to-HDL ratio, and elevated levels of plasma fibrinogen) than do nondiabetic individuals, the CAD risk for diabetic persons varies greatly with the severity of these risk factors. Overall, patients with diabetes are at ~2.6-fold increased risk for cardiovascular death than patients without diabetes.[34] Thus, aggressive treatment of these additional risk factors may help reduce cardiovascular events in diabetic patients.

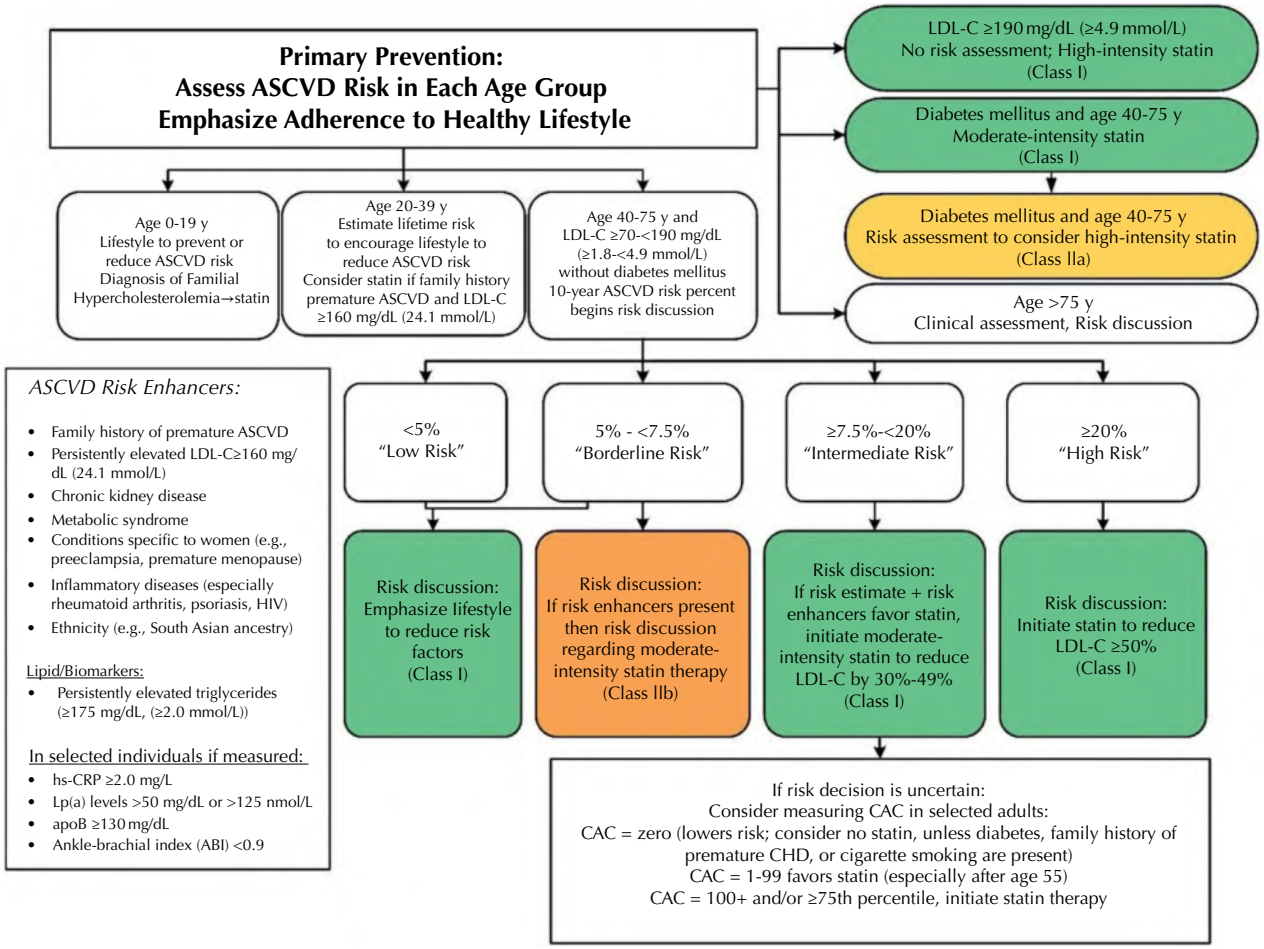
Cigarette Smoking

Cigarette smoking is an important and potentially reversible risk factor for CAD and CAD events such as MI. For both men and women, the risk increases with increasing tobacco consumption.[35] For example, in one study the risk of MI was sixfold increased for women and threefold increased for men who smoked at least 20 cigarettes per day, compared to nonsmoking control patients.[35]

Lifestyle and Dietary Factors

Dietary factors such as a high-calorie, high-fat, and high-cholesterol diet contribute to the development of other risk factors, such as obesity, hyperlipidemia, and diabetes, which predispose to CAD. Red meat consumption too is associated with an increased risk of total, cardiovascular, and cancer mortality.[36] Conversely, a diet that emphasizes fruit and





vegetables, the increased intake of dietary fiber, and the so-called Mediterranean-style diet rich in olive oil and nuts are associated with a decreased risk of CAD.[37,38] Weight gain and obesity directly worsen the major cardiovascular risk factors, whereas weight loss appears to improve them.[39] Epidemiologic data indicate that the moderate intake of alcohol has a cardioprotective effect.[40–42] Elevation of serum HDL levels appears to be the primary mechanism by which alcohol imparts this benefit. It should be stressed that the benefits of alcohol apply only to moderate consumption and are not seen in those who "abuse" alcohol. Furthermore, the protective effects of alcohol do not apply to the risk of hemorrhagic stroke, death due to trauma, or cancer, all of which may be increased in individuals who consume greater amounts of alcohol.

Exercise

Even a moderate degree of exercise appears to have a protective effect against CAD.[43] In one study of middle-aged men, participation in moderately vigorous physical activity was associated with a 23% lower risk of death than that associated with a less active lifestyle, and this improvement in survival was equivalent and additive to other lifestyle measures such as smoking cessation, hypertension control, and weight control.[44] Mechanisms that could account for the benefits of exercise include elevated serum HDL cholesterol levels, reduced BP, weight loss, and a lower incidence of insulin resistance.

Obesity

As already stated, obesity is associated with the development of several risk factors for CAD, including systemic hypertension, impaired glucose metabolism, insulin resistance, hypertriglyceridemia, reduced HDL cholesterol, and elevated fibrinogen. Data from the Framingham Heart Study, the Nurses' Health Study, and other studies have shown the risk of developing CAD that is associated with obesity.[45–47] The distribution of body fat appears to be an important determinant, as patients with abdominal (central) obesity are at greatest risk for subsequent CAD.[48] Patients with central obesity, elevated levels of serum triglycerides, and (to a lesser degree) LDL cholesterol, low HDL cholesterol, insulin resistance, and hypertension are classified as having atherogenic dyslipidemia (metabolic syndrome).[49] This syndrome is more difficult to treat and is associated with a worse prognosis than is an isolated increased LDL level.

Inflammation and Endothelial Dysfunction

Endothelial dysfunction appears to be an early step in the atherosclerotic process and may result from dyslipidemia, hypertension, and diabetes. Recent studies have suggested that coronary artery endothelial dysfunction predicts the long-term progression of atherosclerosis and an increased incidence of cardiovascular events. C-reactive protein (CRP) is an inflammatory biomarker that has been shown to be predictive of cardiovascular events. The JUPITER study has demonstrated that in apparently healthy persons without hyperlipidemia but with elevated CRP levels, rosuvastatin reduced the incidence of major cardiovascular events independent of the LDL-lowering impact.[50] The benefit of statin therapy observed in the JUPITER trial is likely reflective of the plaque-stabilizing effects of statins that have been previously observed.[51] To further assess the role of inflammation in adverse cardiovascular events, the CANTOS trial randomized high-risk patients who had already experienced an MI with elevated CRP to treatment with canakinumab (a monoclonal antibody targeting interleukin-1-beta approved for treatment of several rheumatologic disorders) versus placebo.[52] Treatment with canakinumab in this high-risk group who were already on high-intensity statin therapy resulted in a significant decrease in recurrent cardiovascular events. This benefit, however, came at the expense of life-threatening infection. Due to the high rates of these fatal infections, use of canakinumab is not recommended in the clinical management of these patients, though it does provide further evidence supporting the role of inflammation in cardiovascular disease. While additional studies are clearly necessary, there is a great deal of optimism in targeting inflammation as a novel pathway in the management of cardiovascular disease.

Figure 14-1 Atherosclerotic Cardiovascular Disease (ASCVD) management algorithm. Current guidelines recommend lipid management based on the presence (secondary prevention) or absence (primary prevention) of clinical ASCVD. (a) In patients with clinical ASCVD, moderate- or high-intensity statin is recommended. Addition of ezetimibe or a PCSK9 inhibitor can be considered in very high-risk patients. (b) In patients without clinical ASCVD, current guidelines recommend assessment of 10-year cardiovascular risk in those 40–75 years old and lifetime risk in those 20–39 years old using the ASCVD risk calculator. In patients with LDL >190 mg/dL, high-intensity statin therapy is recommended. In those with diabetes, moderate-intensity statin is recommended. If neither of these is present, consideration for therapy should be based on the 10-year risk as identified by the ASCVD risk calculator with inclusion of risk enhancers. If the risk decision remains uncertain, coronary artery calcium scoring can be considered. CHD, congenital heart disease; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized control trial.

Risk Factor Modification

When atherosclerosis is identified, the immediate goals are to relieve symptoms through improvement of organ perfusion and to prevent plaque rupture. Aggressive risk factor modification to retard or prevent ongoing atherosclerosis is among the most important parts of long-term management. Smoking cessation, meticulous control of hypertension and diabetes, weight management, and aggressive lipid-lowering therapy are recommended. Lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG COA) reductase inhibitors has been shown to reduce mortality in patients with CAD, even when total cholesterol and LDL are only modestly elevated, which may reflect the anti-inflammatory role of statins in preventing plaque rupture.[53,54] A low-fat, low-calorie diet may result in improved serum lipid levels as well as improved weight management, and a cardiovascular exercise program may result in reduced morbidity and mortality from CHD.[55]

Diagnosis

The diagnosis of chronic CAD is usually suspected from the clinical presentation. A history of exertional or resting symptoms including (but not limited to) chest tightness, jaw discomfort, left arm pain, dyspnea, or epigastric distress should raise the suspicion of CAD. Many patients deny "chest pain" per se, but the clinician should recognize subtle symptoms (such as dyspnea, diaphoresis, or epigastric distress) that may limit activity. Some patients with CAD have no symptoms that are identified during careful questioning, but have "silent ischemia" that is demonstrated by noninvasive testing.[55] Careful attention should be directed to the risk factor profile for CAD, since the probability of atherosclerosis is increased in these individuals.[56] A statistical extrapolation of the most recent National Health and Nutrition Examination Survey (NHANES) data suggested that oral healthcare professionals can effectively screen and identify patients that are unaware of their risk for developing CHD.[57]

Diagnostic testing begins with baseline 12-lead electrocardiography (ECG). Unfortunately, this is neither sensitive nor specific for the presence of CAD or prior MI. The presence of abnormal Q waves on the ECG may suggest prior MI, though these are not invariably present, and often only nonspecific changes of the ST segments or T waves are observed in patients with chronic CAD. Even a normal ECG does not exclude the presence of severe or even life-threatening CAD. Stress testing, often combined with nuclear or echocardiographic imaging modalities, remains the mainstay of a noninvasive diagnosis, though there is increasing evidence for use of cardiac computed tomography angiography (CTA) as the primary modality.[58–60] Exercise testing with electrocardiographic monitoring is associated with a relatively low sensitivity and specificity for the detection of CAD and should be performed only if the resting ECG is normal. In low-risk patients, however, a negative exercise ECG strongly predicts a favorable clinical outcome.[61] Even in patients with an intermediate to high clinical risk of CAD, achieving a relatively high workload during exercise with no ischemic ST depression in the ECG is also associated with a very low prevalence of significant ischemia.[62]

Single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) with agents such as thallium 201 and technetium 99m sestamibi is used to assess coronary perfusion at rest and with physical stress. Since the uptake of these agents into the myocardium is an active process, ischemic or infarcted cells exhibit a reduced or absent uptake. A >70% stenosis of a coronary artery typically is associated with decreased myocardial perfusion on the stress images, but with normal myocardial perfusion at rest. This reversible defect is the perfusion pattern associated with stress-induced myocardial ischemia. A fixed defect demonstrates reduced myocardial perfusion both at rest and on exercise. Stress echocardiography detects myocardial ischemia by demonstrating regional differences in left ventricular contractile function during stress. Both myocardial perfusion imaging and stress ECG offer greater sensitivity and specificity than does exercise ECG alone, and they provide important prognostic information as well.

In patients who cannot exercise, exercise can be simulated with use of either coronary vasodilator agents (adenosine, dipyridamole, or regadenoson) or dobutamine, which directly increases myocardial contractility and heart rate. Vasodilator stress tests must be paired with imaging modalities that look directly at myocardial perfusion and therefore can be paired with SPECT-MPI, positron emission tomography (PET), and cardiac magnetic resonance imaging (MRI). Both PET and MRI are superior to SPECT in their sensitivity and specificity.[63,64] While both PET and MRI have superior diagnostic accuracy, they are costlier, not widely available, and are typically reserved for very high-risk patients.

Cardiac CTA has emerged as an important diagnostic tool. Imaging the coronary arteries poses significant challenges owing primarily to the relatively small vessel caliber (2–4 mm) and normal cardiac motion. As such, it requires specialized scanners and protocols to achieve optimal images. It is now, however, a widely available method for detecting CAD, with an excellent sensitivity for detecting clinically significant stenoses. In addition, it has also been shown to be more cost-effective than stress testing.[65] Given that it is a purely anatomic test, however, it does not address the potential physiologic significant of the obstruction, nor does it estimate the ischemic burden, both of which are key in decision-making. When compared to an initial up-front strategy of stress testing, data have been mixed, with the

SCOT-HEART trial demonstrating that cardiac computed tomography (CT) was superior, whereas the PROMISE trial showed no difference.[59] The benefit in the SCOT-HEART trial has been attributed to implementation of more aggressive therapy in patients who were found to have nonobstructive CAD that would have been otherwise missed on a functional test. Because of the apparent clinical equipoise paired with the decreased cost, the UK National Institute for Health and Care Excellence (NICE) guidelines have advocated cardiac CTA as the first-line diagnostic test.[66] While this has not yet become the gold standard globally, it has nonetheless emerged as a very useful tool in select patients presenting with symptoms concerning for CAD.

Despite the multiple noninvasive tools that are currently available to evaluate for the presence of CAD, coronary angiography is often needed to define the anatomy and to assist in planning an appropriate management strategy for selected intermediate- to high-risk patients. At the time of coronary angiography, a purely anatomic assessment, validated functional testing (fractional flow reserve or FFR, instant wave-free ratio or iFR, and resting full-cycle ratio or RFR) can be performed to help assess the physiologic significance of an observed stenosis if indicated.[67–69]

Management

Medical Therapy

The management of chronic, stable CAD depends on several clinical factors, including the extent and severity of ischemia, exercise capacity, prognosis based on exercise testing, overall left ventricular (LV) function, and associated comorbidities such as diabetes mellitus. Patients with a small ischemic burden, normal exercise tolerance, and normal LV function may be safely treated with pharmacologic therapy. The front line of modern medical therapy includes the selected use of aspirin, beta-blockers, ACEis, and statins. These agents have been shown to reduce the incidence of subsequent MI and death.[70,71] Nitrates, calcium-channel blockers, and ranolazine may be added to the primary agents to relieve angina in selected patients.

Revascularization

In the absence of severe disease, percutaneous coronary intervention (PCI) has been shown to improve symptoms of chronic ischemia without preventing death or MI.[72] On the basis of available data, therefore, it seems appropriate to prescribe optimal medical therapy in most patients with CAD and stable angina, and reserve myocardial revascularization for select patients with disabling symptoms despite optimal medical therapy.[73] Patients with a large ischemic burden are likely a specialized subset who may benefit from revascularization.[74] In the highest-risk patients with severe CAD (left main coronary obstruction or diabetic patients with severe multivessel disease), coronary artery bypass surgery is likely superior to PCI,[75–79] though PCI can be performed safely and may be a good option in certain patients.[79,80]

ACUTE CORONARY SYNDROMES

The sudden rupture of an atherosclerotic plaque, with ensuing intracoronary thrombus formation that acutely reduces coronary blood flow, underlies the pathophysiology of an ACS.[81,82] This acute thrombus formation results in myocardial ischemia and subsequent infarction if there is a prolonged and severe reduction in blood flow. ACSs represent a continuous spectrum of disease, ranging from unstable angina (UA) to non-ST-elevation MI (NSTEMI) to acute ST-elevation MI (STEMI). If the intraluminal thrombus following acute plaque rupture is not completely occlusive, the corresponding clinical presentation is that of UA or NSTEMI.[83] An MI is defined by the presence of myocardial necrosis identified by the presence of circulating cardiac biomarkers.[26] The most common biomarker utilized clinically is cardiac troponins, which are a group of proteins found in cardiac myocytes. Troponin elevation is a very sensitive marker capable of detecting very minor levels of cardiac injury. The clinical presentation of both UA and NSTEMI is quite similar, with the latter being distinguished by the presence of a positive troponin. STEMI represents the most severe clinical scenario and reflects acute plaque rupture with prolonged and complete epicardial coronary obstruction.

Diagnosis of Acute Coronary Syndromes

The American College of Cardiology Foundation (ACCF) and the AHA recently updated their guidelines for the management of patients with ACS.[84,85] ACS is typically diagnosed clinically. The patient's history suggests a change in anginal pattern or ischemic symptoms at rest. Acutely, the ECG is the most important diagnostic tool to risk-stratify the patient and to make decisions regarding treatment. The presence of resting ST-segment depressions or dynamic T-wave changes in the distribution of an epicardial coronary artery associated with the typical clinical presentation is highly suggestive of UA or NSTEMI. The presence of ST-segment elevation when associated with classic clinical symptoms is the hallmark of an acute STEMI. Patients presenting with a history suggestive of an acute MI who have a left bundle branch block (LBBB) pattern on the 12-lead ECG are usually treated as if they had STEMI, given the difficulty of interpreting the ECG when this conduction delay is present. It is important to recognize, however, that the presence of a

normal 12-lead ECG does not exclude the possibility of ACS in the correct clinical context.

As indicated earlier, cardiac troponins have emerged as a very sensitive tool to detect myocardial injury as soon as 3 hours after the onset of symptoms.[86,87] The serum levels peak ~24–48 hours after the event and then gradually trend down over the new few days. While troponin elevation is very helpful in the diagnosis of UA and NSTEMI, it is not frequently useful in STEMI presentation when immediate revascularization is indicated. As the assays for troponin have become more and more sensitive, earlier identification of MI is now possible. The high sensitivity of our current troponin assays, however, is a double-edged sword, as low levels of troponin elevation are frequently seen in noncardiac illnesses (type 2 MI).[26] In this setting, an acute stressor such as a gastrointestinal bleed or sepsis can lead to increased myocardial oxygen demand without an abrupt decrease in myocardial oxygen supply, resulting in a troponin elevation. In this setting, the myocardial ischemia is not driven by acute thrombosis but rather by the increased demand of the stressor. Because of the distinct differing pathophysiology, treatments will also be different. Distinguishing between ACS and a type 2 MI therefore is key and is essentially a clinical diagnosis.

Initial Management for Unstable Angina and NSTEMI

The treatment of the unstable coronary syndromes should focus on the relief of myocardial ischemia and the institution of pharmacologic therapy targeting the underlying thrombotic mechanism (Table 14-8). Aspirin should be promptly administered to inhibit platelet function. The selective use of beta-blockers may relieve ischemia by lowering heart rate and BP, which reduce myocardial demand.

Beta-blockers are also antiarrhythmic agents and can suppress associated malignant ventricular arrhythmias. Beta-blockers should not be administered to those with acute decompensated heart failure, bradycardia, heart block, or severe bronchospasm. Sublingual or intravenous nitroglycerin decreases LV preload and dilates the epicardial coronaries arteries, thereby decreasing myocardial ischemia.[84]

In troponin-positive high-risk patients, there is robust clinical evidence of improved outcome when, in addition to aspirin, a second antiplatelet agent is administered. These include clopidogrel (Plavix) or ticagrelor (Brilinta). The choice of these agents depends on the relative degree of ischemic versus bleeding risk. It is important to know that these are potent and long-acting antiplatelet agents whose use is associated with major bleeding risk if a patient is to undergo emergent surgery.[84]

There is some evidence that high-risk patients with ACS will benefit from treatment with intravenous unfractionated heparin or subcutaneous low molecular weight heparin such as enoxaparin (Lovenox).[84] The short-acting intravenous unfractionated heparin is preferred in high-risk patients who may need emergent cardiac catheterization and/or bypass surgery, whereas enoxaparin may have some advantage in all other patients with ACS. Procedural outcomes are improved when dual antiplatelet therapy and heparin are used during angioplasty and stenting (see Table 14-8 for a list of these agents).

In high-risk patients with unstable angina or NSTEMI, implementation of an early invasive strategy (within 24–48 hours) with coronary angiography and PCI is associated with improved outcomes and is the most typical strategy. In lower-risk patients where the diagnosis is less clear clinically or who may be poor candidates for angiography/PCI, further risk stratification with pharmacologic stress testing may also be reasonable.[84]

Table 14-8 Common antithrombotic agents.

Generic Name	Route of Administration
Antiplatelet	
Aspirin	Oral
ADP Receptor Antagonists	
Clopidogrel	Oral
Prasugrel	Oral
Ticagrelor	Oral
Cangrelor	Intravenous
Glycoprotein IIb/IIIa Receptor Asntagonists	
Abciximab	Intravenous
Eptifibatide	Intravenous
Tirofiban	Intravenous
Anticoagulants	
Unfractionated heparin	Subcutaneous/ intravenous
Low molecular weight heparin (enoxaparin, dalteparin)	Subcutaneous
Lepirudin	Intravenous
Bivalirudin	Intravenous
Warfarin	Oral
Direct Oral Anticoagulants	
Dabigatran	Oral
Betrixaban	
Apixaban	Oral
Rivaroxaban	Oral
Edoxaban	Oral

ADP, adenosine diphosphate.

Initial Management for STEMI

Given that the pathophysiology involved in STEMI is due to complete epicardial coronary artery obstruction, the major goals of therapy are to provide revascularization as quickly as possible. In the current era, the therapy of choice is PCI, with a goal to restore perfusion within 90 minutes of clinical presentation (so-called door-to-balloon time). In situations where PCI is not expected to be available within 120 minutes of first presentation, thrombolytic therapy is recommended.[85,88] Thrombolysis with streptokinase, tissue plasminogen activator, and reteplase have all been shown to improve coronary blood flow and to reduce mortality.[89,90] Prospective randomized trials have shown that PCI with stenting in patients with STEMI is superior to thrombolytic therapy when it is completed within 1–2 hours of clinical presentation. Only if a patient with STEMI presents to a center that lacks the ability to perform emergent PCI is thrombolytic therapy the treatment of choice if immediate transfer to a PCI center cannot be arranged. All patients who have received thrombolytic therapy, however, should be immediately transferred to a PCI center.[85,88]

Post-Acute Coronary Syndrome Management

All patients with ACS should be treated with low-dose aspirin (81–100 mg) indefinitely. There is evidence that treatment with a second antiplatelet agent (clopidogrel) is beneficial even if PCI is not performed. If PCI is performed, dual antiplatelet therapy is continued for at least 6–12 months.[84,85,88,91] Treatment for longer duration has been associated with reduced ischemic events, though at the expense of increased bleeding.[92] The Dual Antiplatelet Therapy (DAPT) score has been established as a tool to help guide decision-making, balancing these competing risks on an individual patient basis.[93] In patients for whom the decision has been made to continue dual antiplatelet therapy beyond the initial 6–12 months, temporary interruption if necessary for procedures can be done safely, though consultation with the patient's cardiologist is still recommended. Initiation of a high-intensity statin during the index hospitalization has also been shown to be associated with improved outcomes, though it is not clear that the benefit is necessarily due to the acute exposure to high-intensity statin rather than chronic therapy.[33] Aggressive lipid management after ACS is a key component of secondary prevention, with recent data demonstrating significant incremental risk reduction with LDL lowered to as low as 30 mg/dL with combined use of statins, ezetimibe as well as the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors evolocumab and alirocumab.[31,32,94] Beta-blockers are typically continued after ACS, and in patients with LV dysfunction, ACEi/ARBs have a demonstrated benefit in preventing adverse remodeling. Outpatient cardiac rehabilitation is key to improving functional outcomes after discharge and should also be routinely recommended after an ACS event.[84,85,88,91]

Dental Management Considerations for Patients with Coronary Artery Disease

Several considerations need to be addressed for dental patients with CAD.[95] The primary concern is to prevent ischemia or infarction. The risk for such an event is determined by several factors, including the degree and type of CAD (i.e., stable vs. unstable, past history of angina or MI). Patients with CAD are at increased risk of demand-related ischemia from an increased heart rate or BP, as well as for plaque rupture and acute unstable coronary syndromes. Anxiety will increase the heart rate and BP, and can provoke angina or ischemia,[96] but this risk is relatively low during outpatient dental procedures.

There is longstanding dogma in dental practice that patients who have had an MI within the past 6 months should not have elective dental procedures, but this concern is largely based on a misinterpretation of a study of patients with CVD undergoing noncardiac surgery under general anesthesia. A study of a large Medicare population who underwent a dental procedure within 30–180 days after an ischemic vascular event were not found to be at increased risk of a second event.[97]

Numerous studies have indicated the influence of circadian variation and other triggers for acute coronary events, to include mental stress, hostility, anger, and depression.[98] Most such events occur between 6:00 am and noon. It has been proposed that sympathetic nervous system activation and an increased coagulative state may be precipitating factors.[99] Medications designed to prevent these events include beta-blockers, aspirin, and antihypertensives. Dental care for high-risk patients might ideally be provided in the early afternoon.

Recent protocols suggest that patients may be safely treated in an outpatient dental setting 30 days after an MI unless the patient has decompensated CHF. Considerations for dental patients who have undergone CABG procedures or coronary stenting are similar to those who have had an MI; that is, there are no data to support waiting as long as 6 months before resuming dental treatment. Following open heart surgery (e.g., CABG), however, sitting in a dental chair may be painful, even several weeks after surgery. Elective dental care should therefore be postponed until the patient can sit comfortably for the required time period.

Elective procedures, especially those requiring general anesthesia, should be avoided for at least a month following an MI, as there is a small increased risk of reinfarction.[100] These dental procedures can be undertaken provided the

patient is able to continue on their current antithrombotic therapy uninterrupted. Limited data suggest that the acute risk of administering local anesthesia without vasoconstrictor for 3 weeks after an uncomplicated MI is low, but if epinephrine-containing local anesthetic is necessary, it may be desirable to discuss this with the patient's primary care physician or cardiologist.

Protocols to reduce anxiety should be considered, according to the level of anticipated stress. The patient's nitroglycerin tablets or spray should be available during the procedure. In some situations, patients may be on one or more drugs that interfere with hemostasis. Antiplatelet drugs, such as aspirin, clopidogrel, prasugrel, or ticagrelor, are frequently used in patients with ACS and in all patients after coronary artery stenting. The combination of dual antiplatelet therapy (e.g., aspirin and clopidogrel) is usually continued for a minimum of 4 weeks after placement of a bare metal stent, and for a minimum of 6–12 months following placement of a drug-eluting stent.[101] There are limited data addressing the risk from dental procedures performed following coronary stenting.[102] If the procedure can be performed safely without interruption of the recommended antithrombotic therapy, it is reasonable to move forward with elective dental procedures after 4 weeks. If the procedure cannot be performed safely on dual antiplatelet therapy, consultation with the patient's cardiologist is recommended to weigh the relative risks of dual antiplatelet therapy interruption with delay in the dental procedure, as these are nuanced conversations. In general, purely elective procedures requiring interruption of dual antiplatelet therapy will be delayed by 6–12 months, though more urgent procedures can be considered after 3 months. The concern with early interruption of dual antiplatelet therapy is related to the risk of stent thrombosis in the early time period. During this time, the stent has not yet been fully endothelialized, making it highly susceptible to thrombosis without use of both aspirin and a second antiplatelet agent. Premature discontinuation of antiplatelet therapy has been significantly associated with adverse cardiac events, such as MI and death.[103]

Dental Management Considerations for Patients with Angina

From the standpoint of the patient's history, it is important to know whether angina occurs at rest, and if there are precipitating factors such as exercise, climbing stairs, or emotional stress. Patients should also be asked about the frequency, duration, timing, severity of attacks, and the response to medication. Dental healthcare providers should be aware that angina may present as jaw discomfort, often on the left side. Other cardiac conditions important to the medical history include the presence of noncoronary vascular disease and if the patient has a pacemaker or defibrillator. Patients with angina may be on one or more of the following drugs: nitrates or beta-blockers, which can cause conduction disturbances and fatigue; and calcium-channel blockers, which have side effects including bradycardia, worsening heart failure, headache, and dizziness. Respiratory depressants such as opioids, barbiturates, and other sedatives can worsen the cardiovascular status and should be avoided.

Elective dental treatment is reasonable if the angina is stable without change in severity or frequency over several months. If there is a change in the pattern of angina with more frequent episodes, more frequent sublingual nitroglycerin use, or angina with less exertion, this is concerning for unstable angina. Elective dental treatments should be avoided, and the patient should be referred to their cardiologist for urgent evaluation.

STRUCTURAL HEART DISEASE

Valvular Heart Disease

VHD occurs in ~2.5% of the American population and each year more than 100,000 heart valve procedures are performed.[3] It is typically first identified by the presence of murmur on auscultation. With early identification and appropriate referral, the majority of patients with VHD will live a normal lifespan.

Mitral Valve Disease

The mitral valve sits between the left atrium and left ventricle and when functioning normally, allows for filling of the left ventricle during diastole and during ventricular systole prevents backward flow back into the left atrium. The mitral valve apparatus is complex and comprises two leaflets (anterior and posterior), the mitral annulus, chordae tendinae, and the papillary muscles (see Figure 14-2). Mitral regurgitation (MR) is the most common heart valve disease and is the result of failure of the mitral valve to prevent backward flow during ventricular systole.[3] Mitral stenosis (MS) results from progressive abnormalities in the mitral valve, leading to impedance of normal blood flow from the left atrium into the left ventricle during filling. In addition to the hemodynamic alterations that are present in patients with these conditions, there are additional issues with regard to the prevention of bacterial endocarditis.

Etiology and Pathophysiology

MR is the result of abnormal closure of the mitral leaflets.[104] It can result from intrinsic abnormalities of the valve leaflets themselves, termed primary MR. The most common causes

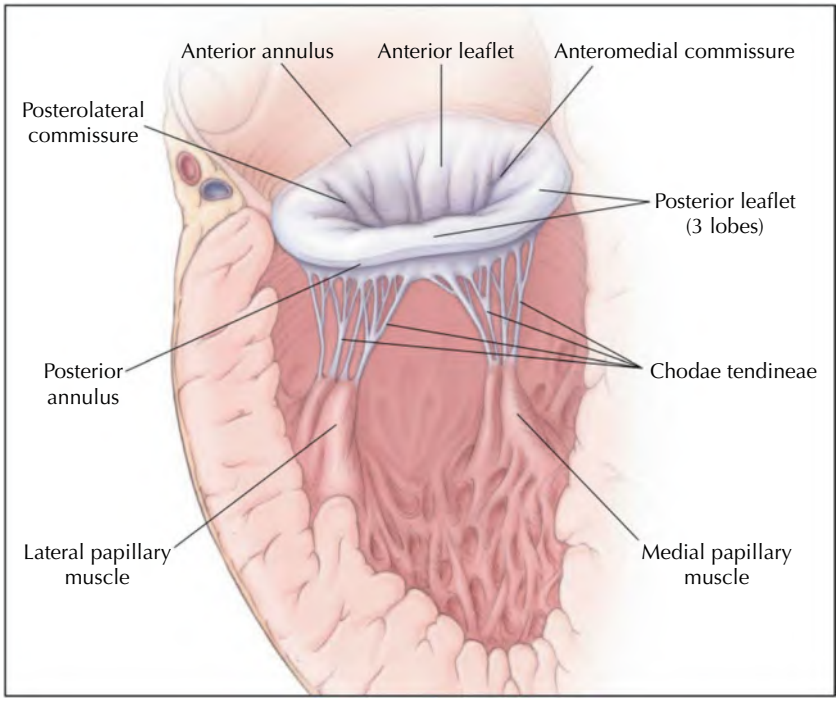


Figure 14-2 Mitral valve anatomy. The mitral valve consists of the mitral annulus, anterior and posterior leaflets, chordae tendinae, and the papillary muscles. Mitral regurgitation (MR) may be due to a disease process that primarily affects the valve leaflets (primary MR) such as a mitral valve prolapse or due to alterations in the structure/function of the left ventricle or atrium (secondary MR) such as those induced with a dilated cardiomyopathy. *Source:* From Otto, C. M. (2001). Evaluation and Management of Chronic Mitral Regurgitation. *New England Journal of Medicine*, 345(10), 740–746. © 2001, Massachusetts Medical Society.

of primary MR include mitral valve prolapse (MVP), calcific degenerative disease, rheumatic heart disease (RHD), endocarditis, and the use of anorectic agents such as fenfluramine and phentermine (fen-phen).[105]

MVP, as mentioned, is a common cause of primary MR, though the clinical syndrome is highly variable. It occurs in ~2.5% of the population[106,107] and is most commonly due to redundant mitral leaflet tissue associated with myxomatous degeneration. MR can occur in the setting of MVP, either due to prolapse of the affected leaflet with associated chordal elongation or due to rupture chordae. The severity of MR is highly variable, with the minority of patients developing severe MR. While this can be seen in patients with connective tissue disorder such as Marfan's and Ehlers–Danlos syndromes, it is typically seen in isolation. MVP may be associated with arrhythmias including premature ventricular complexes, supraventricular tachycardias, and atrial fibrillation, as well as malignant ventricular arrhythmias.[104]

MR can also occur due to structural changes in the left atrium or left ventricle, termed secondary or functional MR. Secondary/functional MR is typically seen in the presence of severe LV dysfunction resulting in apical displacement of the papillary muscles and annular dilation, or in severe left atrial dilation with resultant changes in the mitral valve annular anatomy. This distinction between primary and secondary MR is critical, as treatments vary widely.

In the presence of chronic MR, resistance to ventricular emptying is reduced as the LV is able to eject into the low-impedance left atrium as opposed to the aorta. To preserve forward flow, LV stroke volume and diastolic LV filling increase. This volume load is well accommodated by the LV for quite some time; however, if left unchecked, it ultimately progresses to LV dilation, LV dysfunction, and symptomatic CHF.

The two most common causes of MS are RHD or calcific degeneration. While uncommon in the developed world, RHD remains the dominant form of VHD in developing countries.[108] In RHD, there is characteristic thickening and fusion of the mitral commissures as well as thickening and calcification of the leaflets and subvalvular apparatus. This results in a restriction to LV inflow, subsequent left atrial hypertension and enlargement, atrial arrhythmias, secondary pulmonary hypertension, and right ventricular dysfunction.

Diagnostic Evaluation

MR is typically first identified on physical examination. MR is characterized by a systolic murmur heard best at the apex, while MS manifests as an apical diastolic rumble. Once

identified on physical examination, transthoracic echocardiography (TTE) remains the mainstay of noninvasive diagnosis in patients with mitral valve disease, and Doppler techniques are extremely useful in establishing the severity of stenosis or regurgitation.[109] Because of the dynamic nature of mitral valve disease, exercise stress echocardiography can also be useful to assess for changes in severity of either regurgitation or stenosis at peak exercise, or to look for evidence of exercise-induced pulmonary hypertension, a high-risk feature in both MR and MS. Transesophageal echocardiography (TEE) is useful in further defining the mechanism of MR or MS, better assessing the severity of the hemodynamic lesion,[110] and treatment planning. TEE offers improved image quality due to the proximity of the transducer to the mitral valve and left atrium. Cardiac catheterization has a limited role in the diagnosis of MR and is primarily reserved for those patients who are referred for cardiac surgery to assess for significant CAD.[111] In MS, direct assessment of the pressure gradient across the mitral valve via hemodynamic catheterization can be useful in challenging cases.

Treatment

The ACC, AHA, and ESC have published guidelines for the management of VHD.[112,113] Medical therapy for primary MR is quite limited and decisions regarding treatment typically hinge on the timing of intervention. Surgical valve intervention is currently recommended in patients who are symptomatic from severe primary MR or in asymptomatic patients with progressive LV dilation or dysfunction. There is evidence to suggest that patients with pulmonary hypertension or atrial fibrillation associated with isolated primary severe MR may also benefit from surgical intervention, and guidelines indicate that surgery is also reasonable in this patient population. Primary MR is surgically treated with either repair or replacement. Mitral repair is usually accomplished with the resection of the prolapsing or flail segment and placement of an annuloplasty ring. Due to improved surgical outcomes with repair compared to replacement, repair is preferred if technically possible. If repair is not technically feasible, replacement with either a biologic or mechanical prosthesis may be necessary. In patients who are prohibitive or high-risk surgical candidates, transcatheter mitral valve repair (with use of the MitraClip device) is currently available.[114] In select patients, transcatheter mitral replacement can also be considered.[115] These procedures are performed in a minimally invasive fashion via the femoral veins and do not require cardiopulmonary bypass. Additional devices are currently being investigated for the percutaneous treatment of mitral valve disease.[116,117]

Intervention for secondary MR is more controversial, as the primary driver of the MR in these pathologies is not the mitral valve itself. The benefits for mitral valve surgery in patients with isolated secondary MR have not been demonstrated to outweigh the surgical risks, and therefore it is rarely performed. In patients undergoing cardiac surgery for an alternative reason who also have severe secondary MR, mitral valve replacement (over repair) is typically also performed. The use of the MitraClip in secondary MR has recently been evaluated in two randomized clinical trials with conflicting results, though in the select patient population, transcatheter mitral valve repair is also reasonable.[118,119]

While there are limited medical options for primary MR, patients with MS can benefit from treatment with heart rate–regulating agents such as beta-blockers, calcium-channel blockers, and digoxin (when concomitant atrial fibrillation is also present). Since MS impairs diastolic filling, increasing diastolic filling with heart-rate reduction can improve diastolic filling and thereby relieve symptoms associated with MS. Another important consideration in the management of MS is the risk of atrial fibrillation and the associated thromboembolic risk. Patients with severe MS have a high risk of thromboembolism even when in sinus rhythm. Patients with atrial fibrillation and severe MS should be managed with Coumadin and not direct oral anticoagulant therapy. Anticoagulation can be considered in those with severe MS who have had a prior embolic event and in those with a very severely dilated left atrium. In patients who are symptomatic with severe MS or in those with significant resting pulmonary hypertension despite adequate medical therapy, intervention should be considered. If possible, percutaneous balloon mitral valvuloplasty (PBMV) should be performed, as it can provide lasting benefit with minimal risk. In patients who are not candidates for PBMV, mitral valve repair (if technically possible) versus mitral valve replacement is indicated.[112,113]

Aortic Valve Disease

The aortic valve serves as the gatekeeper between the left ventricle and the aorta. It is comprised of three cusps: left, right, and noncoronary cusps. In 1–2% of the general population, the aortic valve is bicuspid, an anomaly that is associated with accelerated degeneration (either stenosis or regurgitation), thoracic aortic aneurysms, as well as aortic coarctation.[120] Aortic stenosis (AS) accounts for ~25% of all cases of VHD, while aortic regurgitation is less common.[3]

Etiology and Pathophysiology

The most common causes of AS include fibrocalcific degeneration, congenitally bicuspid valve, and RHD. In the United States, fibrocalcific disease is most common, though

worldwide, rheumatic disease remains the most common etiology. Fibrocalcific degeneration is an active disease characterized by inflammation, fibrosis, and calcification, and is not simply an inevitable consequence of aging as was once believed. In the United States, among those <70, bicuspid aortic valve disease is the most common etiology. Regardless of the etiology, AS results in a pressure gradient between the left ventricle and the aorta. In order to overcome this pressure gradient, the left ventricle hypertrophies. While the hypertrophied ventricle can accommodate the pressure gradient for quite some time, it will become maladaptive if left unchecked. The following symptoms can develop in the presence of severe AS: (1) dyspnea, due to stiffening of the hypertrophied myocardium; (2) angina, due to supply–demand mismatch; and (3) syncope, due to inadequate forward flow as a result of the fixed stenosis. These symptoms can occur in the face of normal LV systolic function, though asymptomatic LV dysfunction can also occur.

Aortic regurgitation (AR) results from a wide variety of processes that directly affect the aortic leaflets, including congenital abnormalities, rheumatic disease, infective endocarditis, fibrocalcific degeneration, and the use of anorexigens.[112,113,121] Additionally, abnormalities of the aortic root such as aneurysm or aortic dissection may dilate or disrupt the aortic annulus, resulting in malcoaptation and regurgitation. AR results in an increase volume load on the LV. In acute AR, the ventricle has not had time to adaptively remodel to tolerate this increased volume load and acute heart failure with associated cardiogenic shock is likely. In chronic AR, the increase in volume load is more gradual, thereby enabling the ventricle to adaptively remodel though changes in ventricular compliance. Over time, however, the remodeling becomes maladaptive, with LV dilation, LV contractile failure, and symptoms of CHF.

Diagnostic Evaluation

The auscultatory findings of AS include a harsh crescendo–decrescendo systolic murmur best heard over the right upper sternal border, and a diminished or absent aortic component of the second heart sound. The murmur of AS frequently radiates to the carotid arteries. The carotid pulses are often weak and delayed, and delay between the brachial and radial pulses may also be present. AR is manifested on physical examination by a high-pitched decrescendo early diastolic murmur, heard best at the left sternal border when the patient is sitting upright with breath held after exhalation. Chronic AR often yields findings of a hyperdynamic circulation with bounding or "water hammer" pulses, head bobbing (titubation), "to-and-fro" murmurs heard in the femoral arteries, and Quincke's pulse (visible in the nail beds).

As with mitral valve disease, TTE remains the primary diagnostic modality in the vast majority of patients with aortic valve disease. TEE may be needed to define the mechanism of AR or AS, to evaluate the aortic root and ascending aorta, and to investigate the possibility of endocarditis. Cardiac CT has emerged as a useful adjunctive tool in assessing AS severity when TTE is indeterminate, and is a key component to procedural planning in patients undergoing transcatheter aortic valve replacement (TAVR).[122,123] Cardiac MRI can also be useful in quantify AR severity.[113,124] While cardiac catheterization can be utilized to directly assess AS severity, it is rarely used solely for this purpose given that TTE has been well demonstrated to provide a comprehensive assessment without the associated risk (stroke, vascular injury, etc.). Catheterization is typically reserved to assess for concomitant coronary disease in patients being considered for aortic valve intervention.

Treatment

Management of AS mainly hinges around the decision to pursue aortic valve replacement (AVR). There are no medical therapies that have been shown to prevent progression of AS. It has been well established that the development of symptoms associated with AS is associated with a rapid decline in clinical outcomes. In the era before widespread surgical treatment, the average time to death after the onset of symptoms associated with AS was as follows: angina, 3 years; syncope, 3 years; dyspnea, 2 years; CHF, 1–2 years.[125] Therefore, it is recommended that AVR be performed in any patient with severe AS with symptoms of angina, shortness of breath, or syncope, provided that the symptoms are clinically attributable to the AS. In the absence of symptoms, most patients with AS do quite well, though there is still a low risk of sudden death (<1%).[126] Management of the asymptomatic patient with AS remains complex, though current guidelines recommend careful observation for most patients.[112,113]

In patients with isolated AS, AVR can be performed through either the standard surgical approach (SAVR) or through a percutaneous approach (TAVR). TAVR has been shown to be as effective as SAVR in prohibitive-, high-, moderate-, and low-risk patients.[127,128,129–131] TAVR is typically performed via the femoral artery, though alternative access sites can be used. While outcomes with TAVR have been excellent in general, there remains a risk of vascular injury, stroke (~2%), and the need for permanent pacing (8–12%).[132] Despite advances in TAVR, there is still a significant role for SAVR in patients who are not anatomically candidates for TAVR, those with concomitant complex coronary disease, and in many patients with bicuspid aortic valve disease. Ultimately, the choice between surgical and transcatheter AVR remains a complex one and is best determined by a

multidisciplinary heart valve team that includes cardiologists, interventionalists, imaging specialists, and cardiac surgeons.

Similar to AS, the main treatment decision in managing patients with AR surrounds the timing of AVR. While meticulous hypertension management with diuretics and vasodilators (dihydropyridine calcium-channel blockers, ACEis, ARBs, and hydralazine) can help manage early symptoms and is important in overall cardiovascular care in general, as discussed earlier, surgery remains the only definitive therapy. Surgery is currently recommended in symptomatic patients with severe AR as well as in asymptomatic patients with abnormal contractile function and in those with progressive LV dilation.[113]

Surgical techniques for the management of AR have evolved considerably with a significant reduction in surgical risk.[133,134] If the AR is due primarily due to a dilated aortic root, aortic valve repair is possible and preferred. In the majority of patients with isolated AR, however, SAVR is required. Due to the risk of device embolization and paravalvular regurgitation, TAVR is not currently approved for isolated AR; however, in patients who are not surgical candidates, it can be considered in an off-label fashion.[135]

Prosthetic Heart Valves

There are two types of prosthetic heart valves, mechanical and bioprosthetic. The mechanical valves, which are classified according to their structure, include the oldest type ball-in-cage (Starr–Edwards) valve, the single tilting-disk (Bjork–Shiley) valve, and the currently most widely used bileaflet tilting-disk valves. Bioprosthetic valves are either (1) heterografts made from porcine or bovine tissue or (2) homografts from preserved human aortic valves.

Mechanical valves are extremely durable and fail rarely. As such, they are a good option for younger patients who have a long life expectancy. Patients with mechanical valves do, however, require chronic anticoagulation therapy with warfarin to prevent thromboembolism. Use of direct oral anticoagulants has been shown to be associated with worse outcomes and is contraindicated in patients with mechanical prostheses.[136] The intensity of anticoagulation is based on the overall thromboembolic risk and is influenced by type of mechanical valve (ball-in-cage valves are highest risk and bileaflet tilting-disc valves lowest risk), valve position (mitral position higher risk than aortic position), and other patient factors (presence of atrial fibrillation, prior thromboembolic events, or LV dysfunction). In patients with mechanical valves, the risk of systemic embolization is approximately 4% per patient per year without anticoagulation, 2.2% with aspirin therapy, and 0.796%–1.0% with warfarin therapy.[137] Patients with mitral valve prostheses are at approximately twice the risk of those with aortic valve prostheses.[138] The addition of low-dose aspirin therapy (75–100 mg daily) to warfarin therapy in patients with mechanical prostheses is controversial and definitive modern data are lacking. Currently, the US guidelines have continued to recommend combined aspirin and warfarin therapy in all patients with mechanical prostheses, while the European guidelines have reserved the addition of aspirin only for those patients with concomitant vascular disease.[112,113]

Bioprosthetic surgical valves have a lower thrombogenic potential and do not require long-term anticoagulation. The thromboembolic risk is highest in the early postsurgical period, before full endothelialization, and anticoagulation is recommended for the first 3–6 months after implantation. Despite these recommendations, there is significant variability in real-world utilization due to surgical concerns regarding bleeding.[112,113] Beyond 3 months, low-dose aspirin monotherapy is continued indefinitely. The lack of the need for long-term anticoagulation makes bioprosthetic valves attractive for patients. The disadvantage of bioprosthetic valves when compared to mechanical valves, however, is durability. While data are limited, the average life expectancy of a bioprosthetic valve is ~10–20 years.[139]

Transcatheter valves are also bioprosthetic valves and have a durability that is probably similar to surgical bioprosthetic valves.[127–131] Aspirin and clopidogrel are typically prescribed for the first 6 months after implantation, at which point low-dose aspirin monotherapy is continued indefinitely. Subclinical TAVR leaflet thrombosis detected by cardiac CT has been identified in up to 12% of cases, though the clinical impact on thromboembolic events is not clear.[140] If identified, the antithrombotic therapy is typically intensified to full anticoagulation. In patients who undergo TAVR placement within a failed bioprosthetic valve (valve-in-valve), the risk of thrombosis is similarly elevated and therapy is to full anticoagulation.[141] There remain very limited data on the optimal anticoagulation (warfarin vs. direct oral anticoagulant) strategy in these complex situations and clear guidelines are not yet available.

The recommended anticoagulation therapy for each type of prosthetic valve is summarized in Table 14-9. It is important that although these recommendations serve as broad guidelines, the level of chronic anticoagulation should be individualized and based on the location, type, and number of prosthetic valves, as well as the patient's age, comorbidities, and additional thromboembolic risk factors such as a history of atrial fibrillation or stroke. Thus, the intensity of anticoagulation is determined by weighing the patient's risk of thromboembolic events against the risk of adverse anticoagulation consequences (bleeding risks). It is important to note that direct oral anticoagulants should not be used in patients with mechanical prostheses.[112,113]

Table 14-9 Antithrombotic management in prosthetic valves.

Valve Type	Recommended Therapy
Aortic Valve	
Mechanical AVR without risk factors	Vitamin K antagonist with INR goal 2.5 ± ASA 81–100 mg daily
Mechanical AVR with risk factors	Vitamin K antagonist with INR goal 3 ± ASA 81–100 mg daily
On-X mechanical AVR without risk factors	Vitamin K antagonist with INR goal 1.5–2 ± ASA 81–100 mg daily
Bioprosthetic SAVR	Vitamin K antagonist with INR goal 2.5 for first 3–6 months in low bleeding risk patients, ASA 81–100 mg indefinitely
Aortic valve repair	Vitamin K antagonist with INR goal 2.5 for first 3–6 months in low bleeding risk patients, ASA 81–100 mg indefinitely
TAVR	Clopidogrel 75 mg daily for first 6 months, ASA 81–100 mg indefinitely, *or* Vitamin K antagonist with INR goal 2.5 for first 3 months in low bleeding risk patients, ASA 81–100 mg indefinitely
Mitral Valve	
Mechanical MVR	Vitamin K antagonist with INR goal 3 ± ASA 81–100 mg daily
Bioprosthetic MVR	Vitamin K antagonist with INR goal 2.5 for first 3–6 months in low bleeding risk patients, ASA 81–100 mg indefinitely
Mitral valve repair	Vitamin K antagonist with INR goal 2.5 for first 3–6 months in low bleeding risk patients, ASA 81–100 mg indefinitely

Risk factors include left ventricular dysfunction, atrial fibrillation, hypercoagulable state, prior thromboembolic event, or older-generation valve such as a ball-in-cage. ASA, acetylsalicylic acid; AVR, aortic valve replacement; INR, International Normalized Ratio; MVR, mitral valve replacement; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Prosthetic heart valves increase the risk for infective endocarditis, which typically manifests as fever and as other systemic symptoms.[142] Although endocarditis within 60 days of surgery typically is caused by nonoral bacteria, the cause of endocarditis that occurs 60 days after valve surgery is similar to that of native-valve endocarditis.

Periprocedural Prosthetic Valve Anticoagulation Management

Management of anticoagulation in the periprocedural time period is complex and the risk of procedural bleeding must be weighed against the risk of thrombosis. Due to the high risk of complications without anticoagulation in the setting of mechanical heart valves, it is recommended that patients with mechanical heart valves continue on warfarin therapy uninterrupted when undergoing minor procedures (such dental extractions or cataract removal), provided that bleeding can be controlled easily. If temporary interruption is deemed necessary for the procedure, bridging therapy (with either unfractionated intravenous heparin or subcutaneous low molecular weight heparin) is not necessary in patients with isolated mechanical AVR without additional risk factors (LV systolic dysfunction, atrial fibrillation, or prior thromboembolic events). For patients at highest risk for thromboembolic events (including those with a mechanical mitral valve, older-generation mechanical aortic valve, or mechanical aortic valve with an additional risk factor), bridging therapy is reasonable on an individualized basis, as the specific bleeding and thrombotic risks must be weighed carefully.[112,113] Given that patients with bioprosthetic valves are rarely fully anticoagulated solely for the purpose of the valve, decisions about anticoagulation management should be driven by the primary anticoagulation indication (see below for periprocedural management of anticoagulation for atrial fibrillation).

Congenital Heart Disease

Congenital cardiovascular malformations can be cyanotic (dominant right-to-left shunting), noncyanotic (dominant left-to-right shunting), or without shunting. Cyanotic defects include tetralogy of Fallot, transposition of the great vessels, anomalies of the tricuspid valve, pulmonary atresia, pulmonary stenosis, Eisenmenger's syndrome, and hypoplastic left heart syndrome (aortic atresia). Surgical correction of these defects is often accomplished in infancy and early childhood. Noncyanotic defects include ventricular septal defect, atrial septal defect, patent ductus arteriosus, coarctation of the aorta, aortic valve stenosis, and MVP. Management of these patients is often quite complex and so best done by adult CHD specialists.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common monogenic cardiovascular disorder and occurs in ~1 in 200–500 individuals in the general population. It is estimated that there are ~750,000 individuals with HCM in the United States and 20 million globally, though these are likely underestimates due to the challenges in diagnosis. HCM is inherited in an autosomal dominant pattern and is associated with mutations in cardiac sarcomeric proteins. Clinically, it presents with a thickened and nondilated left ventricle. Depending on the pattern of hypertrophy, this can cause

obstruction of systolic flow from the left ventricle (70% of cases). Patients with HCM can develop symptoms of CHF and are more prone to the development of atrial arrhythmias. The risk of sudden cardiac death is an important part of the assessment of patients with HCM. Not all patients with HCM are at equal risk of sudden death and several risk factors have been identified. In patients with multiple risk factors for sudden death, consideration of implantable cardiac defibrillators (ICDs) is recommended. HCM remains the most common cause of sudden death in athletes and is typically considered a contraindication to competitive athletics, though noncompetitive recreational activity is typically permitted. There has been a great number of advances in the management of patients with HCM over the past 50 years that has resulted in a 90% reduction in mortality, to an annual HCM-related mortality rate as low as 0.5% per year.[143]

Dental Management Considerations

Patients with higher levels of valve dysfunction, whether from valve insufficiency or stenosis, may require cardiac valve replacement. The primary concerns are for a risk of bleeding and a risk for valve infection. Patients with VHD should be questioned carefully about symptoms and ongoing medical management, to include current medications. The extent to which dental treatment should be altered is determined by the degree of compromise (e.g., decreased cardiac output) and tolerance for stressful or prolonged dental procedures. Patients without symptoms, exercise limitation, or arrhythmias can undergo routine dental procedures without significant risk. Otherwise, these patients should be discussed with their primary care provider or cardiologist prior to dental treatment. Many of these patients have concomitant CAD and this is a separate consideration regarding modifications for dental care.

Considerations Concerning Bacteremia and Antibiotic Prophylaxis

The fact that bacteremia from the mouth could cause infective endocarditis (IE) was first suggested well over 100 years ago and was later reinforced by others who targeted viridans group streptococci from poor oral hygiene and dental extractions.[144,145] IE is initiated by a bacteremia in a susceptible host (e.g., prosthetic valve), and has an overall mortality rate of 20%–30%, depending on several host factors and the bacterial species involved.[146–148] The incidence of IE is increasing in some countries due to the use of intravascular catheters and implanted cardiac devices, and injection drug use.[149,150] Although the literature suggests a wide incidence range (20%–60%) for cases of IE caused by viridans group streptococci, over 30% of cases of native-valve IE may originate from oral bacterial species, most commonly the viridans group of streptococci.[147,151]

The origin of many cases of IE is transient bacteremia from the close approximation of oral bacterial plaque adjacent to diseased gingival tissues. The focus has historically been on invasive dental procedures as the source of many cases of IE, but there is an increased emphasis now on patients with poor oral hygiene. Bacteria can traverse the inflamed periodontal tissues to enter the circulation and this can occur with minimal manipulation of inflamed gingival tissues.[152] Although it has been mentioned in the AHA recommendations for antibiotic prophylaxis since the 1970s, there is an increasing consensus that there has been far too much emphasis on dental procedures as the source of IE. Dental office procedure-generated bacteremia may occur one or two times per year on average and therefore result in far fewer, if any, cases of IE by comparison with activities of daily living (e.g., tooth brushing), which may occur hundreds of times per year. Evidence is accumulating to support an emphasis on improved oral hygiene and resolution of periodontal inflammation as the most effective means of reducing oral bacteria-related IE.[10,152]

AHA guidelines and recent studies reflect the lack of evidence for safety or efficacy from the use of antibiotic prophylaxis prior to invasive dental procedures as a means of preventing IE.[11,146,153,154] It is important to emphasize that the AHA guidelines focus on groups of cardiac populations at high risk for a "bad outcome" (higher morbidity and mortality) from IE (Tables 14-10–14-12).[11] Of interest is that these four groups comprise only about 10% of patients at risk for IE.[11,155,156] The AHA-defined "moderate-risk" groups of cardiac patients therefore represent about 90% of people

Table 14-10 Cardiac conditions associated with the highest risk of adverse outcomes from endocarditis for which antibiotic prophylaxis with dental procedures is reasonable.

1) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
2) History of infectious endocarditis
3) Unrepair cyanotic congenital heart disease
4) Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the proceduret
5) Repaired congenital heart disease with residual defects at the site or adjacent to the prosthetic patch or prosthetic device (which inhibit endothelialization)
6) Cardiac transplantation recipients who develop cardiac valvulopathy

Except for the conditions listed here, antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease. Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

Table 14-11 Recommended antimicrobial regimens for dental procedures.

		Regimen: Single Dose 30–60 min before Procedure	
Situation	**Agent**	**Adults**	**Children**
Oral	Amoxicillin		
Unable to take oral medication	Ampicillin	2 g IM or IV	50mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin – oral	Cephalexin*+	2g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone+	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin	600 mg IM or IV	20 kg IM or IV

IM, intramuscular; IV, intravenous.
* Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
+ Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
Source: Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736–1754. doi:10.1161/CIRCULATIONAHA.106.183095.

Table 14-12 Dental procedures for which endocarditis prophylaxis is reasonable.

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa*

* The following procedures and events do not need prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.
Source: Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116(15):1736–1754. doi:10.1161/CIRCULATIONAHA.106.183095.

covered with antibiotic prophylaxis prior to the 2007 change in these guidelines. Antibiotic prophylaxis is no longer recommended for the moderate-risk group, but they remain at risk for IE from oral bacterial species.

HEART FAILURE

Definition and Epidemiology

Heart failure is a complex clinical syndrome that results from an impairment in ventricular filling or ejection of blood.[157] Heart failure may be due to pericardial disease, VHD, or most commonly, myocardial disease resulting in abnormal contractile function (systolic dysfunction) or impaired relaxation (diastolic dysfunction) (Table 14-13). Diastolic dysfunction is characterized by clinical heart failure syndrome with normal LV systolic function on cardiac testing.[158,159] In many series, it represents one of the most common types of heart failure encountered in the general population.[160] Common causes of diastolic dysfunction include hypertension, CAD, longstanding diabetes, and advanced age. In addition, diastolic dysfunction is almost always present in patients with any type of advanced systolic heart failure.

Diagnosis

Dyspnea, orthopnea (shortness of breath while lying flat), bendopnea (shortness of breath when bending forward),

Table 14-13 Heart failure etiologies.

Coronary artery disease (ischemic cardiomyopathy)
Hypertension
Idiopathic dilated cardiomyopathy
Hypertrophic cardiomyopathy
Alcohol
Diabetes
Viruses (Coxsackie virus, enterovirus, human immunodeficiency virus, influenza, SARS-CoV2, etc.)
Infiltrative disorders (amyloidosis, hemochromatosis, sarcoidosis and others)
Toxins (chemotherapeutic agents, etc.)
Metabolic disorders (hypothyroidism, etc.)
Valvular heart disease
Pericardial disease
Tachyarrhythmia-induced
High output states (hyperthyroidism, atrioventricular fistula, thiamine deficiency, etc.)

and paroxysmal nocturnal dyspnea are classic symptoms, but nonspecific complaints such as chest discomfort, fatigue, palpitations, dizziness, and syncope are not uncommon. The onset of symptoms may be insidious, and symptoms may present for medical attention only when an acute decompensation occurs. Asymptomatic patients are sometimes diagnosed when routine testing is performed for other reasons that reveal abnormalities on ECGs, chest radiographs, or echocardiograms.

The physical examination findings in heart failure are numerous. A relative decrease in systolic BP (due to reduced cardiac output) and an increase in diastolic BP (due to peripheral vasoconstriction) may result in a decrease in pulse pressure. Cardiac percussion and palpation reveal an enlarged heart with a laterally displaced and diffuse apical impulse. Auscultation may reveal an apical systolic murmur of MR and the lower parasternal murmur of tricuspid regurgitation. Third and fourth heart sounds can be heard, signifying evidence of systolic and diastolic dysfunction. Rales suggest pulmonary congestion secondary to elevated left atrial and LV end-diastolic pressures. Jugular venous distention, peripheral edema, and hepatomegaly are markers of elevated right heart pressures and right ventricular dysfunction. In advanced heart failure, additional findings may include cool extremities with decreased pulses, generalized cachexia, muscle atrophy, and profound weakness.

Laboratory testing can be helpful at identifying possible etiologies of CHF depending on the specific clinical presentation. Human immunodeficiency virus (HIV), thyroid function testing, iron studies, and tests evaluating for possible light-chain amyloidosis (including serum protein electrophoresis and kappa/lambda light chains) are typically ordered at first diagnosis. Troponin and brain natriuretic peptide may also be helpful from both diagnostic and prognostic standpoints.

Chest radiography may demonstrate cardiac enlargement, pulmonary congestion, and pleural effusions. The ECG is frequently abnormal in a nonspecific manner and may be the only indication of heart disease in asymptomatic individuals. ECG may reveal prolonged repolarization (i.e., interval), and nonspecific ST and T-wave abnormalities. Conduction disturbances such as atrioventricular block, bundle branch blocks, and fascicular blocks are also seen. Criteria for LV hypertrophy with a repolarization abnormality may suggest hypertension as an etiology. ECG may also reveal evidence of arrhythmias such as atrial fibrillation and atrial flutter, as well as premature atrial or ventricular contractions. Supraventricular tachyarrhythmias and nonsustained ventricular tachycardia are also associated with heart failure, as is the development of ventricular fibrillation, usually resulting in sudden cardiac death.

TTE is the most useful noninvasive diagnostic tool for the initial evaluation of a patient with heart failure.[161] TTE provides information not only on overall heart size and function, but also on valvular structure and function, wall motion and thickness, LV mass, and the presence of pericardial disease. Doppler-derived hemodynamic measurements accurately predict the severity of valvular regurgitation seen in heart failure and give a noninvasive estimation of pulmonary artery pressures. Doppler techniques may also be used to evaluate LV diastolic abnormalities, which are frequently present in those with heart failure.

Given that CAD is the most common cause of CHF in the general population, an ischemic evaluation should be performed in all patients. Depending on the pretest probability of ischemic heart disease, this evaluation may be noninvasive (cardiac CTA, nuclear imaging, or cardiac MRI) or with invasive coronary angiography. Cardiac MRI and cardiac PET may be utilized if there is specific clinical concern for infiltrative or genetic cardiomyopathies such as HCM, cardiac sarcoidosis, or cardiac amyloidosis.

Classification

The majority of patients with heart failure have symptoms due to impaired LV myocardial function. While most patients with heart failure have abnormalities in both systolic (contractile) function and diastolic (filling) function, the ejection fraction (EF) is typically used as the main point of classification in patients with heart failure. Patients with heart failure and an LVEF of <40% are classified as heart failure with reduced ejection fraction (HFrEF), 41–49% as heart failure with mid-range ejection fraction (HFmEF), and ≥50% are

classified as heart failure with preserved ejection fraction (HFpEF). Classification stratified by EF is important, as there exist distinct differences among these three groups regarding demographics, comorbid conditions, prognosis, and particularly response to therapy. The ACCF/AHA stages of heart failure classification and the New York Heart Failure (NYHA) functional classification also have important roles in providing useful and complementary information regarding the presence or severity of heart failure. Whereas the ACCF/AHA staging system emphasizes the development and progression of disease in individuals and populations, the NYHA classification focuses on functional capacity and is an independent predictor of mortality (see Table 14-14).[157,162]

Management

Medical Therapy

The optimal management of patients with chronic systolic heart failure is highly evidence based and is associated with dramatic decreases in the risk of heart failure exacerbations, hospitalizations, and death. Both US and European guideline recommendations exist for the optimal treatment of patients with HF.[162,163]

The treatment of heart failure must be individualized to the etiology of the heart failure and to the patient (Table 14-14). Patients with CAD and heart failure should be evaluated for ischemia as well as viable but hibernating myocardium that would improve systolic and diastolic performance with revascularization.[164–166] Patients with alcoholic cardiomyopathy should be advised to abstain from alcohol, in addition to the usual therapeutic options, as this often leads to an improvement in LV performance.[167] Hypertension should be aggressively treated with pharmacologic intervention and dietary measures.

Table 14-14 Classification of heart failure.

NYHA Functional Classification
• Class I—symptoms of HF only at activity levels that would limit normal individuals
• Class II—symptoms of HF with ordinary exertion
• Class III—symptoms of HF with less than ordinary exertion
• Class IV—symptoms of HF at rest
ACCF/AHA Stages of HF
• Stage A—at high risk for HF but without structural heart disease or symptoms of HF
• Stage B—structural heart disease but without signs or symptoms of HF
• Stage C—structural heart disease with prior or current symptoms of HF
• Stage D—refractory HF requiring specialized interventions
Classification by Ejection Fraction
• HFpEF—symptoms of HF with LVEF ≥50%
• HFmEF—symptoms of HF with LVEF 41–49%
• HFrEF—symptoms of HF with LVEF ≤40%

ACC, American College of Cardiology; AHA, American Heart Association; HF, heart failure; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Failure.

The initial treatment in acute decompensated heart failure is stabilization of volume status and end-organ perfusion. In the majority of cases, the presentation is relatively mild, and this can be achieved on an outpatient basis with oral diuretics. For patients who are more acutely ill, inpatient admission with intravenous diuretics, vasodilator therapy, and even intravenous inotropic agents may be necessary. Most patients with symptomatic heart failure will need to stay on oral diuretic therapy, which should be tailored for the specific patient. Doses should be initiated at low levels and gradually titrated up over weeks to months. While diuretic therapy is a key component of symptomatic management, it is important to note that there is no mortality benefit associated with diuretic therapy.

Once the patient has been stabilized, attention should be turned toward therapies that have been demonstrated to improve overall outcomes. In selecting therapies, it is important to accurately classify patients within the HFrEF, HFmEF, and HFpEF categorizations. In patients with HFrEF, there are several medication classes that have been shown to have mortality reduction, including beta-blockers, ACEis/ARBs, aldosterone antagonists, and angiotensin receptor-neprilysin inhibitors (ARNIs). Several beta-blockers have been demonstrated to improve symptoms of CHF and reduce the risk of death and hospitalization from heart failure. These include bisoprolol, carvedilol, and sustained-release metoprolol succinate.[168,169–172]

ACEis and ARBs have also been demonstrated to decrease mortality, reduce symptoms in those with symptomatic HFrEF, and delay the onset of symptoms in asymptomatic patients with LV dysfunction.[173–179] Aldosterone antagonists (spironolactone or eplerenone) have also been shown to improve mortality in patients with symptomatic HFrEF already on beta-blockers and ACEis/ARBs and should be utilized.[180,181] Given the risk of hyperkalemia when used in conjunction with ACEis/ARBs, careful monitoring of potassium is necessary, and an aldosterone antagonist should not be used in those with significant renal dysfunction. The combination of isosorbide dinitrate and hydralazine reduces mortality in African American patients when added to ACEis/ARBs and in all patients who cannot tolerate an ACEi/ARB, and should be considered in these specific subgroups.[182–184]

Most recently, the new class of drugs termed ARNIs has been shown to further improve clinical outcomes when

compared to ACEis/ARBs alone. In patients with mild heart failure with a reduced EF, valsartan-sacubitril was superior to enalapril at reducing heart failure–related mortality and morbidity.[185] Ivabradine is an inhibitor of the If current in the sinoatrial node and is another new addition to the armamentarium in the treatment of HFrEF. In a randomized clinical trial, ivabradine was effective at reducing heart failure hospitalization in those with HFrEF and may be considered in those who are already on maximal doses of beta-blockers.[186]

Several trials have been conducted evaluating the efficacy of digoxin in managing patients with heart failure. While there is evidence that it may help with symptoms and preventing heart failure hospitalizations, there is no evidence to suggest a mortality benefit. The lack of impact on mortality in combination with a relatively narrow therapeutic window limit the broad utilization for digoxin in HFrEF.[187–190]

Pharmacologic therapy specifically aimed at HFmEF and HFpEF is much more limited. Unlike with HFrEF, no specific therapies have been identified that improve mortality in these patients. Aggressive management of hypertension, diuretic use for management of volume overload, and treatment of CAD are recommended. Spironolactone has been specifically studied in HFpEF. While there was no net benefit in heart failure hospitalization of mortality in the study, post-hoc analyses have suggested that there may have been a benefit in the North and South American cohort.[191,192] As such, the 2017 ACCF/AHA guidelines have indicated that spironolactone "might be considered to decrease hospitalizations." In addition to spironolactone, there was also a significant amount of enthusiasm regarding possible benefit of valsartan-sacubitril in HFpEF. The recently published Paragon-HF trial, however, failed to show an overall reduction in mortality and heart failure hospitalization.[193] Among the pre-specific subgroups, there did seem to be a benefit among those with HFmEF and in women, though further studies are necessary to confirm these observations.

In patients with concomitant diabetes and heart failure, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been demonstrated to improve heart failure outcomes.[194–196] The mechanism of impact has not yet been fully elucidated, though it likely includes improvement in filling conditions, changes in LV wall stress, and improved myocardial efficiency.[197,198] As a result of these observations, the US Food and Drug Administration (FDA) has broadened the indication of two of these, empagliflozin and canagliflozin, for use to lower cardiovascular risk in patients with type 2 diabetes and established cardiovascular disease. Additional studies are ongoing evaluating the role of SGLT2 inhibitors in patients with heart failure without diabetes, as there is optimism that this may represent an additional therapeutic pathway among all patients with heart failure regardless of diabetes status.

Anticoagulation with warfarin (Coumadin) in patients with LV dysfunction may reduce morbidity and mortality from cardioembolic events that develop secondary to chamber enlargement and stasis of blood; however, the risks of bleeding need to be considered.[199] Routine anticoagulation in patients with systolic heart failure is generally not recommended.[200, 201] Anticoagulation therapy is likely to be most beneficial for patients with atrial fibrillation or atrial flutter, in patients with severe systolic heart failure who experienced a transient ischemic attack (TIA) or stroke, and in patients in sinus rhythm who were found to have an intracardiac clot in the echocardiogram.

Implantable Cardiac Device Therapy

Patients with systolic heart failure whose ECG shows wide QRS complexes due to LBBB have markedly increased symptomatology, quality of life, and even mortality compared to patients with similar LVEFs but no LBBB.[202] Cardiac resynchronization therapy with implanted biventricular pacemakers has been shown to have a significant beneficial effect on morbidity and mortality in this subgroup of patients with heart failure.[203] ICDs are also increasingly used for primary prevention of sudden death in patients with chronic heart failure whose LVEF remains below 30%–35% despite optimum medical management.[204] Given the challenges of managing volume status in patients with severe CHF (HFrEF, HFmEF, and HFpEF), there has been a great deal of enthusiasm for devices that can detect early changes in cardiac hemodynamics. The CardioMems device is a sensor that is placed in the pulmonary artery percutaneously and has been shown to be effective at detecting early changes in cardiac hemodynamics; when utilized within the context of a robust heart failure clinic, it has been shown to reduce morbidity and mortality associated with CHF.[205]

Advanced Heart Failure Management—Left Ventricular Assist Devices

Left ventricular assist devices (LVADs) are increasingly used to treat end-stage heart failure not only as a bridge to heart transplantation, but also as definitive "destination" therapy.[206] With the most recent generation of LVADs, the 2-year overall survival is ~80%. Full anticoagulation is required for patients with an LVAD to prevent device thrombosis. While overall clinical outcomes with LVADs have improved significantly, bleeding, thromboembolic events, and infectious complications remain important drivers of morbidity in these patients.[207] Despite the technical advances in LVAD design, successful implementation is also dependent upon close monitoring by an experienced heart failure clinic, as well as significant patient and family engagement.

Dental Management Considerations for Patients with Heart Failure

Patients with CHF will often have a history of CAD and they may be on multiple medications and dietary measures to control and balance cardiac function. Anticoagulation with warfarin may reduce morbidity and mortality from cardioembolic events, and the risks of bleeding during and following invasive dental procedures needs to be considered (see subsequent section on anticoagulation and antiplatelet therapy and invasive dental procedures).

Concerning stages of CHF, well-compensated patients need no special modifications for routine dental care.[208,209] However, for patients with decompensated CHF, it is prudent to inquire about the patient's ability to be placed in a supine position, as this may cause shortness of breath. Stressful or prolonged dental procedures put an increased demand on the heart that may exacerbate CHF and result in further inability for ventricles to pump blood. Patients should be questioned about signs of poor compensation, which include paroxysmal nocturnal dyspnea, orthopnea, shortness of breath or dyspnea on exertion, pedal edema, and body weight fluctuations. Appointments should be kept short, and stress reduction and pain control are important for patients who are decompensated.

Cardiac Transplantation

In patients with severe advanced heart failure, heart transplantation remains the treatment of choice in those who are appropriate candidates. The 1-year survival is >90% and the average survival is 13 years.[210] Despite the good outcomes with cardiac transplantation, the increasing numbers of patients with end-stage heart failure coupled with a relatively fixed pool of donors have resulted in a severe mismatch between demand and supply that has significantly hampered implementation of this life-saving therapy.[211] Patients with heart transplants require life-long immunosuppressive therapy. These patients should be closely followed in an advanced heart failure program to monitor for signs of organ rejection, development of transplant-related coronary artery vasculopathy, and other complications from chronic immunosuppressive therapy, such as infectious issues.[212]

Dental Management Considerations for Cardiac Transplantation

Concerns for this patient population are life-long immunosuppression and their current cardiac status. The impact of immune suppression on risks both for and from oral infection, and the risk for infections of the transplant from a bacteremia, are unclear. The focus for immunosuppression is on lymphocytes rather than leukocytes, and lymphocytes have far less to do with suppression of infection due to oral bacterial species than do polymorphonuclear leukocytes. Immunosuppression is maintained at a higher level in the first 3–6 months following transplantation, during which there may be more of a concern for bacteremia from an invasive dental procedure. Tricuspid valve damage can occur as a result of frequent routine surveillance catheter-based endomyocardial biopsies, and these patients are recommended for antibiotic prophylaxis for specific dental procedures (Tables 14-12–14-14).[11] Patients with a heart transplant may be anticoagulated with warfarin, and considerations are similar to those for other anticoagulated patients (see subsequent section on anticoagulation and antiplatelet therapy and invasive dental procedures).

Patients in the precardiac transplant period may have odontogenic infection requiring an invasive and/or stressful dental procedure(s). The first determination is the timing for dental procedures.[213] Patients may be best managed by having dental treatment several weeks following, rather than before, cardiac transplantation, depending on their overall medical status and the nature of the indicated dental treatment. A severely compromised patient in cardiac failure may be at greater risk from stressful dental treatment of any kind before transplantation, in spite of the concern for post-transplant, procedure-related bacteremia in the presence of immunosuppression. Therefore, it is prudent to avoid elective dental treatment with less stable patients. A recent systematic review and dental management guidelines for pre–heart transplant patients failed to show a benefit from pretransplant dental treatment, largely based on a lack of studies on this topic.[214]

These patients should also be observed for oral complications or side effects from medications, such as xerostomia, oral candidiasis (secondary to steroids), and cyclosporine-induced gingival hyperplasia. They may also have orthostatic hypotension as a result of medication or their cardiac condition. If reclined for a procedure, they should be brought to a sitting position in several stages and over several minutes, after which they should sit with their feet on the floor for at least 2 minutes before standing up. Patients may also have urinary urgency during morning appointments in response to a diuretic medication and may want to use the bathroom before the procedure.

ARRHYTHMIA

Definition and Incidence

Typical electrical activation of the heart begins in the right atrium at the sinus node. This initial electrical impulse is

transmitted throughout the atria via specialized tissue until it reaches the atrioventricular (AV) node, which is located in the interatrial septum at the AV junction. The AV node serves as a break signal to allow for atrial systole to complete before ventricular systole ensues. After the physiologic AV delay, the ventricles are activated initially through a unified His-Purkinje system before bifurcating into the right bundle and left bundle. The left bundle splits further into the left anterior and posterior fascicles.

Arrhythmias can be broadly defined as any deviation from the normal cardiac pacemaker and conduction mechanism. Tachyarrhythmias, when the heart rate is >100 bpm, occur as a result of increased automaticity of cardiac pacemaker cells or due to a micro- or macro-reentrant mechanism, where the electrical impulse circulates rapidly in certain areas of the heart. Bradyarrhythmias occur due to sinoatrial node dysfunction or conduction block at any level of the conduction system. Bradyarrhythmias are defined as heart rates of <60 bpm. Both tachyarrhythmias and bradyarrhythmias may be hemodynamically well tolerated in patients with normal cardiac function, or they may result in cardiovascular collapse if cardiac output is significantly compromised.

Bradyarrhythmias

Bradycardias can result from abnormalities at any point in the conduction system and are identified by ECG. While the majority of bradyarrhythmias occur as a result of a degenerative process, they can also occur as a result of severe metabolic derangements, medications, and infections. The most common bradyarrhythmia is sinus bradycardia. This is typically a completely normal rhythm seen commonly in patients who are highly physically active. In the absence of symptoms, no treatment is necessary. Some patients will have an abnormality in the sinus node, termed sinus node dysfunction or sick sinus syndrome, resulting in sinus bradycardia. This is relatively uncommon and occurs in ~0.8 in 1000 patient-years.[215] Sinus node dysfunction may manifest with resting bradycardia or with chronotropic incompetence, whereby patients lack the ability to augment their heart rate with exercise. While the predominant symptoms associated with resting sinus bradycardia are typically dizziness or light-headedness, exertional dyspnea or a decline in exercise capacity may be seen in those with chronotropic incompetence. In minimally or asymptomatic patients with sinus node dysfunction, conservative therapy with avoidance of beta-blockers and non-dihydropyridine calcium-channel blockers is recommended. However, in patients who have symptomatic sinus node dysfunction, implantation of a permanent pacemaker (PPM) is reasonable.[204]

Abnormalities in cardiac conduction below the sinus node represent some degree of AV block. AV block can be further classified into first-degree, second-degree, and third-degree. Third-degree heart block represents a complete lack of communication between the atria and ventricles and is also termed complete heart block. While ventricular activation will still occur as a result of intrinsic pacemaker functions in the ventricular myocytes, this rate is typically quite slow, will not augment with exercise, and is highly likely to lead to cardiac syncope. As a result, implantation of a PPM is indicated for patients with complete heart block without a clear reversible cause.[204]

Identifying the level of conduction block for the remaining types of heart block is key, as block above the level of the AV node (supra-Hisian disease) rarely devolves into complete heart block/syncope, while block below the AV node (infra-Hisian disease) is much higher risk. First-degree and type 1 second-degree AV block are the result of supra-Hisian abnormalities, typically mediated by excessive vagal tone, as can be seen in the setting of good cardiovascular fitness, anesthesia, or obstructive sleep apnea, to name a few. These bradyarrhythmias rarely cause symptoms and their risk for developing into complete heart block is extremely low. In contrast, type 2 second-degree heart block is at high risk for progressing to complete heart block. PPM therapy therefore is typically recommended in these patients as well.[204] Distinguishing between the various bradyarrhythmias is beyond the scope of routine dental practice and interpretation/evaluation should be deferred to either internal medicine or cardiology.

Tachyarrhythmias

Tachyarrhythmias can be physiologic, as is the case with sinus tachycardia in the setting of exercise, infection, or dehydration, or pathologic. Among the pathologic causes, they can be further categorized into supraventricular tachycardias (SVTs) and ventricular tachycardias (VTs).

Supraventricular Tachycardia

Reentrant SVTs such as atrioventricular nodal reentrant tachycardia (AVNRT) occur commonly in the absence of structural heart disease and are usually well tolerated from a hemodynamic standpoint. AVNRT is the most common form, where the AV node is functionally dissociated into two discrete electrical pathways.[216,217] These pathways have different refractory periods and conduction velocities, which are both prerequisites for reentry. AVNRT is usually triggered by a fortuitously timed premature atrial or ventricular impulse, and therefore may be observed in settings where there is increased atrial ectopy due to anxiety or other types of sympathetic stimulation.[218] Interrupting conduction

within the reentrant circuit in the AV node can terminate the tachycardia.[219] This interruption can be achieved with maneuvers that increase vagal tone or use of AV nodal agents such as beta-blockers and/or non-dihydropyridine calcium-channel blockers. In patients who remain symptomatic despite conservative measures, catheter ablation is also reasonable.

Atrioventricular reciprocating tachycardia (AVRT) is another form of reentrant SVT. Unlike AVNRT, however, where the additional pathway is located within the AV node, in AVRT there is an accessory pathway between the atria and the ventricles that is independent of the AV node. The presence of an accessory pathway is characteristic of Wolff–Parkinson–White (WPW) syndrome. An accessory pathway can often be identified on the 12-lead ECG by the presence of a short P-R interval and the slurred onset of the QRS complex (called a delta wave). AVRT results from a reentrant mechanism where the anterograde (atrium to ventricle) conduction is through the normal AV node-His bundle axis, and retrograde conduction from the ventricles to the atria is through the accessory pathway. A less common but more dangerous arrhythmia in WPW syndrome occurs when patients develop atrial fibrillation. Because the accessory pathway cannot filter atrial impulses as well as the AV node, this constellation of atrial fibrillation and WPW can result in excessive ventricular rates and may precipitate ventricular fibrillation. In clinically stable patients, intravenous procainamide can be used; unstable patients must undergo immediate electrical cardioversion.

Atrial tachycardia (AT) is another cause of SVT. ATs occur due to increased automaticity from an atrial focus. These are typically managed conservatively with beta-blockers and/or non-dihydropyridine calcium-channel blockers; however, in refractory cases, catheter ablation is also reasonable. Given the paroxysmal nature of most SVTs, it is rare that the arrhythmia is fully captured on 12-lead ECG and more commonly the SVT is diagnosed on single-lead telemetry. As such, distinguishing between AVNRT, AVRT, and AT is often challenging and invasive electrophysiology study (EPS) is frequently necessary to fully characterize the SVT further. Given that most are typically managed similarly (with the exception of WPW, for which the delta wave is typically present on the resting 12-lead ECG), conservative therapy for most SVTs is preferred, with EPS reserved for medically refractory cases.

Atrial Fibrillation and Atrial Flutter

Atrial fibrillation is the most common sustained dysrhythmia that occurs both with and without structural heart disease (Table 14-15).[220] It represents rapid and chaotic atrial activity with an irregular and rapid ventricular response. In atrial fibrillation, the chaotic atrial activity results in ineffective atrial contraction and in stasis of blood within the left atrium and left atrial appendage. This stasis may lead to thrombus formation and markedly increases the risk of embolic events, including cerebral and peripheral embolization. Patients with MS and mechanical heart valves who also have atrial fibrillation are at highest risk for thromboembolic events. Atrial fibrillation in this setting is termed valvular atrial fibrillation.[221] Atrial fibrillation in all other patients, including those with bioprosthetic valves, AS, and MR, is classified as nonvalvular atrial fibrillation. In patients with nonvalvular atrial fibrillation, yearly thromboembolic stroke can be as high as 15%.[222] Risk factors for stroke in nonvalvular atrial fibrillation include a history of previous TIA or stroke, age above 65, significant hypertension, CHF, diabetes, female sex, and vascular disease (coronary or peripheral), and are reflected in the CHA_2DS_2-Vasc scoring system.[222] Anticoagulation is effective at reducing stroke in patients with atrial fibrillation who are at high risk and is recommended in patients with CHA_2DS_2-Vasc ≥ 2. In nonvalvular atrial fibrillation, anticoagulation with direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban as well as warfarin, is a reasonable option.[223–226] DOACs are at least as effective as warfarin, with equal or less bleeding risk in general. They do not require frequent International Normalized Ratio (INR) monitoring and are not affected by dietary intake or other medications. Cost remains the major barrier for widespread usage, though insurance coverage has improved in recent years. While DOACs are an option for those with nonvalvular atrial

Table 14-15 Etiologies of atrial fibrillation.

Hypertension
Valvular heart disease
Coronary artery disease (including both acute myocardial infarction and ischemic cardiomyopathy)
Congenital heart disease (atrial and ventricular septal defects, Ebstein's anomaly, patent ductus arteriosus, tetralogy of Fallot, etc.)
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Peripartum cardiomyopathy
Pulmonary embolism
Pericardial disease
Primary pulmonary disorders (chronic obstructive pulmonary disease, pulmonary fibrosis, etc.)
Obstructive sleep apnea
Thyrotoxicosis
Autonomic dysfunction
Post-surgical (cardiac and noncardiac surgeries)
Medication induced (theophylline, caffeine, digitalis, etc.)
Familial/genetic
Pheochromocytoma

fibrillation, warfarin remains the recommended treatment option for those with valvular atrial fibrillation.[221]

In many patients with a first episode of atrial fibrillation, the cardiologist will usually try to restore and maintain normal sinus rhythm.[221] In patients who have had atrial fibrillation for more than 48 hours or uncertain duration, cardioversion can be performed, either following at least 3 weeks of adequate anticoagulation (either uninterrupted DOAC use or warfarin at a therapeutic INR), or following a transesophageal echocardiogram that did not reveal a clot in the left atrium or left atrial appendage.[227] Following cardioversion, anticoagulation needs to be continued for at least 4 more weeks, because clots can still form during this period. After the 4-week period, the ongoing requirement for anticoagulation is dictated by the CHA_2DS_2-Vasc score.[221]

In patients with recurrent paroxysmal or persistent atrial fibrillation, there are two treatment options available: rate control and rhythm control. The rate control strategy makes no attempt at restoration or maintenance of sinus rhythm, but simply tries to achieve an asymptomatic or minimally symptomatic condition by controlling the heart rate with beta-blockers, calcium-channel blockers (verapamil, diltiazem), and/or digoxin.[228] In the rhythm control strategies, therapies are aimed to prevent atrial fibrillation from occurring. Several studies have shown an overall similar clinical outcome with rate control and rhythm control, especially in the elderly and in those with a normal EF.[229,230] Younger patients and those with HFrEF may have better outcomes with rhythm control.[230–232]

When a rhythm control strategy is chosen, maintaining sinus rhythm can be attempted with antiarrhythmic drug therapy or with catheter ablation. In experienced centers with contemporary techniques, catheter ablation for atrial fibrillation is probably more effective antiarrhythmic drug therapy and can be performed safely.[233–235] Despite its improved efficacy over pharmacologic therapy, it is rarely curative, as long-term atrial fibrillation recurrence rates are ~50%.[233] While there is no data to suggest a survival advantage to catheter ablation in all-comers, among patients with HFrEF catheter ablation has been demonstrated to reduce mortality and hospitalization.[232] Based on these data, it is reasonable to consider catheter ablation in patients with HFrEF, particularly in symptomatic patients.

Ventricular Tachyarrhythmias

Ventricular tachycardia (VT) and ventricular fibrillation (VF) typically occur in patients with structural heart disease, such as those with CAD, various forms of dilated cardiomyopathy, and HCM. Rarely, VT/VF may occur as an idiopathic event in an individual with a structurally normal heart due to genetic conditions (long QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, etc.) or as a result of QT prolongation from drug effects.

Patients with sustained VT and resuscitated VT/VF require a thorough evaluation for the underlying structural or functional abnormality. Prevention of subsequent episodes may be achieved by treating the underlying cause if reversible. If such a cause is found, patients with structurally normal hearts and a history of clinically stable VT may undergo antiarrhythmic drug therapy trials. Beta-blockers appear to be the safest and most effective class of medications for this indication.[236] Patients who had a hemodynamically unstable VT or resuscitated VF without reversible cause, on the other hand, are typically treated with an ICD.[237] The indications for ICD therapy will be discussed below.

Dental Management Considerations

As discussed above, the spectrum of arrhythmias is broad and encompasses both benign and very severe disorders. Therefore, being familiar with the specific diagnosis is important in the dental assessment. All patients with a known history of arrhythmia should be asked about dizziness, fatigue, chest pain, exercise intolerance, angina, shortness of breath, and awareness of irregular heart beats, as well as medications taken. If the patient has syncope or near syncope, or sustained periods of irregular rhythm, they should be under medical supervision. It is also important to know whether the patient has an implanted device such as a pacemaker or defibrillator (see the next section on Cardiovascular Implantable Electronic Devices).

Premature atrial or ventricular beats and SVTs are common and are generally not of concern. Patients who are being actively treated for these arrhythmias should continue their current therapy and can typically move forward with dental care safely. The majority of patients with atrial fibrillation or atrial flutter will be treated with anticoagulant therapy, for which decisions regarding continuation or cessation should be tailored on a patient-by-patient basis.[238] In general, with the increased use of direct oral anticoagulant therapy, anticoagulation for atrial fibrillation/flutter can be safely stopped for 24–48 hours prior to invasive dental procedures at low risk, though these decisions should always be discussed with the patient's primary care physician or cardiologist. Aside from antithrombotic management, the vast majority of patients with known atrial fibrillation or flutter will be able to undergo dental treatment without further modification of their medical regimens.

Patients with genetic conditions such as long QT or Brugada syndrome are at risk of VT and sudden cardiac death. These conditions can be triggered by emotional stress, auditory stimuli, and medications, including some used for topical anesthesia.[239] Procaine is contraindicated in this population. Providing adequate analgesia during dental care for these patients, however, is very important, and a recent

randomized study has demonstrated that topical lidocaine with or without epinephrine can be safely used even among these very high-risk patients.[16] Despite this evidence that dental care can be provided safely for these patients, given the potential for life-threatening complications, even if rare, these patients may be best managed in a hospital setting where emergency medical services are readily available.[12]

CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES

Implantable Loop Recorders

Implantable loop recorders (ILRs) are implantable cardiac monitors that provide continuous heart rhythm monitoring for up to 3 years. The device is quite small (at the time of publication, the current device is 2.5 g and has dimensions $45 \times 7 \times 4$ mm) and is placed subcutaneously in the left sternal area. The device is placed under sterile conditions and the risk of complication such as infection is exceedingly rare.[240] The most common indications for ILR placement include evaluation of atrial fibrillation burden, recurrent syncope of unknown origin, and evaluation for ventricular arrhythmias in those with known cardiomyopathies and in the workup for cryptogenic stroke. In patients with cryptogenic stroke without a clear etiology, ILRs were seven times more effective than standard of care at identifying atrial fibrillation in these high-risk patients.[241]

Pacemakers

Permanent cardiac pacing is used in a wide variety of cardiac conditions, most commonly symptomatic bradycardia and heart block. Transvenous pacemakers are most commonly used and allow for atrial and ventricular pacing (both single ventricle and biventricular). In transvenous pacemaking systems, electrodes are placed into the venous system and anchored into the heart. The electrodes are then connected to a generator, which is placed subcutaneously. More recently, leadless pacemakers have been developed that are placed transfemorally. The generator and lead are contained within the device, which is inserted into the right ventricle. Leadless pacemakers have been shown to be safer than standard transvenous devices.[242] Despite these advantages, current leadless pacemaking systems do not allow for synchronized atrial-ventricular pacing, which represents a significant limitation of the current generation of leadless pacemakers. Guidelines for the implantation of cardiac pacemakers have been established by the ACC and AHA joint task force on the basis of available evidence in the medical literature.[243]

Implantable Cardiac Defibrillators

As discussed earlier, ICDs are utilized to detect VT/VF and deliver automatic defibrillation if identified. Most ICDs are transvenous and as such are similar to transvenous pacemakers, though the electrode and generators have different capabilities. While all transvenous defibrillators have the capability to provide backup pacing function, the converse is not true. Recently, subcutaneous ICDs have been developed. These devices do not have any endovascular component and are placed underneath the skin in the chest wall. Subcutaneous ICDs are effective at detecting and terminating VT/VF and offer the advantage of a very low infectious risk.[244] Unlike transvenous ICDs, however, subcutaneous ICDs lack the ability to pace. Nevertheless, these devices remain a good option for those at increased infectious risk and/or younger patients who are low risk for developing an indication for PPM. ICDs are indicated in patients who have had sudden cardiac death due to VT/VF without a clear reversible cause, for secondary prevention, and in patients who are at high risk for VT/VF, for primary prevention. Studies have demonstrated that ICDs improve survival in patients with NYHA class II or worse heart failure symptoms and an LVEF <35%, patients with NYHA class I symptoms with an LVEF <30%, and in those with ischemic heart disease, documented evidence of nonsustained VT, and an LVEF <40%.[237,245,246]

Cardiovascular Implantable Electronic Device Infection

Cardiovascular implantable electronic device (CIED) infection represents a major complication associated with both pacemakers and ICDs. The risk of infection with ILRs is very low. Overall, the rate of cardiac device infection is relatively low at 1–2%. Despite these relatively low rates, when it does occur, CIED infection is a lethal disease with a 1-year mortality of 18%–20%.[247] Leadless pacemakers represent an important innovation in PPM therapy and have been shown to have very low infection rates.[248] Subcutaneous ICDs offer the theoretical advantage of infection reduction given that they have no endovascular component; however, data is not yet available confirming this. Patients with established CIED infection are treated with device removal and antibiotic therapy. The decision to reimplant and the timing will depend on the severity of the infection, concomitant valvular involvement, and the primary indication for the device.

Dental Management Considerations

Implanted devices, such as cardiac pacemakers, ICDs, and LVADs, are increasingly important in the management of heart

failure and the prevention of sudden death from arrhythmia. According to current ACHA guidelines, antibiotic prophylaxis is not indicated for patients with pacemakers or other ICDs, unless the patient presents with an odontogenic abscess.[11,154] The exception to this may be LVADs, because, like patients in the AHA "higher-risk" group, these patients are more likely to have a bad outcome if they get infective endocarditis.

The issue of interference of pacemaker function by ultrasonic scalers and electrosurgical units is controversial. This is of particular concern, however, for patients with cardiac channelopathies that can lead to sudden VF and death. Some studies suggest that modern pacemakers are not influenced by any type of dental equipment, including high-speed rotary instruments or ultrasonic devices, and others suggest that these devices do impact pacemakers.[249]

VENOUS THROMBOEMBOLIC DISEASE

Definition and Epidemiology

Venous thromboembolic (VTE) disease comprises both pulmonary embolism (PE) and deep venous thrombosis (DVT). It is a relatively common disease with an incidence of first acute VTE event of 0.7–1.4 in 1000 person-years.[250] The socioeconomic burden of VTE is substantial, with increasing rates of hospitalization for acute VTE and an estimated annual cost for management of VTE in the United States ranging from $13.5 billion to $27.2 billion.[251,252] Despite improvements in outcomes with management of acute VTE, the 1-year mortality after diagnosis remains ~30%.

VTE occurs as the result of thrombus formation in the venous system, in the case of DVT, and subsequent transit of that thrombus into the pulmonary circulation, in the case of PE. The most important distinction in considering the etiology of VTE is whether it occurred in a provoked versus an unprovoked setting. VTE is commonly seen after prolonged immobilization, such as after surgery or lengthy air/car travel or in the presence of certain medications (particularly estrogen-containing hormonal therapies). VTE in this setting is considered to be a provoked event. VTE that does not occur in these settings is considered unprovoked. Risk factors for unprovoked DVT include inherited thrombophilias such as protein C/S deficiency, acquired thrombophilias such as antiphospholipid antibody syndrome, malignancy, prior episode of VTE, age, obesity, and a family history of VTE.

Diagnosis

Patients with DVT typically present with unilateral leg pain and swelling, while those with PE may present with shortness of breath, pleuritic chest pain, and hemoptysis. Tachycardia is very common and in large PEs, syncope and hypotension can also be present. The diagnosis of VTE is made in several steps. Clinical decision-making tools are available to help assess the likelihood of VTE. If VTE is unlikely clinically, laboratory testing with D-dimer is typically performed. D-dimer testing has excellent sensitivity and a negative test is effective at excluding patients with VTE. If the clinical suspicion for VTE is high, imaging rather than D-dimer testing is recommended. If DVT is suspected, vascular ultrasound is the diagnostic modality of choice. If PE is suspected, CTA protocoled to evaluate for PE is recommended.[253] Given the significant increased risk of VTE in the setting of malignancy, it is recommended that all patients with unprovoked VTE undergo appropriate routine cancer screening. More extensive evaluation, however, is not recommended. Targeted hypercoagulability workup in select patients is reasonable, though it should not be reflexively performed in all patients with VTE, as the yield particularly in older patients is quite low.[254]

Management

Anticoagulation is recommended in all patients with VTE. In those patients with provoked events, 3 months of anticoagulation is recommended. In patients with unprovoked VTE, indefinite anticoagulation, assuming the bleeding risk is not high, is recommended. In patients with cancer, anticoagulation is continued for as long as the cancer remains active. For nonmalignancy-related VTE events, use of DOACs is recommended over warfarin.[255] In patients who continue on long-term anticoagulation, there are data to suggest that dose reduction after 1 year provides significant protection against recurrent events at low bleeding rates.[256,257] Management of cancer-related VTE differs slightly. Low molecular weight heparins have been shown to be superior to warfarin in this patient population.[258] There are increasing data on the safety and efficacy of DOACs in cancer and recent guidelines have included DOACs as an option in cancer-related VTE as well.[259–261]

Dental Management Considerations for Anticoagulation and Antiplatelet Therapy and Invasive Dental Procedures

Most patients with a history of VTE can safely have their anticoagulation interrupted if needed for invasive procedures. In addition, given the short half-lives of DOACs, 24 hours of cessation are typically adequate for minor

procedures and 48 hours for major procedures.[262] This is in contrast to warfarin, which due to its mechanism of action can take 3–5 days before the INR returns to normal. In a select group of patients in whom the risk of recurrent VTE is high (within the first 30 days after an acute VTE event, recurrent events despite anticoagulation, or recurrent events while temporarily off anticoagulation), use of low molecular weight heparin as a bridging agent can be considered. While the majority of patients can undergo temporary interruption if necessary, consultation with the patient's cardiologist is recommended.

Many cardiac patients will have impaired hemostasis due to one or more medications, which may dictate modifications in dental management.[249,263] For example, anticoagulant therapy is used to treat and prevent thromboembolism, and different medications are used based on the patient's underlying condition, for example atrial fibrillation or atrial flutter, VHD, prosthetic heart valves, coronary stents, ischemic heart disease, cerebrovascular accidents, PE, and DVT. The major groups of medications used for anticoagulation are drugs with antiplatelet activity and those with antithrombin activity, and more recently DOACs.

The most common antiplatelet drug is low-dose aspirin (81 mg daily), which irreversibly decreases platelet aggregation. For invasive dental procedures, the dose and duration of aspirin may be irrelevant, since one aspirin tablet essentially blocks platelet aggregation for the lifetime of the platelet.[264] This is the basis for the recommendation by some clinicians that aspirin be stopped for 5 days prior to a procedure because the half-life of the platelet is about 10 days, and so about 50% of the platelets should have been regenerated. The same is true for clopidogrel. Although a bleeding time test is often recommended to evaluate a qualitative defect in platelets, this test has not been shown to have a correlation with impaired intraoral hemostasis unless bleeding time is significantly longer than 15–20 minutes.[265–268] Less is known about the risk of oral bleeding following dental procedures in patients taking the newer class of antiplatelet drugs (e.g., clopidogrel), but there is a growing consensus that these antiplatelet drugs should not be stopped for dental procedures.

The longstanding vitamin K antagonist medications are the dicumarols (warfarin), which inhibit the biosynthesis of vitamin K–dependent coagulation proteins (factors II [prothrombin], VII, IX, and X). The full therapeutic effect of warfarin is reached after 48–72 hours and lasts for 36–72 hours if the drug is discontinued. Efficacy of warfarin therapy is monitored by the INR. The desired therapeutic level of the INR is dependent on the underlying medical condition, but is usually kept in the range of 2.0–3.0. In some patients with mechanical prosthetic heart valves, the target INR is higher, frequently from 2.5 to 3.5. Some of these patients may also be on low-dose aspirin. INR values fluctuate in some patients such that a past result may not reflect the INR value in subsequent days. For an accurate assessment, an INR measurement should be performed within several hours of a planned invasive dental procedure.[269]

The vitamin K antagonists are now often replaced by the DOACs (e.g., dabigatran, rivaroxaban, apixaban, and edoxaban). They are being prescribed to larger numbers of patients for several purposes, such as atrial fibrillation and DVT.[255] They have the benefit of avoiding the need for routine INR testing. Little is known about differences in the dental management of patients on DOAC drugs by comparison with warfarin.[270–272] As with warfarin, there is a consensus that the risk to the patient if these drugs are discontinued or reduced for any period of time far exceeds the problem of prolonged oral bleeding.[273,274]

Dental care for patients on anticoagulation therapy has been discussed in numerous dental and medical publications, and various protocols have been suggested.[265,270,275–278] The debate surrounding invasive dental procedures centers on the potential risk for excessive bleeding during or after the procedure if anticoagulation therapy is not adjusted (i.e., lowered) versus the risk of a thromboembolic event if the anticoagulation therapy is altered.[279,280] In the case of warfarin, there is little or no indication for altering anticoagulation therapy before routine oral surgical procedures when the patient's INR is <3.5.[263,281] This conclusion is based on a minimally increased risk of clinically significant intraoral bleeding at this level of anticoagulation and the ease with which most intraoral bleeding can be stopped with local measures, by comparison with the potentially devastating consequences of thromboembolic events (e.g., embolic stroke) if warfarin therapy is reduced or withheld.

The problem of developing a uniform protocol for anticoagulated patients is the ability to quantify risk using parameters that can be applied to the majority of patients.[265,282–284] Several relevant issues need to be considered, including the underlying medical condition requiring anticoagulation therapy, the type of medication(s) used to achieve anticoagulation, the degree of anticoagulation, the timing of dental care, and the cost and inconvenience to the patient. This consideration is also influenced by the timing of the recent thromboembolic event, and patients can be stratified into high, moderate, or low risk of thrombosis.[285]

Data that address the risks of bleeding from invasive dental procedures in patients who take antiplatelet drugs are limited.[266,286] For patients taking aspirin, current thinking is that the risk of clinically significant bleeding from anything other than highly invasive oral surgical procedures is small, and postextraction bleeding is relatively easy to manage. Antiplatelet therapy should not be discontinued for dental

procedures, to include uncomplicated extractions.[263,287–289] This is especially important for patients taking antiplatelet drugs following placement of coronary stents, as it has been reported to result in stent thrombosis.[103] When used in combination, dual antiplatelet therapy may increase the risk for surgical bleeding, and this risk increases further with the addition of warfarin or other oral anticoagulants. Such anticoagulant combinations may be expected in patients who underwent coronary stenting and for those who have atrial fibrillation, atrial flutter, or a history of DVT or PE. In general, the risk for those patients from prolonged oral bleeding following an invasive procedure (e.g., single extraction) is far less than the risk from altering (lowering) the patient's anticoagulation.

Historically, three different protocols have been used to treat patients who require moderately or highly invasive dental procedures and who have an elevated INR. In the first protocol, warfarin is continued without a change in the dose. This approach virtually eliminates the risk of an adverse thromboembolic event. With the second protocol, warfarin therapy is discontinued for about 5 days prior to surgery and then restarted after surgery. It takes an additional 2–3 days after surgery to regain the full therapeutic effect of the medication, during which patients may be in a hypercoagulable state and at increased risk for a thromboembolic event. In the third protocol, used for patients at high risk of thromboembolism, warfarin therapy is discontinued, and the patient is placed on an alternative anticoagulation therapy such as low molecular weight heparin. This protocol has both advantages and disadvantages. The advantage is that the risk for developing a thromboembolic event is theoretically minimized below that of the second protocol. When unfractionated heparin is used for bridging the warfarin-free period, the patient may be admitted to hospital, have their oral anticoagulation (warfarin) therapy discontinued, be administered vitamin K, and be started on parenteral heparin therapy. Heparin is continued until approximately 6 hours before surgery and is reinstituted after surgery in combination with oral anticoagulation therapy until a desirable INR has been reached. This is both a time-consuming and costly protocol that is rarely indicated for dental procedures. The advantages of using heparin are a short half-life of 4–6 hours and the availability of an antidote, protamine sulfate. An alternative to using standard unfractionated heparin is to have the patient self-administer a subcutaneous injection of low molecular weight heparin on an outpatient basis.

Formal guidelines exist for managing intra- and postoperative bleeding and it is not clear whether there is an increased benefit from one protocol over another. Local measures include the use of resorbable gelatin sponge and sutures and tranexamic acid mouthwash.[284]

If the patient has other underlying medical conditions that predispose to impaired hemostasis, such as uremia or liver disease, and/or takes other anticoagulants (e.g., non-aspirin, NSAIDs), the possibility of oral bleeding following invasive procedures likely increases.[263,265,266,276,287,290,291] Little or no data exist to help with decisions concerning invasive dental procedures in patients with multiple coagulopathies. Nevertheless, altering anticoagulation likely proves a greater risk than the risk of clinically significant bleeding. Given fluctuations in INR test results over time for some patients, the concern for systemic disease, and the impact of medications (e.g., NSAIDs and aspirin), there is increased concern for invasive procedures. There may need to be medical (e.g., hematology, cardiology) consultation beforehand.

Caution should be used with the prescription of antibiotics for patients on warfarin, as they may interfere with the role of intestinal bacteria in vitamin K homeostasis.[285] Concerns also exist for drug toxicity from the use of azole antifungals. Additionally, anticonvulsants (e.g., carbamazepine) may have severe pharmacokinetic interactions. Some dietary changes may alter vitamin K consumption. INR testing may be indicated to identify these alterations in anticoagulation. The DOACs do not have most of these considerations. However, clarithromycin and azole antifungals, as well as carbamazepine, are a concern and medical advice should be sought before their use.[285]

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15

Diseases of the Gastrointestinal Tract

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This chapter aims to review diseases affecting the gastrointestinal tract, with an emphasis on the medical aspects, the oral healthcare professional's (OHCPs) role in screening for undiagnosed conditions, and their role in monitoring patient compliance with recommended medical therapy for gastrointestinal conditions that are likely to be encountered in practice of dentistry. OHCPs are expected to recognize, diagnose, and treat oral conditions associated with gastrointestinal disease, as well as provide dental care for these individuals. To provide safe and appropriate oral care, OHCPs are expected to be able to correctly diagnose oral manifestations of gastrointestinal disorders and their possible implications for homeostasis, risk of infection, drug actions and interactions, as well as any impact on the patient's ability to withstand the stress and trauma of dental intervention and, when necessary, arrange an appropriate medical referral. These management issues are discussed, where appropriate, for each gastrointestinal disorder.

Both OHCPs and gastroenterologists have a primary focus within the gut. While embryologically the oral cavity originates from the ectoderm layer and the gastrointestinal tract from the endoderm layer and they are initially separated by the buccopharyngeal membrane, they share a common function. This commonality is illustrated by the finding of a heterotopic gastric mucosal cyst in the oral mucous membranes or on the tongue.[1] However, in addition to these relatively rare anomalies, gastroenterologists and OHCPs often share mutual patients.

The digestive tract is a long muscular tube that moves food and accumulated secretions from the mouth to the anus. As ingested food is slowly propelled through this tract, the gut assimilates calories and nutrients that are essential for the establishment and maintenance of normal bodily functions. Protein, fats, carbohydrates, vitamins, minerals, water, and orally ingested drugs (prescription and nonprescription) are digested in this tract. This digestive process depends on the hydrolysis of large nonabsorbable molecules into smaller absorbable molecules through secreted enzymes and the absorption of substances through the epithelial lining of the digestive tract. From

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there, digested substances are transported by blood vessels and lymphatic channels through the body. The remaining contents of undigested food, typically cellulose fiber, are excreted out of the digestive tract through the rectum and anus. The digestion and absorption of nutrient materials depend on (1) an optimal hydrogen ion concentration (pH) in the gut; (2) the presence of conjugated bile salts; (3) adequate concentrations of enzymes to split fats, proteins, and carbohydrates; (4) adequate intestinal mobility; and (5) a normal gut microbiome.

Some of the foods entering the blood from the digestive tract can be used unaltered by cells. However, the majority of the absorbed food passes to specific organs, such as the liver, where it undergoes intermediate metabolism to prepare it for use by cells. The gastrointestinal tract is also a primary route for drug administration, absorption, biotransformation, detoxification, and excretion. Many dental patients require drug therapy in which pharmacokinetic parameters may be altered by gastrointestinal and hepatobiliary dysfunction. OHCPs therefore require a clear understanding of the gastrointestinal system and how normal and abnormal function may affect the oral health and care of patients.

Digestion normally begins within the oral cavity, where ingested material is moistened with saliva, masticated, formed into a bolus, and swallowed by the coordinated muscular function of the tongue, pharynx, and epiglottis. The digestive system comprises the esophagus, stomach, small intestine, and large intestine. Each of these components, assisted by the exocrine functions of the salivary glands, pancreas, liver, and gallbladder, performs specific functions as ingested substances pass through it, enabling assimilation of dietary calories and nutrients.

This chapter is organized under the following anatomic divisions: esophagus, stomach, small intestine, large intestine, and hepatobiliary tree. A final section addresses gastrointestinal syndromes that can affect both the oral cavity and the gastrointestinal tract, but are not primarily of oral or gastrointestinal etiology.

DISEASES OF THE UPPER DIGESTIVE TRACT

Gastroesophageal Reflux Disease

Medical Aspects

A distinction needs to be made between gastroesophageal reflux (GER) and reflux leading to symptoms or disease (GERD). GER can be a physiologic phenomenon that occurs in asymptomatic individuals. In contrast, GERD is defined as a condition in which reflux leads to "troublesome symptoms and/or complications."[2] Patients may experience mild symptoms with an esophagus that appears to be clinically normal, or they may have severe symptoms with surface abnormalities that can be detected with an endoscope. The process by which GER leads to GERD consists of a sequence of events spanning the esophagogastric junction, the esophageal body, and the central nervous system.

GERD is one of the most commonly occurring upper gastrointestinal tract conditions with up to 10% of the population experiencing symptoms daily. There is no gender difference in a condition that can have a significant effect on daily activities.

"Heartburn" is the cardinal symptom of GERD and is defined as a sensation of burning or heat that spreads upward from the epigastrium to the neck.[3] Although symptoms of GERD are variable, they primarily arise in relation to mucosal injury, for example esophagitis, esophageal ulceration, stricture, and dysplasia. Other symptoms include chest pain, which due to its similarity to that arising from an acute cardiovascular event may prompt the patient to seek medical advice and dysphagia.

Airway problems such as laryngitis, chronic cough, hoarseness, and asthma may arise as a result of microaspiration of refluxate into the airway.[4,5] This constellation of symptoms is known as laryngopharyngeal reflux (LPR) or extraesophageal reflux disease (EERD). However, these symptoms may also arise from disorders of the upper or lower respiratory tracts.

GORD complications include premalignant and malignant conditions of the esophagus. Barrett's esophagus is a variant of GERD in which normal squamous epithelium is replaced by columnar epithelium.[6] Patients with this phenomenon show an increased incidence of adenocarcinoma. This condition may increase the incidence of carcinoma by as much as 10%,[7] although the majority of patients with Barrett's esophagus die from unrelated causes.[8,9] The major reason to evaluate patients with chronic symptoms of GERD is to recognize Barrett's esophagus. Endoscopic screening is recommended for patients with multiple risk factors for cancer in Barrett's esophagus, including chronic GERD, hiatal hernia, advanced age, male sex, white race, cigarette smoking, and obesity with an intra-abdominal body fat distribution. During the last decade, new techniques have been introduced for diagnosis of GERD and Barret's esophagus.[10]

The relaxation of the lower esophageal sphincter for the purpose of relieving pressure in the stomach (from gas and the ingestion of food) is called the "burp" mechanism. This phenomenon is a physiologic process and only occurs when a person is in an erect posture; gastric contents are thereby prevented from flowing into the esophagus and possibly being aspirated. The gastroesophageal junction prevents regurgitation (retrograde or upward flow) of gastric contents and is composed of an internal lower esophageal sphincter. External pressure on the junction by the diaphragm also assists in this

function. When this barrier fails, gastric contents may make their way into the esophagus and cause symptoms. The cause of lower esophageal sphincter incompetence, while not mechanical, remains unclear. However, surgery, scleroderma, and drugs, including anticholinergics, cardiac vasoconstrictors, nicotine, and estrogen-progesterone combinations used in contraceptives, can cause an incompetent sphincter, as may also happen during pregnancy.

Symptoms occur when refluxate proceeds through the junction. The severity of the symptoms depends on the amount of acid in the refluxate, the speed with which the esophagus can clear the refluxate, and the presence of buffering agents, such as swallowed saliva. An insufficient amount of alkaline fluid prohibits the esophagus from properly buffering the acid that has moved up from the stomach. Patients who smoke tobacco, take certain drugs, have had high-dose head and neck radiotherapy, or suffer from diseases such as Sjögren's syndrome may not produce sufficient saliva to protect the esophagus from the acid in the refluxate. Increased abdominal pressure as a result of obesity, pregnancy, or a large meal may predispose patients to gastric content reflux. Moving into or out of various positions, for instance lying down too soon, especially after eating, will also promote reflux.

Medical Management

Lifestyle modification is often effective, with weight loss having a dose-dependent association with symptom reduction: a 3.5 kg/m^2 reduction in the body mass index can achieve nearly a 40% reduction in the risk of having frequent symptoms. Other lifestyle modifications include elevation of the head of the bed and avoidance of meals 2–3 hours before bedtime, if there are nocturnal symptoms. Patients should also avoid foods that specifically trigger their symptoms. Tobacco and alcohol cessation, while often recommended, has not been shown to improve symptoms overall. Drugs with anticholinergic or smooth muscle–relaxing properties may exacerbate reflux symptoms, as may those causing a chemical esophagitis, such as oral bisphosphonates.

If symptoms persist, the addition of acid suppression therapy, in the form of H_2 receptor antagonists, may improve or eliminate the symptoms of "heartburn" and regurgitation and heal mild to moderate esophagitis. However, proton pump inhibitors (PPIs) such as omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole (available by prescription), which block the final common pathway of acid secretion by irreversibly binding to and inactivating the proton pump (H+/K+-ATPase exchange) are commonly used. These are more effective in reducing symptoms and in healing erosive esophagitis than H_2 receptor antagonists ($84\% \pm 11\%$ vs. $52\% \pm 17\%$).[11] Daily PPI treatment provides the best long-term reduction of symptoms for patients with moderate to severe esophagitis.

Surgical intervention is generally reserved for those patients unresponsive to maximal medical therapy or unable to tolerate treatment. Laparoscopic fundoplication is the most common procedure and is highly effective in well-selected patients. Fundoplication involves construction of a cuff of gastric (fundus) tissue around the lower esophageal sphincter junction.[12] This improves function via a variety of mechanical factors and also modifies the reflexes involved in the pathophysiology. The strongest predictors of success include abnormal 24-hour pH scores, classic symptoms of GERD, and a positive PPI trial.[13] Gastric bypass surgery and laparoscopic gastric banding decrease GERD symptoms primarily through the resulting weight loss.[14]

Oral Health Considerations

Patients who experience GERD may complain of extraesophageal symptoms including laryngitis, asthma, cough, chest pain, dental erosion, dysgeusia (foul taste), halitosis, tongue sensitivity, burning sensations, dental sensitivity related to hot or cold stimuli, and/or pulpitis.[15]

Oral mucosal changes are minimal; however, erythema and mucosal atrophy may be present as a result of chronic exposure of tissues to acid. Noncarious tooth surface loss (NCTSL), comprising erosion, attrition, and abrasion, is multifactorial and it is rarely possible to identify a single etiology in a specific patient.[16] Factors that determine whether an individual with GERD will or will not develop dental erosion have not been clearly identified and the strength and prevalence of the association are highly variable.[17] However, a significantly lower oral pH was found in patients with GERD and bulimia nervosa as compared to healthy individuals.[18] The chemical dissolution of enamel (erosion) may lead to exposed dentin and resultant thermal sensitivity or, if severe, irreversible pulpal (nerve) damage necessitating root canal therapy. The rate of progression and severity of erosion may be exacerbated by associated attrition and abrasion, inadequate oral hygiene, poor or reduced salivary flow, consumption of acidic beverages or foods, occupation, alcoholism, and eating disorders. OHCPs should therefore closely examine their patients for evidence of NCTSL and instigate appropriate prevention and treatment. In particular, patients with erosion on the palatal and lingual surfaces should be questioned for a history of GERD, with a view to onward referral to their primary care physician if appropriate. Dental management should be tailored to the extent and rate of progression of the condition and any associated symptoms, and include early dietary and preventive advice, and topical fluoride applications to ensure optimal dental mineralization and reduction of thermal sensitivity. The restoration of lost tooth structure will provide symptomatic relief as well as enhancing function and esthetics and help to minimize further hard tissue damage.

The medical management of GERD may impact on dental care. Many of the listed potential drug interactions, for example cimetidine and H_2 receptor antagonists with local anesthetic agents, are either theoretical and may not have been seen in dental practice, or are relevant to much higher doses used for different indications. Reports of serious drug interactions associated with currently recommended doses of local anesthetics and vasoconstrictors in the dental setting are exceedingly rare.[19] Similarly, while H_2 receptor antagonists and PPIs may be associated with a degree of xerostomia, this is not usually clinically significant. Likewise, although H_2 receptor antagonists may cause central nervous system effects, from fatigue and lethargy to confusion, delirium, and seizures, these effects are dose dependent and are rarely problematic. As cimetidine inhibits the absorption and therefore the blood concentration of azole antifungal drugs such as ketaconazole (via inhibition of the cytochrome P-450 3A4 [CYP3A4] enzyme system), topical antifungal therapy should be considered in the first instance. Finally, soft tissue changes such as esophageal stricture and fibrosis may complicate intubation if the patient requires general anesthesia for dental treatment.

Hiatal Hernia

Medical Aspects

The esophagus passes through the diaphragmatic hiatus and into the stomach just inferior to the diaphragm. The hiatus causes an anatomic narrowing of the opening into the stomach, which helps prevent reflux of stomach contents into the esophagus. Some patients have a weakened or enlarged hiatus, possibly due to hereditary factors. It may also be caused by increased intra-abdominal pressure, for instance from obesity, or chronic straining when passing stools. When a weakened or enlarged hiatus occurs, a portion of the stomach herniates into the chest cavity through this enlarged hole, resulting in a hiatal hernia.[20] Hiatal hernias are quite common; occurrence rates are between 20% and 60%.[20] The incidence of hiatal hernia increases with age, although the condition is also seen in infants and children. As the diaphragm separates the thorax from the abdomen, symptoms of hiatal hernia often include chest pain, which may mimic those of myocardial infarction. If the hiatal hernia is small, there may be no symptoms, while if the area of the hiatus is very weak, there may be entry of acidic digestive juices into the esophagus.[20]

Hiatal hernias are classified into one of four types (I, II, III, and IV) based on the location of the gastroesophageal junction in relation to the pillars of the crura.[20] A type I hernia is the classic "sliding" form and the most common. In this type, the herniated portion of the stomach slides back and forth through the diaphragm into the chest. These hernias are normally small and often present with minimal (if any) symptoms. The remaining three types are true paraesophageal hernias and account for only 5%–15% of all hiatal hernias.[20] The common feature of these is herniation of the stomach into the thoracic cavity, due to laxity of the gastrosplenic and gastrocolic ligaments in addition to crural deformation.[20] Complications associated with these hernias include obstruction, volvulus, and ischemia.

Infants with hiatal hernia usually regurgitate bloodstained food and may also have difficulty in breathing and swallowing. Adult patients with hiatal hernia may experience chronic acid reflux into the esophagus, with its associated symptoms. Chronic gastroesophageal reflux can erode the esophageal lining, causing bleeding, which may lead to anemia or cause inflammation and scarring, leading to esophageal narrowing. This narrowing may impair the passage of food into the stomach, resulting in dysphagia and an uncomfortable feeling of fullness or "bloating." In contrast to abdominal hernias, hiatal hernias have no outward physical signs and are usually discovered on endoscopy, manometry, or other radiographic studies investigating GERD or other upper gastrointestinal complaints.[20]

Medical Management

Defects present at birth may sometimes correct themselves. Until this occurs, however, the infant should sleep in a crib with the head raised and be given an altered diet consisting of food that has a thicker than normal consistency. In adults the management is similar to that of GERD, for example weight loss, antacids, elevation of the head of the bed, and avoidance of meals 2–3 hours before bedtime (if there are nocturnal symptoms), as well as avoidance of foods that trigger symptoms and H_2 receptor antagonists.

Lifestyle modification and drug therapy usually allow patients to minimize the symptoms of hiatal hernia without significant inconvenience and form the preferred management.[21] When conservative measures fail to control the condition, laparoscopic[22] or open surgical correction, which may be complex, can be considered.

Oral Health Considerations

If a hiatal hernia is associated with reflux into the oral cavity, those oral manifestations seen in GERD may be present. While medical intervention may include xerostomic medication, it is rarely clinically significant.

Disorders of the Stomach

The stomach acts as a reservoir and secretes hydrochloric acid, mucus, pepsinogen, and intrinsic factor. The secreted hydrochloric acid is responsible for killing swallowed organisms, while the mucus helps coat and lubricate the stomach's lining epithelium in order to assist propulsion of the ingested contents through the digestive system.

Pepsinogen, a proteolytic enzyme, helps digest protein, and intrinsic factor, a glycoprotein, facilitates the absorption of dietary vitamin B_{12}. The stomach's role as a reservoir enables the semifluid chyme, consisting of partially digested food, to be released into the duodenum over a period of time.

Peptic Ulcer Disease

Peptic ulcer disease (PUD), often termed "stomach ulcers," is a common benign (nonmalignant) ulceration of the epithelial lining of the stomach (gastric ulcer) or duodenum (duodenal ulcer). PUD is most commonly associated with *Helicobacter pylori* and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin; in populations without these risk factors, the incidence of PUD is very low.[23] In the United States, PUD has a significant negative effect on patients' quality of life, activity, and overall work productivity. As PUD includes both gastric and duodenal ulcers, a general discussion of peptic ulcer disease is presented first, followed by specific information on gastric and duodenal ulcers, under the corresponding anatomic region.

PUD accounts for approximately 500,000 new cases and 4,000,000 recurrences each year in the United States, responsible for 2.7 million physician office visits[24] and a total estimated annual treatment cost of $3.1 billion.[25] Beginning in the 1970s, the frequency of inpatient and ambulatory care for PUD declined by 51%, and by a further 68% between 1993 and 2005.[25] However, the increasing geriatric population, coupled with the growing use of NSAIDs, will contribute to the rising costs of this disease.

The lifetime prevalence of peptic ulcers ranges from 11% to 14% for men and 8% to 11% for women. The 1-year point prevalence of active gastric and duodenal ulcers in the United States is about 1.8%.[26] Genetic factors appear to play a role in the pathogenesis of peptic ulcers, with the concordance among identical twins approximately 50%. In first-degree relatives of sufferers, the lifetime prevalence is roughly threefold greater than that in the general population.[26]

Gastric ulcers primarily result from altered mucosal defenses, whereas duodenal ulcers are associated with increased acid production. *H. pylori* plays a pivotal role in peptic ulcer development at both sites. A complex relationship exists between host defense mechanisms, the presence of elevated acid, pepsin levels, and *H. pylori*. Chronic *H. pylori* infection affects approximately half of the world's population and is typically acquired early in life, especially among those in lower socioeconomic groups.[27] Although *H. pylori* infection results in chronic inflammation of the underlying gastric mucosa, most infected patients do not experience any clinically significant symptoms.

The incidence of duodenal ulcers is increased in cigarette smokers, patients with chronic renal disease, and alcoholics. *H. pylori* is observed in the mucosa in duodenal ulcers (90%–100%) and gastric ulcers (70%–90%). The proposal that bacteria play a significant role in PUD is supported by its usual resolution with targeted antimicrobial treatment and elimination of the bacterium.[28]

Many patients with duodenal ulcers have demonstrable hyperacidity, and it is thought that this is the dominant factor in the development of ulcer disease. Concomitant inflammation and chronic infection with *H. pylori* are noted in the non-acid-secreting gastric antrum causing increased gastrin release, which in turn induces excess acid secretion from the fundic mucosa and damage and ulceration of the duodenal mucosa.[27] In gastric ulcers, however, the relative importance of the two major factors of acid amounts and mucosal resistance is reversed. Typically, the concentration of gastric acid is normal or reduced, and prior injury (mucosal) from other causes appears to be a prerequisite for the development of gastric ulcers.

Most patients with PUD have recurrent pain requiring intervention and 10%–20% suffer a life-threatening complication (e.g., hemorrhage, perforation, or obstruction).[29] Overall around 6% of the patients attending an OHCP will have a peptic ulcer and it is important that the OHCP (1) recognizes the symptoms associated with undiagnosed or poorly managed PUD and its associated morbidity and (2) makes an appropriate referral when these symptoms present.

Medical Aspects

The incidence of gastric ulcers is one-tenth to one-fourth that of duodenal ulcers. Gastric ulcers are more common in lower socioeconomic groups and in those over 50 years of age, and are seen at a male to female ratio of 3:1. Gastric ulcers are of more concern, as approximately 3%–8% represent malignant ulceration of the gastric mucosa.[29] Similarly, gastric ulcers with *H. pylori* infection have an increased risk of mucosa-associated lymphoid tissue (MALT) lymphomas, which in the early stages may go into remission after antibiotic eradication of the bacteria.[30]

Accurate diagnosis, in both cases, involves endoscopy to obtain multiple biopsies and brush specimens for cytologic examination. In gastric ulcers, gastric acidity levels are additionally taken to establish the presence or absence of histamine-fast achlorhydria, as it is associated with a very high chance of malignancy.

Patients with gastric ulcers often present with epigastric pain radiating to the back which, unlike the pain of duodenal ulcers, is aggravated by food. The management of gastric ulcers involves antacid compounds, antibiotics to eradicate *H. pylori*, H_2-blocking agents, and other protective drugs. Follow-up studies to confirm healing are essential. Additional information about PUD and its implications for oral healthcare is presented in the following section on duodenal ulcers.

Disorders of the Small Intestines

The small intestine comprises the duodenum, jejunum, and ileum. The duodenum is the principal site of digestion and absorption. When chyme enters the duodenum, it stimulates the pancreas to secrete sodium bicarbonate (to neutralize the gastric acid) and digestive enzymes for normal digestion of food, and the gallbladder to discharge stored bile through the common bile duct. Vitamin B_{12} in the presence of intrinsic factor is absorbed in the distal small intestine (ileum), while the bile acids that promote fat absorption in the duodenum are themselves reabsorbed in the small bowel, returned to the liver, and re-secreted into the bile. The motor activity of the small intestine propels the chyme forward to the large intestine, whose major role is to receive the ileal effluent, absorb most of the water and salt, and thus produce solid feces.

Duodenal Ulcer Disease

Medical Aspects

A duodenal ulcer represents a break through the mucosa into the submucosa or deeper, the base of which is necrotic tissue consisting of pus and fibrin. Continued erosion may lead to hemorrhage from associated vessels, involvement of adjacent organs, or perforation into the peritoneal cavity. When conditions are favorable, the ulcer heals, with granulation tissue and new epithelium. However, chronic ulceration is associated with scar tissue formation and possible deformity.

The incidence of duodenal ulcer is thought to be declining, but it is still a common disorder, developing in about 10% of the US population. Of all peptic ulcers, 80%–85% are duodenal, and duodenal ulcers occur at a male to female ratio of 4:1. The most common primary cause is *H. pylori* infection, but NSAID use can also be an associated etiologic factor. Less commonly, factors such as stress, exogenous glucocorticosteroids, parathyroid disease, malignant carcinoid, cirrhosis, gastrinoma of the pancreas (Zollinger–Ellison disease), polycythemia vera, and chronic lung disease have been associated with duodenal ulcers.[27] The ulceration, which is often recurrent, is usually located in the first part of the duodenum, because the acidic chyme ordinarily becomes alkaline after pancreatic secretions enter the intestines in the second part of the duodenum.

The most common symptom of an uncomplicated ulcer is epigastric pain, frequently perceived as a burning or gnawing sensation, sometimes associated with nausea and vomiting. This usually occurs when the stomach is empty or when not enough of a meal remains in the stomach to adequately buffer the acid stimulated by the meal. The pain is characteristically relieved within a few minutes by buffering or diluting the gastric acid with ingestion of an antacid, milk, or food. When an ulcer perforates and hemorrhages, the patient often vomits gross blood, which on interacting with acid can appear as coffee grounds. Bleeds can also be associated with black or tar-like stools, or these may sometimes contain gross blood. Repeated blood loss can lead to iron-deficiency anemia, while acute, severe blood loss may cause the patient to feel weak, lightheaded, or short of breath.

The early diagnostic cues for duodenal ulcers lie in the history of a periodic pain pattern: duodenal ulcers usually feel better postprandially, while the pain of gastric ulcers is frequently exacerbated by meals. Physical examination is often unremarkable and the mainstay of the diagnosis is an upper gastrointestinal radiologic examination (barium swallow), which will demonstrate the presence of an ulcer in up to 85% of patients, or endoscopy. Endoscopy has a greater sensitivity and offers the opportunity for a biopsy if malignancy or the presence of *H. pylori* is suspected.[31]

Zollinger–Ellison syndrome can cause multiple ulcers and debilitating diarrhea. It is caused by a pancreatic gastrinoma that secretes gastrin, a potent acid producer, and the diagnosis is made on the basis of extremely high levels of gastric acid and elevated levels of serum gastrin.[32] The usual investigations include a full blood count to detect anemia and leukocytosis, an examination of the stool for occult blood, and a serum calcium test to investigate the possibility of an associated hyperparathyroidism or endocrine tumors.

Medical Management

In the absence of complications such as massive bleeding, obstruction due to scarring, or perforation, medical rather than surgical treatment is preferred. Conservative measures include antacids and avoidance of foods that cause discomfort and of substances and drugs that have potent acidogenic properties, including alcohol, tobacco, aspirin, and NSAIDs. If NSAIDs cannot be avoided, the patient should also be treated with misoprostol. Attempts to eradicate *H. pylori* are necessary in all patients with a peptic ulcer in which the organism can be demonstrated. Bismuth, metronidazole, amoxicillin, and tetracycline have been shown to be effective.[31] In addition to elimination of *H. pylori*, medical treatment may include the following six other classes of drugs: (1) sedatives to reduce mental stress if anxiety is thought to be etiologic; (2) antacids to neutralize acid; (3) drugs that act by covering and protecting the ulcer; (4) anticholinergic drugs to decrease the production of acid by the gastric mucosa; (5) histamine H_2 receptor antagonists (cimetidine, famotidine, nizatidine, or ranitidine), which block the action of histamine on the gastric parietal cells, thus reducing food-stimulated acid secretion up to 75%; and (6) omeprazole, which also suppresses gastric acid secretion but has a different mechanism of action from that of anticholinergics or H_2

receptor antagonists. Anticholinergics are sometimes prescribed, particularly for reducing acid production at night. However, limited effectiveness and side effects such as oral dryness make anticholinergics less attractive than histamine H_2 receptor antagonists. In most patients, the pain is controlled within 1 week, and most ulcers heal by the sixth week. Intractable symptoms or complicated duodenal ulcers may require surgery.[32]

Oral Health Considerations

If a patient presents with symptoms of epigastric pain, as described previously, the OHCP should refer them to the primary care physician. Oral manifestations of PUD are rare, but may occur in relation to severe anemia from repeated gastrointestinal bleeding. In this case there may be new or worsening recurrent oral ulceration, depapillation, and soreness of the dorsum of the tongue due to loss of the filiform papillae. Such patients should be referred to an appropriate clinician to establish their hematologic parameters and correct any deficiency that may delay wound healing or otherwise complicate surgical procedures or anesthesia. Anemia also predisposes to oral candidosis, which may cause mucosal or tongue soreness, particularly in denture wearers. Exceptionally, dental erosion of the palatal aspect of the maxillary teeth due to persistent regurgitation of gastric acid as a result of pyloric stenosis has been reported. Vascular malformations of the lip have also been reported and range from a very small macule to a large venous pool.[33,34]

H. pylori has been isolated from dental plaque[35] and its eradication has been reported to reduce the frequency and severity of recurrent aphthous stomatitis (RAS) in patients who tested positive.[36]

OHCPs should avoid administering drugs that exacerbate ulceration and cause gastrointestinal distress, such as aspirin and other NSAIDs where possible. Similarly, exogenous corticosteroid administration may promote or exacerbate PUD via its action on the mucus layer. Corticosteroid therapy should therefore be minimized and appropriate prophylaxis provided to minimize the risk. Similarly, as many antacids contain calcium, magnesium, and aluminum salts that bind antibiotics, for instance erythromycin and tetracycline, patients should be advised to take their antibiotics 1 hour before or 2 hours after their antacids to avoid a significant (75%–85%) reduction in antibiotic absorption.

Hyposalivation and dry mouth (xerostomia) may occur in patients taking anticholinergic drugs. This is most likely to present in those patients who wear either complete or partial acrylic dentures. While denture adhesives and artificial saliva may aid in the retention of their dental prostheses, the reduced salivary flow predisposes them to an increased risk of oral candidosis. Dentate patients are at increased risk of dental caries, particularly affecting cervical margins and exposed root surfaces, if the hyposalivation is prolonged or if they place sugar-containing foods into the mouth in an effort to stimulate saliva flow. In these cases, appropriate preventive measures should be instituted. If the patient specifically complains of dry mouth, it may be possible to alter the specific drug type or dosage in consultation with the patient's physician. Commonly used sialagogues, such as pilocarpine or cevimeline, may be contraindicated due to their parasympathomimetic action.

Cimetidine and ranitidine, which are commonly prescribed for duodenal ulcer patients, have occasionally been associated with thrombocytopenia and may compete with antibiotics or antifungal medications.[19]

DISEASES OF THE LOWER DIGESTIVE TRACT

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) consists of two not entirely discrete conditions: Crohn's disease (CD) and ulcerative colitis (UC). The etiopathogenesis of IBD involves an immune-mediated inflammatory response, in genetically susceptible individuals, to an unknown environmental trigger, that interacts with the gut microbiome and primarily affects the gut.[37,38]

The genetic influence on IBD is well recognized. Twins studies demonstrate increased concordance for both CD and UC,[39] while first-degree relatives have a fivefold increase in the risk of developing IBD.[40] Genome-wide association studies supports a polygenic process, with 41 CD-specific and 30 UC-specific genetic polymorphisms identified as well as 137 associated with both conditions.[41]

The host-adaptive immune response is also involved with amplified T cell–mediated responses in both conditions. In CD this is via a T-helper (Th) 1 and Th17 response, which increases inflammation via interleukin (IL)-17, interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α). In UC, the response is Th2 mediated, activating B cells and natural killer T cells, via IL-5 and IL-13.[40]

The intestinal barrier is intimately involved with host innate immunity and its disruption has been shown to lead to IBD in animal models.[42] Genetic susceptibility is a key feature in the development of IBD and cell defects, often related to gene abnormalities in NOD2, linked with the development of CD.[43] Environmental factors are also important, with diets high in saturated fat and processed meats and disturbance of the host microbiome, for instance from antibiotics, increasing the risk of IBD,[40] while high-fiber diets decrease the risk of CD.

IBD is frequently associated with extraintestinal manifestations, including a wide range of oral lesions.[44] The orofacial presentation includes cervical lymphadenopathy, lip swelling, angular cheilitis, oral ulceration, mucosal tags, cobblestone appearance of the oral mucosa, full-thickness gingivitis, submandibular duct "staghorning," fibrous banding, and oral ulceration,[45,46] as well as the rarer pyostomatitis vegetans.[47] The oral manifestations of IBD may precede the onset of intestinal radiographic lesions by as much as 1 year or more.[48] Both diseases are of interest to the dentist because of their associated oral findings, the potential overlap in presentation with that of orofacial granulomatosis (OFG),[44] which may occur separately or in association with CD,[45] and the impact of their medical management on dental care.

There is significant variation in the incidence and prevalence of CD and UC around the world.[37,38] The current data, for North America, for these and other parameters are summarized in Table 15-1.

IBD is most common in Western countries, particularly those in northern Europe and North America. There is no gender preference for either condition and the apparent ethnic differences reported in African Americans are due to social and economic inequalities rather than biologic or genetic differences.[54] IBD is, however, more common among Ashkenazi Jews than among the Sephardim and the general population. The prevalence in Israel is between 17 and 80 per 100,000 among the Ashkenazi versus 19 and 55 per 100,000 among the Sephardim.[55] As countries industrialize, their incidence of IBD increases. Similarly, those who live in urban centers are also more likely to be afflicted than those living in a rural setting.

Ulcerative Colitis

Medical Aspects

The inflammation in UC most commonly affects the rectum, but can spread to affect more proximal parts of the colon.[56] Macroscopically, the mucosa may have a granular appearance if the disease is mild, while stripping of the mucosa, with areas of sloughing, ulceration, and bleeding, may be seen when more severe. As the superficial mucosal lesions enlarge, they may be perpetuated by secondary bacterial invasion.[23–32]

Patients usually complain of cramping abdominal pain that is worse prior to a bowel movement, which is associated with rectal bleeding and bloody diarrhea. The frequency and volume of blood present give an indication of the activity of the condition. Typically patients will pass 5–8 movements in a 24-hour period, including at night.[23–32] Extraintestinal manifestations present and include erythema nodosum, characterized by red swollen nodules that are usually on the thighs and legs; ocular changes such as episcleritis, uveitis, corneal ulcers, and retinitis; and joint symptoms usually affecting the ankles, knees, and wrists.[23–32] Severe oral ulceration may be seen secondary to ulcerative colitis (Figure 15.1). A microcytic, hypochromic anemia may result from blood loss, while leukocytosis occurs in active disease, as may electrolyte imbalances, hypoalbuminemia, and low serum magnesium and potassium levels with severe diarrhea.[23–32]

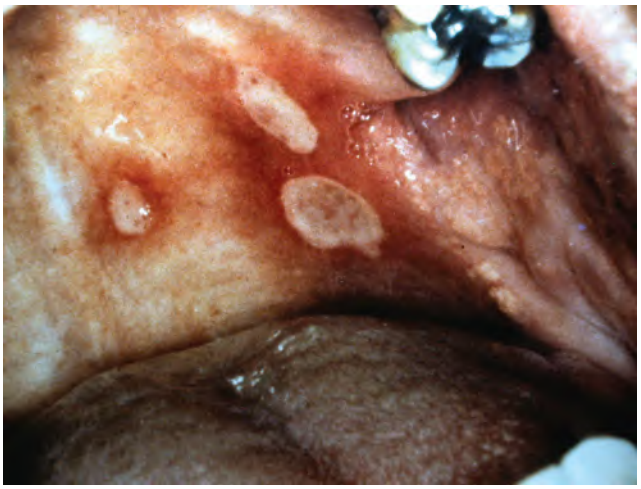

Figure 15-1 Large aphthous-like ulcerations of the soft palate in a 44-year-old female patient with ulcerative colitis.

Table 15-1 Epidemiology of inflammatory bowel disease.

	Crohn's Disease	Ulcerative Colitis
Cases per annum (per 100,000)[49]	0–20	0–20
Population point prevalence (per 100,000)[50]	25–300	35–250
Peak age of onset (years)		
First peak[37,49]	20–30	30–40
Second peak[51]	60–70	60–70
Median age at diagnosis (years)[52]	30	40–45
Mean age at diagnosis (years)[53]	35	40–45

Medical Management

The diagnosis of UC is based on a careful history, physical examination, gastrointestinal radiography, and direct visualization via sigmoidoscopy and endoscopy revealing multiple tiny mucosal ulcers covered by blood and pus.

The aim of therapy is to reduce the inflammation and correct the effects of the disease. Sulfasalazine in the form of its active component 5-aminosalicylic acid (5-ASA) is the standard therapy for mild to moderately active UC[57] and most patients respond to 2–3 g 5-ASA, with higher doses used in those with more severe symptoms or those not responding initially. Oral corticosteroids are superior to 5-ASA,[58] but have significant side effects and are reserved for patients with failure of response or who are intolerant to oral and/or rectal 5-ASA. The current recommended dose is 40 mg once daily[59] and approximately 50% of patients experience short-term adverse events such as acne, edema, sleep and mood disturbance, glucose intolerance, and dyspepsia.[59] The dose should be tapered over 6–8 weeks.

Patients with chronic active UC failing 5-ASA therapy may benefit from ciclosporin[60] or thiopurine therapy in the form of azathioprine or its active metabolites, 6-mercaptopurine or thioguanine.[61] However, as the range of alternatives grows and costs of biologics fall, there is strong justification for moving directly to other immunosuppressive drugs with less toxicity that may be easier to manage.[61] Thiopurines still have a role as combination therapy and to reduce immunogenicity, but the therapeutic pyramid is changing rapidly.[60] Infliximab and other anti-TNF drugs are often effective, but it is also important to consider surgery in patients failing a therapeutic agent, particularly as there is generally a reduction in response to each successive immunosuppressive or biologic drug.[56] Proctocolectomy combined with ileostomy is a curative procedure for UC.

Crohn's Disease

Medical Aspects

CD is an inflammatory disease that can affect any part of the small or large intestine, from the mouth to the anus. Discontinuous segments of disease ("skip lesions"), ileal involvement, and granulomatous inflammation are suggestive of CD, as is a tendency for inflammation to be worse in the proximal colon.[62] Gross examination may reveal mucosal ulceration (aphthous ulcers within the mucosa that appear normal, deep ulcers within areas of swollen mucosa, or long linear serpiginous ulcers). Microscopic examination reveals inflammatory infiltrate in all layers of affected bowel, with plasma cells and lymphocytes predominating in the lamina propria.[23–32]

Epidemiologic evidence suggests that there are two forms of CD: a nonperforating form that tends to recur slowly, and a perforating or aggressive form that evolves more rapidly. Patients with the aggressive perforating type are more prone to develop fistulae and abscesses, whereas the more indolent nonperforating type tends to lead to stenotic obstruction.[23–33] Intestinal fistulas occur in about 20%–40% of patients with CD[63,64] and can link to any adjacent structure, including to the bowel, bladder, skin, or vagina. Strictures can present throughout the gastrointestinal tract and present with obstructive features, including abdominal pain, nausea, and vomiting. Up to one-third of patients with CD have perianal involvement, most commonly presenting as fistulas, fissures, abscesses, or skin tags.[65]

The severity of CD and its location determine the associated symptoms and signs, resulting in a broad spectrum of presentations. The clinical presentation usually involves a young person with colicky abdominal pain, frequently associated with, and relieved after, bowel movements, together with watery diarrhea and weight loss. Involvement of the terminal ileum is common and may result in pain being localized to the right lower quadrant. The pain tends to come and go, reflecting disease activity, but if acute and severe may resemble appendicitis.

Inflammation of the small intestine may impair the absorption of vital nutrients, leading to deficiency states. Duodenal involvement affects calcium, iron, and folate, while disease in the terminal ileum affects bile salts and vitamin B_{12}. Widespread involvement of the small or large intestines may affect fat, fat-soluble vitamins, salt, water, protein, and iron.

Medical Management

The signs and symptoms of CD are often subtle and may delay the diagnosis, which is usually made on the basis of a careful history, physical examination, and diagnostic testing. Ileocolonoscopy with biopsy is the first-line investigation for suspected Crohn's disease.[66] CD is likely where there is (1) involvement of the small intestine or the upper part of the alimentary canal; (2) segmental disease of the colon, with "skip" areas of normal rectum; (3) the appearance of fissures or sinus tracts; and (4) the presence of well-formed noncaseating granulomas.[23–32] Luminal barium fluoroscopic techniques have largely been replaced by cross-sectional imaging techniques.[66] Computed tomography enterography (CTE), magnetic resonance enterography (MRE), and small bowel ultrasound (SBUS) all have high sensitivity and specificity, with no consistent difference in diagnostic accuracy.[67]

Systemic corticosteroids (prednisolone) and immunosuppressive medication in the form of thiopurines (azathioprine [AZA]/5-mercaptopurin [5-MP]) or methotrexate (MTX) are well recognized in the induction of remission in CD. Corticosteroid therapy is associated with multiple adverse effects and is therefore not useful for long-term treatment. Similarly, some patients with severe disease or those who are refractory or intolerant to immunosuppressives require

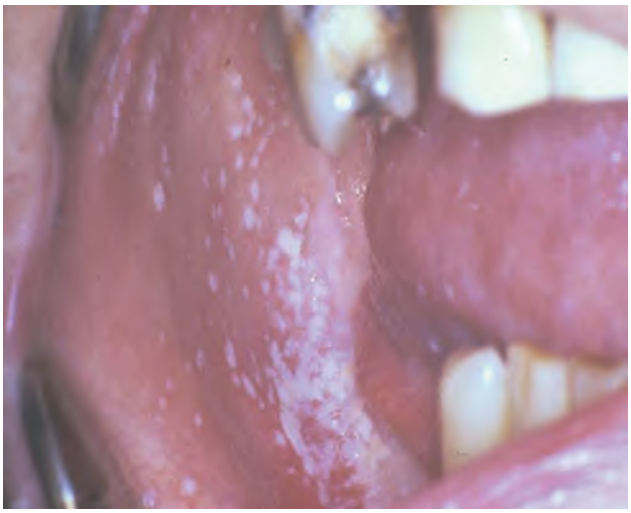

Figure 15-2 Pseudomembranous plaques of *Candida albicans* in a patient with Crohn's disease treated with sulfasalazine. The plaques were easily removed with wet gauze sponges.

alternatives.[68] The anti-TNF medications such as infliximab and adalimumab are often utilized in these situations, but are associated with primary nonresponse and secondary loss of response.[69]

Patients with CD who have inadequate response, loss of response, or intolerance to therapy with corticosteroids, immunosuppressives, or anti-TNF are now treated with immune cell trafficking or cytokine signaling inhibitors.[70] Vedolizumab, a monoclonal antibody directed against α4β7 integrin,[71] prevents circulating immune cells from homing to the mucosa and is gut-selective through interactions with mucosal adhesion molecules. Ustekinumab, a monoclonal IgG1 antibody against the p40 subunit of IL-12 and IL-23, targets T-helper cell pathways.[72] Both medications are effective in inducing and maintaining remission and are increasingly considered as potential first-line biologic agents in preference to anti-TNF medications.

Oral Health Considerations

The first consideration in both CD and UC is oral manifestations, which can arise either as a direct presentation of the condition or secondary to the effects of the condition or its treatment.[44]

Management of UC and CD often involves the use of corticosteroids or immunosuppressive or other medications, which frequently increase the risk of opportunistic oral infections. These include oral candidosis, especially in the form of angular cheilitis (redness, crusting, and splitting of the corners of the mouth), denture stomatitis (erythema of the mucosa in contact with the fit surface of a denture), acute pseudomembranous candidosis, (Figure 15.2) or oral soreness/burning affecting the tongue or oral mucosa.[44] Similarly, the long-term use of corticosteroids may necessitate monitoring of blood pressure and evaluation of blood glucose, and consideration of the need for replacement therapy prior to stress-inducing procedures. The latter is based on the dosage and length of time on glucocorticoids and the nature of the planned dental treatment.

In contrast, the disease-specific presentations vary:

- *UC*: Oral features are generally secondary to the underlying condition or its treatment. Rarely, pyostomatitis vegetans,[47] a generalized ulceration of the oral mucosa, may be the initial presentation of previously occult UC (see below).
- *CD*: The common oral features of CD include ulceration, diffuse swellings of the lips and/or cheeks, "cobblestoning," mucosal tags, vertical lip fissures, full-thickness gingivitis, angular cheilitis, perioral erythema, cervicofacial lymphadenopathy (Figure 15.3).[45] Other features include minor salivary gland enlargement[73] and altered taste sensation.[74] The orofacial manifestations are more common in cases presenting under the age of 16[75] and may predate any gastrointestinal symptoms by several years.[44] Patients may present with oral and perioral disease ("oro-facial Crohn's disease") without any other apparent gut involvement.[76] However, 10%–48% of such patients may have asymptomatic gut lesions.[77] OFG affects the oral cavity without gut lesions.[45,76] The anterior part of the mouth is most commonly affected, especially enlarged swollen lips. OFG may respond better to exclusion diets than anti-TNF or immunosuppressives.[45]

Several forms of stomatitis have been reported in association with IBD and particularly CD:[44]

- *Pyostomatitis vegetans*: Although rare, this is a highly specific[78] oral marker for IBD (primarily UC). It is characterized by multiple small yellowish pustules on an erythematous mucosa and may be accompanied by small vegetating lesions. The lesions may ulcerate, suppurate, or become necrotic and often demonstrate a snail-track pattern.[79] Most areas of the oral cavity may be involved, although the dorsum of the tongue is rarely affected. Treatment remains difficult and while topical corticosteroid mouth rinses (see below) may be beneficial, resolution is most commonly associated with treatment of the underlying IBD with systemic corticosteroids and azathioprine.[80]
- *Pseudo-pyostomatitis vegetans*: This resembles pyostomatitis vegetans clinically.[81] However, direct immunofluorescence reveals deposits of IgG in the basement membrane zone in a linear pattern and indirect immunofluorescence, on salt-split normal skin, reveals IgG reactive to the roof of the induced split in keeping with pemphigoid. Therefore, pyostomatitis vegetans cannot simply be diagnosed clinically and immunofluorescence studies are essential.

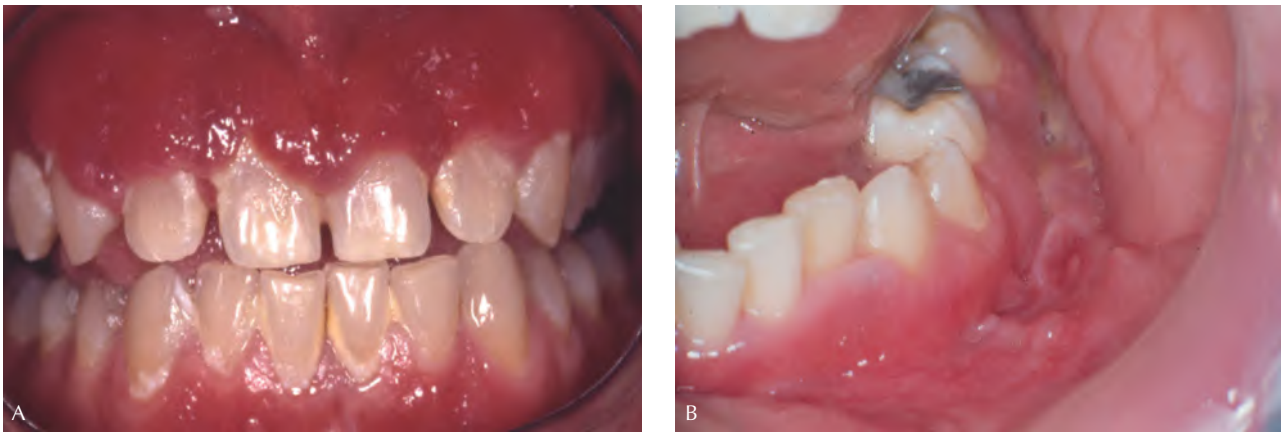

Figure 15-3 (A) Hyperplastic cobblestone-like gingival architecture in a 31-year-old female patient with Crohn's disease. (B) Epithelial tags and linear ulceration in the lower buccal sulcus and cobblestoning of buccal mucosa.

- *Stomatitis gangrenosum*: This condition, associated with CD, presents with often foul-smelling, deep ulcers of varying size with rolled margins and a grayish fibrinous base. Incisional biopsy and histopathologic examination reveal ulceration with a fibrino-purulent membrane and a chronic inflammatory infiltrate.
- *Staphylococcal mucositis*: This is associated with CD and presents as a panoral erythematous stomatitis, from which *S. aureus* can be isolated and for which antimicrobial treatment provides rapid relief.[82]

Malabsorption may lead to iron, vitamin B_{12}, or folate deficiency, while blood loss is most commonly associated with iron deficiency.[23–32] In almost all cases such deficiency states may lead to anemia, which may be associated with delayed healing and necessitate postponing surgical treatment until the disease is under control. Anemia may present orally with depapillation of the tongue (glossitis), burning mouth sensation, angular cheilitis, or oral ulceration.[44] Correction of the underlying deficiency state is usually associated with symptom improvement and resolution.[44]

Numerous medications, including anti-inflammatory and sulfa-containing preparations commonly used to manage IBD patients, have been reported to cause oral lichenoid drug reactions.[83,84] OHCPs are responsible for treatment of oral manifestations of IBD, particularly if the lesions are symptomatic.

Antibiotic-Induced Diarrhea and Pseudomembranous Enterocolitis

Medical Aspects

Antibiotic-associated diarrhea (AAD) is a common condition affecting 5%–39% of people treated with antibiotics.[85] This condition arises from an antibiotic-related imbalance of the gut microbiota, the result of which includes decreased short-chain fatty acid absorption, leading to osmotic diarrhea.[86]

Most cases of AAD are mild and self-limiting, with resolution following cessation of antibiotic therapy. However, one form of AAD, *clostridium difficile* infection (CDI), can cause more severe gastrointestinal disease, including life-threatening pseudomembranous enterocolitis. *Clostridium difficile* is a gram-positive, spore-forming anaerobic bacillus. *C. difficile* is spread via the feco-oral route, and causes disease through the production of two protein exotoxins (toxin A and toxin B), which are cytotoxic to colonic epithelial cells.[87]

The host's adaptive immune response following exposure to *C. difficile* is important in determining the severity of the disease, with high IgG antitoxin level production being protective.[87] Antibiotic-related loss of gut microbial communities, which protect against gut infection, facilitates the germination and vegetative growth of the organism when it enters the gut of vulnerable people. Specific risk factors for CDI include almost all antibiotics (particularly cephalosporins, clindamycin, and some penicillins), acid-suppressant medications (PPIs and H_2 receptor antagonists), increasing age (particularly >65), recent hospitalization, and immunosuppression. The clinical presentation is variable, with diarrhea and fever occurring in almost all cases, while the most severe are characterized by colitis, toxic megacolon (dilatation of the colon, with the risk of perforation), multiorgan failure, or even death.

Diagnosis may be difficult, as most tests lack sensitivity and specificity, although an abdominal radiograph is the preferred test for toxic megacolon and abdominal CT is sensitive for the presence of CDI-related colitis. Lower gastrointestinal endoscopy may demonstrate edema, erythema, or classical pseudomembranes; that is, raised yellowish plaques that may be intermittently scattered throughout affected colonic mucosa.

Treatment of CDI classically required metronidazole administered orally or intravenously or vancomycin

administered orally or per rectum. Intravenous immunoglobulin (IVIg) has also been used for severe disease, with surgical intervention (colectomy) reserved for refractory cases. The increasing failure rate with metronidazole, recurrence following treatment, and hypervirulent strains of *C. difficile*, such as the NAP1/027 strain, have necessitated alternative approaches.[88] These include the orally administered macrocyclic antibiotic fidaxomicin and manipulation of the gut microbiota through probiotics and fecal microbiota transplantation (FMT). Probiotics have proved of limited benefit, while FMT using a stool sample from a healthy screened donor to produce a liquidized bacterial suspension or a capsularized freeze-dried slurry, which is then delivered into the gut of the affected patient, has proved successful in refractory and recurrent cases.[89]

Oral Health Considerations

The primary role of the OHCP is to recognize the signs and symptoms of AAD and consider the possibility of *C. difficile* infection or the more serious condition of pseudomembranous colitis in patients who are either taking, or have recently completed, an antibiotic regimen. Cessation of the antibiotic and prompt referral to the patient's physician to enable a definitive diagnosis should be considered.

Diseases of the Hepatobiliary System

This section will consider the liver, biliary tract, and pancreas, which have interrelated functions in relation to the digestive system. Of these the liver is both the largest structure and has the highest number of roles, and therefore has a greater focus.

The liver serves as the major locus of synthetic, catabolic, and detoxifying activities in the body and is the site of all intermediary metabolism of foodstuffs. The liver is essential in the excretion of heme pigments, and also participates in the immune response. Impairment of the hepatocyte interferes with the liver's ability to synthesize and store glycogen, a major source of glucose. Should glycogen stores be depleted, liver gluconeogenesis from amino acids is initiated to maintain glucose levels.

Lipids are metabolized in the liver to form cholesterol and triglycerides. Cholesterol is the major building block of cell membranes, steroids, and bile salts. Bile salts are essential in the absorption of fat in the small intestine. Proteins, albumin, and clotting factors I, II, IV, VII, IX, and X are synthesized and stored in the liver. Since some of the clotting factors (II, VII, IX, and X) are also dependent on vitamin K, coagulopathy can occur from hepatocyte dysfunction and/or vitamin K malabsorption due to biliary problems.

The metabolism of drugs is principally performed by the cytochrome P-450 microsomal enzyme system in the hepatocyte. Local anesthetics, analgesics, sedatives, antibacterials, and antifungals are all metabolized in the liver. Consequently, cautious use of these drugs in a person with liver dysfunction is essential. Lastly, the liver inactivates or metabolizes hormones such as insulin, aldosterone, antidiuretic hormone, estrogens, and androgens.

Liver dysfunction can manifest through multiple symptoms, most commonly as jaundice, and the disease process can lead to liver failure and cirrhosis.[90–93] Accordingly, jaundice and cirrhosis are considered separately below.

Liver disease may be systemic in etiology or due to traumatic injury. Causes of abnormal liver function tests include trauma, viral or chemically induced hepatitis, alcohol intake, nonalcoholic fatty liver disease, autoimmune liver diseases, and hereditary diseases such as hemochromatosis, α_1-antitrypsin deficiency, and Wilson's disease. Many patients with liver disease are treated with multidrug regimens, compounding the problem of liver toxicity. Knowledge of liver involvement in systemic diseases is important for the accurate diagnosis of liver damage and to avoid unnecessary examination and treatment.[94]

Jaundice

Jaundice (or icterus) is a yellow discoloration most often seen in the skin, mucous membranes, and sclera of the eye, which results from excess bilirubin in the circulation and its resultant accumulation in the tissues. This excess bile pigment may be caused by (1) increased production of unconjugated bilirubin as a result of hemolysis of red blood cells (hemolytic jaundice); (2) disturbances of bile flow caused by diseases either in the hepatocytes, intrahepatic bile ducts, or extrahepatic biliary system, preventing the excretion of bilirubin (obstructive jaundice); or (3) liver parenchymal disease (hepatocellular jaundice). Each of these processes is briefly reviewed in this section, and the role of the OHCP in relation to oral healthcare discussed.

Hemolytic Jaundice

Unconjugated hyperbilirubinemia is usually a result of too much bilirubin presented to the conjugating machinery (from increased red blood cell destruction).[95] Increased red blood cell breakdown may be caused by erythrocyte membrane disorders,[96] erythrocyte enzyme disorders,[97] hemoglobin disorders,[98] autoimmune erythrocyte destruction,[99] and some cancers (Table 15-2).

The excess turnover of red blood cells leads to increased heme metabolism, producing large amounts of bilirubin that overwhelm the conjugating machinery, resulting in decreased excretion (increased circulating unconjugated bilirubin) and clinical jaundice.

Table 15-2 Causes of hemolytic anemia.

Erythrocyte membrane disorders[95]	Elliptocytosis Ovalocytosis, Spherocytosis
Erythrocyte enzyme disorders[96]	Glucose-6-phosphate dehydrogenase deficiency Glucose-6-phosphate isomerase deficiency Pyrimidine-5′-nucleotidase deficiency Pyruvate kinase deficiency
Hemoglobin disorders[97]	Sickle cell anemia Thalassemia
Autoimmune erythrocyte destruction[98]	Cold reactive Drug induced (associated with ~150 drugs) Mixed type Warm reactive
Cancers	Myeloproliferative neoplasms (especially polycythemia vera)

The diagnosis of hemolytic jaundice is based on laboratory investigations demonstrating the presence of anemia with a high reticulocyte count, a decreased level of serum haptoglobins, and elevated serum bilirubin. The specific cause of the increased hemolysis of red blood cells requires additional investigations, such as hemoglobin electrophoresis, erythrocyte fragility studies, and Coombs' test for antibodies to red cells.

Treatment to control the excessive hemolysis is usually associated with a return to normal liver function and resolution of the jaundice without long-term damage to the liver.

Obstructive Jaundice (Cholestasis)

This form of jaundice is associated with partial or complete cessation of bile flow and arises from obstructions of the extrahepatic biliary tree or intrahepatic abnormalities. In either case, the flow of bile through the liver and out of the common bile duct can be impeded, resulting in an increase in bilirubin in the tissues.

Extrahepatic cholestasis is caused by structural abnormalities of the biliary tract, including the obstruction of bile ducts and the gallbladder. Gallstones and malignancies are the causes of most cases of extrahepatic cholestasis. Tumors of the pancreatic head are the most common malignant cause of extrahepatic cholestasis, and adenocarcinoma is the most frequent. Surgical treatments are usually required to restore physiologic function.

The causes of intrahepatic cholestasis include neoplasms (e.g., metastatic carcinomas, lymphomas), toxic drugs and chemicals, hepatitis, parenteral nutrition, sepsis, ischemia, endocrine diseases, and hereditary disorders of metabolism.

Hereditary Disorders of Conjugation

Indirect Hyperbilirubinemia

In healthy individuals unconjugated bilirubin is normally conjugated with one to two molecules of glucuronic acid via the action of uridine 5'-diphosphoglucuronosyltransferase 1A1 (UGT1A1) ready for excretion. Genetic mutations in this enzyme prevent this reaction, leading to accumulation of bilirubin in the liver and blood and hence jaundice.

Gilbert syndrome is one such benign condition affecting approximately 10% of Caucasians.[100] TA repeat polymorphism (UGT1A1*28) in the promoter of the UGT1A1 gene is the most commonly affected region and results in mild intermittent jaundice.[101]

Crigler–Najjar syndrome is also caused by mutations in the UGT1A1 gene.[102] Type I is a rare autosomal recessive disorder with complete loss of enzymatic function, which may necessitate liver transplantation, while type II retains some enzymic activity and may be controlled with medical therapy.

Direct Hyperbilirubinemia

Over 100 inherited diseases have been identified as causing cholestatic liver disease that initially present with jaundice.[101] In each case the underlying genetic mutation has been identified and includes:

- Progressive familial intrahepatic cholestasis (e.g., PFIC1, ATP8B1).
- Bilirubin transport defects, e.g., rotor syndrome (SLCO1B1), Dubin–Johnson syndrome (ABCC2).
- Inborn errors of bile acid metabolisms, e.g., bile acid synthetic defects (HSD3B7).
- Metabolic liver disease, e.g., Wilson's disease (ATP7B), alpha-1-antitrypsin deficiency (SERPINA1), Niemann–Pick disease type C (NPC).

The diagnosis of these conditions requires a careful clinical history and examination coupled with biochemical investigation, including levels of total and direct bilirubin, aspartate transferase, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP). A low serum GGT level disproportionate to the severity of cholestasis is indicative of inherited cholestasis such as PFIC and inborn errors of bile acid synthesis.[101] The definitive genetic diagnosis is provided by next-generation sequencing (NGS) panels incorporating a limited number of genes[103] and expanded panel-based NGS involving more than 50 genes.

Further investigations of biliary obstruction may involve multiple imaging modalities, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography, and percutaneous, intraoperative, or endoscopic retrograde cholangiography. Interpreting these examinations and choosing an optimal management strategy can be difficult and may involve nutritional support, biliary diversion surgery, and in some cases liver transplantation.[104]

The OHCP's primary function is the recognition of the clinical signs of jaundice and appropriate referral to a primary care physician for diagnosis and treatment. Once successful disease management is achieved, routine dental care can continue, with appropriate liaison with the patient's physician to ascertain the patient's liver function, ability to undergo dental treatment, and any additional measures required.

Hepatocellular Jaundice

Hepatocellular jaundice can be caused by hepatitis and cirrhosis. Alcoholic hepatitis and drug-induced hepatotoxicity are discussed in the next section, along with cirrhosis.

Alcoholic Liver Disease and Alcoholic Hepatitis

Medical Aspects

Alcoholic liver disease (ALD) represents a spectrum of injury, ranging from steatosis to alcoholic hepatitis to cirrhosis. Regular alcohol use leads to fatty changes in the liver that can develop into inflammation, fibrosis, and eventually cirrhosis. Alcoholic hepatitis (AH) is acute inflammation of the liver, which can occur in patients with ALD, and accounts for 44% of all deaths associated with liver disease.[105]

AH generally occurs with excessive alcohol intake over a period of at least 20 years and so usually presents in the fourth or fifth decade of life.[106] The risk of AH and cirrhosis is increased in those consuming in excess of over 30–60 g/day of alcohol,[107] as is the risk of hospitalization in those exceeding 120 g/day.[106] While alcohol intake plays a role in AH, the fact that only 10% develop cirrhosis suggests that other factors are important. Factors known to increase risk include pattern of drinking (e.g., binge drinking), type of alcohol (e.g., spirits), female sex,[108] and obesity. Genetic factors related to polymorphisms on the genes coding for alcohol metabolism may confer a predisposition to alcoholism and an association with alcoholic cirrhosis.

There are significant geographic differences in the incidence of ALD and AH, which are highest in eastern and southern Europe and the United Kingdom, lower in the United States, and lowest in Muslim populations.[109] AH has a strong association with malnutrition, while nutrient deficiencies are implicated in ALD. Associated liver diseases, particularly hepatitis C, may also accelerate progression.[110]

The pathogenesis of ALD involves multiple factors, including hepatocyte damage due to alcohol and its metabolites, cholestasis, recruitment and activation of innate immune cells by gut-derived pro-inflammatory danger signals, Kupffner cells, and recruited macrophages and neutrophils in the liver.[105] The ongoing presence of these factors triggers ineffective anti-inflammatory pathways, resulting in activation of stellate cells and myofibroblasts in the liver, which lead to fibrosis and alcoholic cirrhosis.[111]

The earliest indication of ALD is an enlarged liver. The patient may also exhibit signs of both AH (jaundice, fever, anorexia, and malaise) and more chronic liver disease, which may include spider angiomas, gynecomastia, jaundice, ascites, changes in mental status, and ethanol intoxication.[91,105] AH, which is at least partially reversible, is often found superimposed on cirrhosis that is already established. Often there is little correlation and sometimes considerable disassociation between the apparent severities of injury, based on clinical findings, relative to the evidence subsequently found on liver biopsy.

The clinical problems associated with AH reflect the disordered metabolism and circulation in the liver. Jaundice reflects the inability of the hepatocyte to conjugate and excrete bilirubin, bleeding the decreased synthesis of clotting factors, and mental confusion the failure of the liver cells to metabolize and excrete toxins such as ammonia. There may be an associated thrombocytopenia in cases of alcoholic jaundice, while spider angiomas and gynecomastia result from elevated levels of estrogen, which is normally metabolized by hepatocytes.[91]

Medical Management

AH requires consideration in the case of any patient who has a history of regular alcohol use. Laboratory investigations include full blood count and differential, clotting studies, liver function tests, and gamma-glutamyl-transpeptidase assay, carbohydrate deficient transferrin, and viral hepatitis serologies.

Abdominal imaging studies, including ultrasound, CT, and MRI, may be useful in the diagnosis of ALD. However, confirmation of the diagnosis and assessment of the extent of injury is best done by performing a liver biopsy.

The treatment of AH is dependent on the patient's prognosis. This can be objectively measured by using the Maddrey Discriminate Function (MDF), which incorporates the prothrombin time and bilirubin at the time of diagnosis. Values of >32 in this measure indicate severe disease and poor prognosis with significant mortality.[112]

Abstinence is the mainstay of the treatment of AH. However, this is difficult or unachievable for most patients

due to addiction, which often requires psychiatric help or participation in formal withdrawal programs.[105] Nutritional support for the malnourished patient is important. Beyond this, the primary therapeutic intervention for AH involves corticosteroids, which is limited to a narrow patient population (MDF >32), has limited benefit, and has a high side effect profile. In these patients the Lille score at day 7 is used to decide whether corticosteroid therapy should be stopped or continued for a 1-month course.[105] More recent therapies aim to inhibit inflammation by targeting cytokine-mediated pathways (e.g., IL-1) and by improving gut barrier function.[113] The use of liver transplantation, while reportedly successful, remains controversial.[105]

Oral Health Considerations

The orofacial manifestations associated with AH are primarily related to dysfunction of the hepatocyte and include jaundice, which usually occurs when total serum bilirubin reaches levels ≥3 mg/dL. There may be extraoral and/or intraoral petechiae, ecchymosis, or gingival crevicular hemorrhage due to clotting factor deficiency. Yellow pigmentation of the mucosa may also be observed, accompanied by cutaneous and scleral jaundice. Additional oral findings such as pallor, angular cheilitis, and glossitis may be present as a result of associated malnutrition, vitamin deficiencies, and anemia.[90]

The presence of sweet ketone breath, indicative of liver gluconeogenesis, should raise the suspicion of hepatotoxicity. This together with the above clinical features, as well as a history or symptoms suggestive of alcohol abuse, should warrant a referral to the patient's primary care physician for evaluation. Any elective dental treatment should not be carried out in a patient who appears intoxicated.

Patients with parenchymal liver disease have impaired hemostasis and a clotting screen including prothrombin, together with any necessary medical preparation, is indicated prior to surgical intervention. The type and severity of the liver disease, as well as induction or inhibition of hepatic drug-metabolizing enzymes, by previous or current medications, mean that the effects of drugs are not entirely predictable.[90] The drug effects may also be enhanced by depressed protein binding due to hypoalbuminemia. Adverse interactions between alcohol or resultant ALD and medications used in dentistry include but are not limited to acetaminophen, aspirin, ibuprofen, some cephalosporins, erythromycin, metronidazole, tetracycline, ketoconazole, pentobarbital, secobarbital, diazepam, lorazepam, chloral hydrate, and opioid analgesics.[114]

The prevalence of dental disease may be increased due to self-neglect. Routine dental treatment for a patient with a history of ALD is not contraindicated unless there is significant cirrhosis and resultant impaired hepatic function. The OHCP should therefore confirm the patient's liver function status with the appropriate physician prior to commencing treatment.

Drug-Induced Hepatotoxicity

Medical Aspects

Drug-induced liver disease is an uncommon but challenging clinical problem that can mimic any acute or chronic liver disease. Patients may present with fulminant hepatic failure from an intrinsic hepatotoxin such as acetaminophen, or may simply present with an incidental finding of an abnormal liver function test result on routine screen. Ingested drugs are absorbed into the portal circulation and pass through the liver en route to distant sites of action. The liver is responsible for the conversion of lipid-soluble drugs, which are difficult to excrete, into polar-soluble metabolites that are easily excreted through the kidneys. This solubilization and detoxification may paradoxically produce toxic intermediates.

The diagnosis of drug-induced liver disease is largely based on exclusion of other causes. The timing of the onset of injury after the implicated agent has been started (latency), resolution after the agent is stopped ("dechallenge"), recurrence on reexposure (rechallenge), knowledge of the agent's potential for hepatotoxicity (likelihood), and clinical features (phenotype) are the major diagnostic elements.[115,116]

Drugs may be conjugated, oxidized, or reduced through the cytochrome P-450 system. This system can be induced by the long-term use of alcohol, barbiturates, or other drugs. With some hepatotoxic drugs, the relative activity of the cytochrome P-450 system is crucial; a drug that exerts its toxic actions through the generation of cytochrome P-450 metabolites may be relatively more toxic in a patient who uses alcohol or other agents that are capable of inducing cytochrome P-450.

Drug-induced hepatotoxicity can be classified as one of three general patterns, direct, idiosyncratic, or indirect, each of which has a typical phenotypic presentation[117] (Table 15-3).

Regardless of the mechanism involved, drug-induced hepatotoxicity can result in hepatocellular injury, cholestatic drug reactions, abnormal lipid storage, cirrhosis, and vascular injury. Hepatocellular injury and cholestatic drug reactions account for the majority of drug reactions encountered in dentistry.

Oral Health Considerations

The OHCP's role in recognizing the potential for drug-induced hepatotoxicity from drugs they prescribe, other medications (either prescribed or over the counter) being taken by the patient, and drug interactions is critical. Herbal

Table 15-3 Drug-induced hepatotoxicity.

Variable	Direct	Idiosyncratic	Indirect
Frequency	Common	Rare	Intermediate
Dose-related	Yes	No	No
Predictable	Yes	No	Partially
Reproducible in animal models	Yes	No	Not usually
Latency (time to onset)	Typically rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes	Acute hepatic necrosis, serum enzyme elevations, sinusoidal obstruction, acute fatty liver, nodular regeneration	Acute hepatocellular hepatitis, mixed or cholestatic hepatitis, bland cholestasis, chronic hepatitis	Acute hepatitis, immune-mediated hepatitis, fatty liver, chronic hepatitis
Most commonly implicated agents	High doses of acetaminophen, niacin, aspirin, cocaine, intravenous amiodarone, intravenous methotrexate, cancer chemotherapy	Amoxicillin-clavulanate, cephalosporins, isoniazid, nitrofurantoin, minocycline, fluoroquinolones, macrolide antibiotics	Antineoplastic agents, glucocorticoids, monoclonal antibodies (against tumor necrosis factor, CD20, checkpoint proteins), protein kinase inhibitors
Cause	Intrinsic hepatotoxicity when agent given in high doses	Idiosyncratic metabolic or immunologic reaction	Indirect action of agent on liver or immune system

Source: From Hoofnagle, J. H., & Björnsson, E. S. (2019). Drug-Induced Liver Injury – Types and Phenotypes. *New England Journal of Medicine*, 381(3), 264–273. © 2019, Massachusetts Medical Society.

and other alternative (nontraditional) drugs have also been reported to elicit hepatocellular toxicity.

As idiosyncratic reactions often have an immuno-allergic basis, the patient may present with fever, dermatitis, arthralgias, and eosinophilia in addition to features associated with the hepatic damage such as jaundice. Amoxicillin-clavulanate is the most frequent cause of idiosyncratic prescription drug-related hepatotoxicity, accounting for 10% of all reported reactions,[118] nearly twice as many reactions as the next most commonly reported drug. Other common oral healthcare medications with an occurrence rate >1% include azithromycin, ciprofloxacin, diclofenac, phenytoin, and azathioprine.[118] Where this follows the commencement of a new medication, the prescribing clinician will need to consider withdrawal of the medication and its replacement with an alternative from a different class. Fortunately, most of the regularly prescribed medications in oral healthcare have safe and effective alternatives and hence stopping the suspected medication is the appropriate course of action. Consideration should also be given to onward referral to enable biochemical assessment.

For those drugs that produce idiosyncratic drug toxicity, there is no way to predict or prevent such reactions.[118] Any patient who experiences an abrupt episode of hepatocellular injury should be considered to have an idiosyncratic drug reaction and should not be challenged again. For those patients who take medications associated with dose-dependent drug reactions, the primary precaution is to prescribe the minimum effective dosage. This is particularly important for those medications where there is a narrow therapeutic window. The use of therapeutic levels (e.g., phenytoin) should also be considered when available, as should biochemical monitoring (e.g., carbamazepine).

Liver Cirrhosis

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis. Histologically it is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa and pronounced distortion of hepatic vascular architecture.[119] This distortion results in increased resistance to portal blood flow, leading to portal hypertension and hepatic synthetic dysfunction. While it was previously regarded as an end-stage disease, there is a widely varying 1-year mortality ranging from 1% to 57%, depending on the occurrence of clinical decompensating events.[120] This, coupled with the fact that fibrosis regresses with specific treatment, such as antiviral treatment for chronic hepatitis B[121] and C,[122] underlines that it is better termed advanced liver disease to reflect its dynamic nature.

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries, being the 14th most common cause of death worldwide but 4th in central Europe. It is the cause of 1.03 million deaths per year worldwide,[123] 170,000 per

year in Europe[124] and 33,539 in the United States.[125] The main causes in more developed countries are infection with hepatitis C virus, alcohol misuse, and, increasingly, nonalcoholic liver disease; infection with hepatitis B virus is the most common cause in Sub-Saharan Africa and most parts of Asia.[126]

Medical Aspects

Most chronic liver disease is asymptomatic until clinical decompensation occurs, when the presenting features include ascites, sepsis, variceal bleeding, encephalopathy, and nonobstructive jaundice.[126] Imaging by ultrasonography, CT, or MRI of an irregular and nodular liver together with impaired liver synthetic function is sufficient for the diagnosis of cirrhosis.[126] Less frequently seen are nonspecific findings of clubbing, cyanosis, and spider angiomas.[91] A liver biopsy is seldom needed, but study of a sample can provide a definitive diagnosis and confirm the etiology in cases of uncertainty.[126] Conventional imaging can lead to false-negative diagnosis in early cirrhosis and noninvasive markers of fibrosis are increasingly used.[126]

In keeping with the dynamic nature of the condition, it is considered to comprise four stages: stage 1 (compensated with no esophageal varices) has an estimated mortality of 1% per year; stages 2 (compensated with varices), 3 (decompensated with ascites), and 4 (decompensated with gastrointestinal bleeding) have annual mortality rates of 3.4%, 20%, and 57%, respectively.[120] Decompensating events are generally triggered by precipitating factors that include infection, portal-vein thrombosis, surgery, and hepatocellular carcinoma.[126]

Medical Management

The medical management of liver cirrhosis is dependent on the underlying etiology. The main objective is to prevent further injury to the liver. Discontinuation of alcohol and other toxins (e.g., cigarette smoking) as well as weight loss for those overweight is essential.[126] Specific treatments include immunosuppression for autoimmune hepatitis, venesection for hemochromatosis, and copper chelators or zinc for Wilson's disease.[126] Patients with viral hepatitis should be assessed for potent antiviral treatment, for example entecavir or tenofovir, which can improve the prognosis.[122]

Specific complications may also require intervention. Beta-blockers are helpful for portal hypertension, with statins added if the patient is hyperlipidaemic,[122] while NSAIDs, PPIs, and aminoglycosides should be avoided. Ascites benefits from a low-salt diet, diuretics, and antibacterial prophylaxis against spontaneous peritonitis. Bleeding esophageal varices can be treated with endoscopic banding, ligation, and nonselective beta-blockers.[126]

Liver transplantation is the therapeutic option for patients who develop decompensation or hepatocellular carcinoma with cirrhosis.[126]

Oral Health Considerations

The oral cavity may show evidence of cirrhosis, with the presence of hemorrhagic changes, petechiae, hematoma, jaundiced mucosal tissues, gingival bleeding, or icteric mucosal changes.[127] Oral mucosa pigmentation is rarely observed in cases of hemochromatosis.[127] Patients with cirrhosis are frequently malnourished and may have nutritional deficiencies or anemia, resulting in mucosal pallor, glossitis, and angular cheilitis, which may be complicated by candidal infection.[127]

Salivary gland dysfunction secondary to Sjögren's syndrome may be associated with primary biliary cirrhosis. Patients with chronic hepatitis C (HCV)–related cirrhosis may report oral and ocular dryness.[128] As the virus has not been shown to directly infect salivary gland tissue,[129] the HCV-related sicca syndrome is considered to be the product of a host immune-mediated mechanism, rather than a direct viral effect.[130] Histologic examination of salivary gland biopsies in HCV-infected patients shows pericapillary and nonpericanalary lymphocytic infiltration with sparing of the glandular canals.[131] Sialosis, a bilateral, painless hypertrophy of the parotid glands, may be associated with cirrhosis. The enlarged glands are soft, nontender, and are not fixed.[128] Ultrasound examination reveals enlarged glands with a homogeneous appearance.

The dental patient who presents with a history of liver cirrhosis can usually undergo routine dental treatment provided any necessary precautions are undertaken in consultation with the patient's physician. Patients with cirrhosis may present several specific challenges:

- Hemostatic defects, because of an inability to synthesize clotting factors and the presence of a secondary thrombocytopenia.[90] The current status and need for any preoperative measures (e.g., fresh frozen plasma or platelets) should therefore be established prior to any surgical procedure.[90]
- Reduced ability to detoxify substances so that drugs and toxins may accumulate.
- Encephalopathy due to an ammonia buildup from the incomplete detoxification of nitrogenous wastes.
- Induction of liver enzymes, leading to a need for increased or decreased dosages of certain medications.
- Ascites, which may make it difficult for them to fully recline in the dental chair because of increased pressure on abdominal vessels.
- Immunosuppression associated with liver transplantation patients and hence an increased risk of opportunistic and postoperative infections as well as acute graft-versus-host disease (mucositis) or chronic graft-versus-host disease, which resembles oral lichen planus.

GASTROINTESTINAL SYNDROMES

Plummer–Vinson Syndrome

Plummer–Vinson Syndrome (PVS; also termed Paterson–Brown–Kelly syndrome) classically presents as a triad of dysphagia, iron-deficiency anemia, and esophageal web. It mostly affects women in the age group of 40–70 years[132] and confers an increased risk of developing squamous cell carcinoma of the pharynx and the esophagus.[133]

The exact etiopathogenesis of PVS and formation of the esophageal web (a thin mucous membrane, composed of squamous epithelia[133]) is uncertain. However, the iron deficiency may induce iron-dependent enzyme dysfunction, leading to oxidative stress and DNA damages in epithelia of esophageal mucosa.[133] This may lead to atrophy of the mucosa and degradation of pharyngeal muscles, resulting in the development of esophageal webs.[134] Other possible factors include nutritional deficiencies (B vitamins), genetic predisposition, or autoimmune processes.[135]

The longstanding iron-deficiency anemia is responsible for the associated clinical features. General findings include dyspnea or difficulty in breathing, tachycardia, weakness, pallor, and koilonychia or spoon nails. Painless dysphagia may also be present, initially to solids but progressing to liquids over several years if untreated. The oral manifestations include atrophic glossitis with erythema or fissuring, angular cheilitis, and the development, or worsening, of oral ulceration.

Evaluation involves hematologic assays to determine the cause of the iron deficiency and the severity of the anemia. The upper gastrointestinal tract is assessed by video-fluoroscopy[136] or fiberoptic endoscopy, which enables assessment and diagnosis of any esophageal web or squamous cell carcinoma (which occurs in 10%–30% of patients[137]).

Medical management includes iron supplementation and will resolve the dysphagia in many patients.[133] Esophageal webs require endoscopic balloon dilatation or the use of dilators.[138,139]

Polyposis Syndromes

The gastrointestinal polyposis syndromes are a group of inherited cancer-predisposing syndromes with complex presentation,[140,141,142] and include those of Gardner, Peutz–Jegher, and Cowden. Despite these often, but not always, being associated with specific germline mutations, the phenotype may vary between individuals.[143] The specific diagnosis and treatment are therefore often determined by a combination of clinical assessment, inquiry of the family history, review of polyp pathology, and germline testing for causative genes.[144]

Gardner Syndrome

Gardner syndrome (GS), a rare autosomal dominant inherited disease, is a subgroup of familial adenomatous polyposis (FAP) and accounts for approximately 10% of FAP patients.[145] It is characterized by the presence of multiple polyps in the intestine as well as bony, cutaneous, dental, and ocular abnormalities,[146] due to mutations of the adenomatous polyposis coli (APC) gene on chromosome 5q21-22. The incidence of FAP is between 1 in 8300 and 1 in 14,025 births, affecting both sexes equally, with a uniform worldwide distribution.[147]

FAP is characterized by premalignant, adenomatous polyps of the colon and rectum, which progress to malignancy in untreated gene carriers. Carcinoma may develop at any age from the second to the seventh decade,[145] with a median age of 40 years.[145]

The clinical diagnosis of GS may be difficult due to the variable presence of extraintestinal features.[145] The extraintestinal manifestations include multiple osteomas, multiple impacted supernumerary teeth, connective tissue tumors, thyroid carcinomas, and hypertrophy of the pigmented epithelium of the retina. These lesions present themselves in a different chronologic order, but typically, cutaneous and bony lesions appear 10 years earlier than intestinal polyposis.[148]

As craniofacial bony and dental signs of GS often precede gastrointestinal symptoms,[146] OHCPs may play an important role in the diagnosis of FAP. In a patient with a family history of GS, dental radiography (such as a panoramic radiograph) can provide the earliest indication of the presence of this condition.[149] Dental abnormalities are present in 30%–75% and osteomas in 68%–82% of GS patients.[150,151]

Osteomas are slow growing and predominantly affect the mandible and maxilla, but can additionally affect the skull and long bones.[151] Bony exostoses, also called peripheral osteomas, can be palpable and be detected by routine radiography.[151,152,153] In the mandible, the osteomas may be central (characteristically near the roots of the teeth) or lobulated arising from the cortex, most commonly at the angle of the mandible.[151,153]

Dental anomalies include impacted teeth, supernumerary teeth, odontoma, congenitally missing teeth, and hypercementosis.[151] The simultaneous presence of osteoma(s) with dental anomalies is highly suggestive of underlying GS.[154]

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome (PJS) is an autosomal dominant condition characterized by characteristic hamartomatous polyps and distinctive mucocutaneous pigmentation.[155,156,157] It is caused by germline mutations of the STK11 tumor suppressor gene,[158] and has an incidence of between 1:50,000

and 1:200,000 births,[143,158,159] while the age at initial presentation varies from a few months to the fifth decade.[159]

The hamartomatous polyps occur most frequently in the small intestine (60%–90%), followed by the colon (25%–50%), stomach, and rectum.[158] They are characterized histopathologically by the unique finding of mucosa with interdigitating smooth muscle bundles in a characteristic branching tree appearance. They can cause abdominal pain, anemia, and gastrointestinal bleeding by intussusception or obstruction.[155,160].

Almost all patients present with mucocutaneous pigmentation, in the form of macules. These are often the first clinical sign and may affect the perioral tissues, lips, gingiva, hard palate, and buccal mucosa. The perioral pigmentation is distinctive in crossing the vermillion border and, while most of the cutaneous macules fade with age, the buccal mucosal pigmentation often persists.[156] Histologically, increased melanocytes are observed at the epidermal-dermal junction, with increased melanin in the basal cells.

A clinical diagnosis of PJS requires any two of (1) two or more Peutz–Jeghers-type hamartomatous polyps of the gastrointestinal tract; (2) typical hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; or (3) family history of PJS.[143] Patients fulfilling these criteria warrant germline mutation assessment. Consideration should also be given to esophagogastroduodenoscopy (EGD), colonoscopy, and video capsule endoscopy, no later than the early teenage years,[158] as well as ongoing surveillance, since malignancies in the gastrointestinal tract and elsewhere in the body occur in 10% of patients with this syndrome.[161] No specific oral treatment is necessary.

Cowden Syndrome

Cowden syndrome (CS) is an autosomal dominant disorder caused by a phosphatase and tensin homolog (PTEN) tumor suppressor gene mutation.[143] It has an estimated prevalence of 1:200,000[162] and is said to be a cutaneous marker of internal malignancies.[163–168]

The syndrome was originally described as being characterized by the presence of facial trichilemmomas, acral keratoses, papillomatous papules, and mucosal lesions,[163] and the diagnosis was based on the presence of these "pathognomonic" features together with other "major" and "minor" features. The subsequent identification of the PTEN gene and the ability to molecularly confirm a clinical diagnosis, as well as further research, have identified the association of a broader spectrum of clinical features with PTEN mutations.[143] As a result, an operational diagnosis is now made on the basis of a combination of major and minor criteria.[143]

In an individual this requires either:

- three or more major criteria, but one must include macrocephaly, Lhermitte–Duclos disease, or gastrointestinal hamartomas; or
- two major and three minor criteria.

In a family, where one individual meets PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a PTEN mutation, either:

- any two major criteria with or without minor criteria; or
- one major and two minor criteria; or
- three minor criteria.

The responses of facial papules to different treatment modalities, including topical 5-fluorouracil, oral retinoids, curettage, electrosurgery, cryosurgery, laser ablation, and surgical excision, are variable.[165–168]

Patients with CS require lifelong follow-up and repeat coloscopy in line with current recommendations,[143] while family members should be screened for the disease.

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16

Renal Diseases

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Kidneys play a vital role in maintaining internal balance (homeostasis) and a pivotal role in a number of basic physiologic functions, including filtration and excretion of metabolic waste products and toxins, blood pressure control, salt and water homeostasis, blood cell production, acid–base balance, and calcium (Ca^{2+}) homeostasis. Therefore, kidney diseases are one of the leading causes of morbidity, mortality, and healthcare expenditure. The traditional view of kidney function is limited and focuses on its regulation of excretory, endocrine, acid–base, and electrolytes domains. The more expanded view encompasses the role of kidneys in determining the composition of blood, contributing to immunologic balance, and engaging in constant cross-talk with the heart, gut, brain, and other vital organs.

This chapter provides a comprehensive and evidence-based overview of the renal structure, function, and diagnostic tools for impaired renal function, as well as oral symptoms and signs observed in patients with chronic kidney disease prior to and during in-center hemodialysis, patients undergoing peritoneal dialysis, and those received

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a kidney transplant. Finally, we describe the most current understanding of these diseases' etiology and pathogenesis, provide evidence-based dental therapy approaches, and highlight the importance of the interprofessional interaction between dental practitioners and the nephrology team.

KIDNEY STRUCTURE AND FUNCTION

The human kidneys are bean-shaped organs located in the retroperitoneum at the level of the waist. Each adult kidney weighs approximately 160 g and measures 10–15 cm in length. Coronal sectioning of the kidney reveals two distinct regions: an outer region called the cortex and an inner region known as the medulla (Figure 16-1). Structures that are located at the corticomedullary junction extend into the kidney hilum and are called papillae. Each papilla is enclosed by a minor calyx, which collectively communicates with the major calyces to form the renal pelvis. The renal pelvis collects urine flowing from the papillae and passes it to the bladder via the ureters. Vascular flow to the kidneys is provided by the renal artery, which branches directly from the aorta. This artery subdivides into segmental branches to perfuse the upper, middle, and lower regions of the kidney. Further subdivisions account for the arteriole–capillary–venous network or vas recta. The venous drainage of the kidney is provided by a series of veins leading to the renal vein and ultimately to the inferior vena cava.

The kidney's functional unit is the nephron (Figure 16-2) and each kidney is made up of approximately 800,000–1,600,000 nephrons. For a given individual, nephron endowment depends on maternal health, mainly intrauterine environment; micronutrients and protein deficiencies; exposure to tobacco, alcohol, and certain nephrotoxic medications; genetics; and other environmental factors. Each nephron consists of Bowman's capsule (surrounds the glomerular capillary bed), the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule (which empties into the collecting ducts). The glomerulus is a unique network of capillaries that is suspended between afferent and efferent arterioles enclosed within Bowman's capsule and that serves as a filtering funnel for waste. The filtrate drains from the glomerulus into the tubule, which alters the concentration along its length by various processes to form urine. The glomerulus funnels ultra-filtrate to the remaining portion of the nephron or renal tubule. Following filtration, the second step of urine formation is the selective reabsorption and secretion of filtered substances, which occur along the length of the tubule via active and passive transport processes.

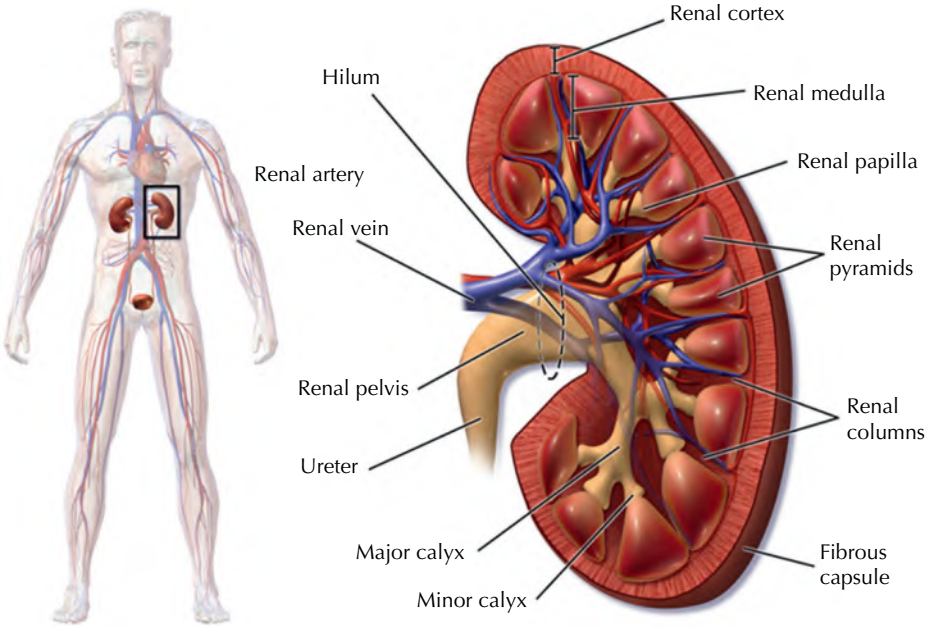

Figure 16-1 Coronal sectioning of the kidney reveals two distinct regions: an outer region called the cortex and an inner region known as the medulla. *Source:* https://commons.wikimedia.org/wiki/File:Blausen_0592_KidneyAnatomy_01.png. Licensed under the Creative Commons Attribution 3.0 Unported license.

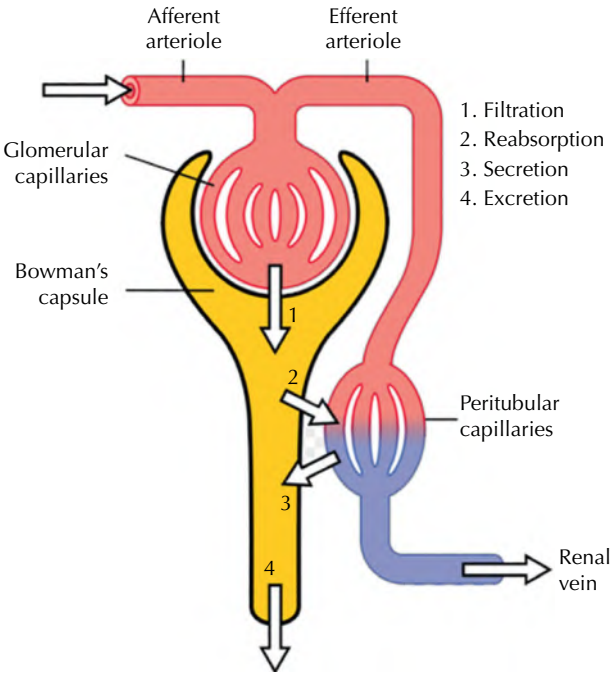

Figure 16-2 The kidney's functional unit is the nephron. *Source:* https://commons.wikimedia.org/wiki/File:Physiology_of_Nephron.png. Licensed under the Creative Commons Attribution 3.0 Unported license.

Table 16-1 Major functions of the kidneys.

Nonexcretory functions
Degradation of polypeptide hormones
Insulin
Glucagon
Parahormone
Prolactin
Growth hormone
Antidiuretic hormone
Gastrin
Vasoactive intestinal polypeptide
Synthesis and activation of hormones
Erythropoietin (stimulates erythrocyte production by bone marrow)
Prostaglandins (vasodilators that act locally to prevent renal ischemia)
Renin (important in regulation of blood pressure)
1,25-Dihydroxyvitamin D_3 (final hydroxylation of vitamin D to its most potent form)
Excretory functions
Excretion of nitrogenous end products of protein metabolism (e.g., creatinine, uric acid, urea)
Maintenance of ECF volume and blood pressure by altering Na^+ excretion
Maintenance of plasma electrolyte concentration within normal range
Maintenance of plasma osmolality by altering water excretion
Maintenance of plasma pH by eliminating excess H^+ and regenerating HCO_3^-
Provision of route of excretion for most drugs

ECF, extracellular fluid; H^+, hydrogen; HCO_3^-, bicarbonate; Na^+, sodium; pH, hydrogen ion concentration.

Each day, the kidneys excrete approximately 1.5–2.5 L of urine; although the removal of toxic and waste products from the blood remains their major role, the kidneys are also essential for the production of hormones (such as vitamin D and erythropoietin) and the modulation of salt and water excretion (Table 16-1). Once destroyed, nephrons do not regenerate. However, the kidney compensates for the loss of nephrons by hypertrophy of the remaining functioning units. Low nephron endowment and/or destruction from diseases reduce the number of nephrons significantly enough to cause hypertrophy (nephromegaly) and hyperfiltration of remaining nephrons. Most kidney donors maintain near normal kidney function after kidney donation that results in 50% reduction in nephron mass, with excellent long-term outcome and a very small risk of development of hypertension and albuminuria explaining a successful and orderly pattern of functional adaptation with nephron loss.[1] Structural and functional adaptations of kidneys compel us to rethink our view that progressive kidney diseases are due to the disorderly and inefficient function of nephrons. In reality, progressive kidney diseases such as hypertensive and diabetic nephropathies likely represent an extremely efficient function of too few nephrons unable to carry out their required tasks in spite of maximum functional adaptation in the face of ongoing destructive disease processes. Unfortunately, in the United States, progressive kidney diseases disproportionately affect minorities such as patients of African American and Hispanic origins, hence a preventive focus and treatment of hypertension (HTN) and diabetes mellitus (DM) play a pivotal role in order to decrease their incidence and prevalence.

FLUIDS, ELECTROLYTES, AND ACID–BASE HOMEOSTASIS

With advancing nephron destruction, water and electrolyte regulation becomes increasingly more difficult. Adaptations to sudden shifts in intake occur slowly, resulting in wide

swings in water and solute concentrations. The first clinical sign of diminished renal function is a decreased ability to concentrate the urine (isosthenuria). As a result of this inability to conserve water, dehydration ensues. With early renal insufficiency, sodium is also lost in the urine. This loss is often independent of the amount of water lost. As the renal disease progresses, salt and water handling becomes progressively less efficient, resulting in volume overload and leading to hypertension and congestive heart failure. When glomerular filtration becomes markedly diminished, the distal tubule can no longer secrete sufficient potassium, leading to hyperkalemia.

In a healthy body, the acid–base balance is maintained via buffers, respiration, and the amounts of acid or alkaline wastes in the urine; this is because the daily load of endogenous acid is excreted into the urine with buffering compounds such as phosphates. As the glomerular filtration rate (GFR) progressively decreases, the tubular excretory capacity for positive hydrogen (H^+) ions is overwhelmed because renal ammonia production becomes inadequate. In its early phases, the resultant acidosis usually has a normal anion gap. As the kidney deteriorates, metabolically derived acids accumulate, leading to an increase in the anion gap. Clinically, this metabolic acidosis is manifested as anorexia, nausea, fatigue, weakness, and Kussmaul's respiration (a deep gasping respiration similar to that observed in patients with diabetic ketoacidosis).

DIAGNOSTIC PROCEDURES IN KIDNEY DISEASES

Biochemical Profile

In the presence of kidney dysfunction, changes in homeostasis are reflected in serum chemistry. Sodium, chloride, blood urea nitrogen (BUN), glucose, creatinine, carbon dioxide, potassium, phosphate, and Ca^{2+} levels provide useful tools to evaluate the degree of renal impairment and disease progression. Serum creatinine and BUN are often important markers to the GFR. Both of these products are nitrogenous waste products of protein metabolism that are normally excreted in the urine, but they may increase to toxic levels in the presence of renal dysfunction. A characteristic profile of changes occurs with advancing renal dysfunction, including elevations in serum creatinine, BUN, and phosphate, compared with low levels of serum Ca^{2+}. Laboratory findings commonly seen in renal disease are summarized in Table 16-2.

Creatinine originates from the nonenzymatic hydrolysis of creatine and phosphocreatine found almost exclusively in muscles. This hydrolysis occurs at a constant rate. Serum creatinine concentration not only depends on muscle mass but also on tubular secretions, dietary protein intake, hepatic synthesis (low in liver diseases), and intestinal exchange. BUN and cystatin C also share properties of acceptable markers for renal clearance (Table 16-2). Combined GFR estimates based on creatinine and cystatin C have been presented, and their use will likely increase in future.[2]

Urinalysis

The most important aspects of urine examination in patients with renal disease include the detection of protein or blood in the urine, determination of the specific gravity or osmolality, and microscopic examination. The hallmarks of renal dysfunction detected by urinalysis are hematuria (the presence of blood in the urine) and proteinuria (the presence of protein/albumin in the urine). Hematuria can result from bleeding anywhere in the urinary tract. Rarely, hematuria is a sign of clinically significant renal disease. Microscopic hematuria in patients younger than 40 years is almost always benign, and further workup is rarely indicated. Occasionally, significant underlying disease, such as a neoplasm or proliferative glomerulonephritis, can cause hematuria. However, the accompanying active sediment of proteins and red blood

Table 16-2 Laboratory changes in progressive renal disease.

Laboratory Test	Normal Range	Level in Symptomatic Renal Failure
Glomerular filtration rate	90–120 mL/min/1.73 m^2	< 15 mL/min
Creatinine clearance	85–125 mL/min (female)	10–60 mL/min (moderate failure)
	97–140 mL/min (male)	< 15 mL/min (severe failure)
Serum creatinine	0.6–1.20 mg/dL	> 5 mg/dL
Blood urea nitrogen	8–18 mg/dL	> 50 mg/dL
Serum calcium	8.5–10.5 mg/dL	Depressed
Serum phosphate	2.5–4.5 mg/dL	Elevated
Serum potassium	3.8–5.0 mEq/L	Elevated

cell casts makes the diagnosis relatively straightforward. In older people, hematuria warrants further evaluation, including urologic studies to rule out prostatic hypertrophy and neoplasia, urine cultures to rule out infection, urine cytology, and advanced renal studies (such as renal ultrasound or noncontrast computed tomography [CT] scan of the abdomen and pelvis) to rule out intrinsic abnormalities.

Proteinuria (a urine dipstick will only detect albumin) is probably the most sensitive sign of renal dysfunction. The upper limit of normal urinary protein is 150 mg per day; anything greater should be considered pathologic and warrant further investigation. Patients who excrete >3 g of protein per day have, by definition, a glomerular pathology and carry a diagnosis of nephrotic syndrome (discussed below). However, many benign conditions (including exercise, stress, and fever) can produce transient elevated protein in the urine. Daily proteinuria estimation can be ascertained by measuring the total protein-to-creatinine ratio (expressed in grams of protein/grams of creatinine), which can be extrapolated to grams of proteinuria per day. Should any doubt still exist, or precise quantification is necessary, 24-hour urine collection can be performed. This procedure has fallen out of favor, as it is cumbersome and somewhat difficult for the patient to complete accurately. The 24-hour urine test remains a useful tool for determining daily salt intake, calculating creatinine and urea clearance, and while analyzing the urinary metabolic profile in recurrent nephrolithiasis. Urine specific gravity is measured to determine the concentration of urine. In chronic kidney disease (CKD), the kidney initially loses its ability to concentrate the urine and then loses its ability to dilute the urine, resulting in a relatively fixed osmolality near the specific gravity of plasma. This occurs when approximately 80% of the nephron mass has been destroyed.

Creatinine Clearance Test

The GFR assesses the amount of functioning renal tissue and can be calculated indirectly by the endogenous creatinine clearance test. Creatinine is a breakdown product of muscle, liberated from muscle tissue, and excreted from the urine at a constant rate. This results in a steady plasma concentration of 0.7–1.5 mg/dL (often slightly higher in men because of increased muscle mass). Creatinine is 100% filtered by the glomerulus and is not reabsorbed by the tubule. Although a very small portion is secreted by the tubule, this test is an effective way to estimate the GFR. GFR is estimated by incorporating the serum creatinine into a formula, along with the patient's age, weight, and race, and is expressed in milliliters per minute (min) of clearance (mL/min/1.73 m^2). The two most common equations used are the Cockcroft–Gault formula and the modified diet in renal disease formula (Figure 16-3).

In some instances, it is necessary to measure absolute GFR. To accomplish this, a 24-hour urine specimen and a blood sample in the same 24-hour period are required. This has fallen out of favor, however, as the test is cumbersome and inconvenient for the patient.

Renal Ultrasonography

Grayscale ultrasonography and Doppler ultrasonography are the most commonly used and relied-upon techniques for radiologic examination of the kidneys. These diagnostic procedures use high-frequency sound waves (ultrasound) directed at the kidneys to produce reflected waves or echoes from tissues of varying densities, thereby forming images (sonograms). Ultrasound is a noninvasive method to determine kidney size, presence of retained urine within the renal pelvis or calices (hydronephrosis), identification and limited evaluation of vascular structures, and presence of fluid-filled cysts within the kidney parenchyma.[1–4] Renal ultrasonography is also utilized to localize the kidney during a percutaneous biopsy. Because it is noninvasive, readily available in most imaging centers, does not use radiation or intravenous (IV) contrast, and is quick, renal ultrasonography is the imaging modality of choice for initial evaluation of the kidneys. It is also the modality of choice for pregnant patients because it does not use radiation to obtain clinical images. Doppler ultrasound is used to assess

Cockcroft-Gault Equation:

$$\text{eGFR} = \frac{[\,(140\text{-age}) \times \text{Mass(kg)} \times (0.85 \text{ if female})]}{72 \times \text{SCr (mg/dL)}}$$

MDRD Formula:

$$\text{eGFR} = 170 \times \text{SCr}^{-0.999} \times \text{Age}^{-0.176} \times [0.762 \text{ if female}] \times [1.18 \text{ if Black}] \times \text{BUN}^{-0.170} \times \text{Albumin}^{0.318}$$

Figure 16-3 Cockcroft–Gault equation and MDRD formula. *Source:* Adapted from Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31–41; and Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461–470.

vascular function and flow. Grayscale ultrasound also helps identify kidney stones, cysts, and parenchymal disease processes, and in assessment of bladder function in more complex kidney diseases.

Computed Tomography

CT imaging is utilized when the entire genitourinary (GU) tract or retroperitoneum needs evaluation. It provides more information about the structures of the GU tract (ureters, bladder, urethra, and prostate) and retroperitoneum, as well as surrounding structures that could contribute to renal pathology (tumors, lymphadenopathy, masses). Furthermore, because of technologic advances over the years, CT scanners are far more cost-effective, quicker, and more readily available in hospitals or imaging centers. Like other CT scans, the procedure can be performed with or without IV contrast for vascular enhancement; with CKD, caution must be used with IV contrast media, as this can incur further renal decline (see the Acute Kidney Injury section). Contrast-induced nephropathy is likely secondary to a vasoconstrictive effect of contrast media in addition to oxidative kidney injury. A noncontrast CT scan of the abdomen and pelvis is the imaging modality of choice when investigating the presence of kidney stones. A newer modality of CT scan, dubbed CT-urography, can be used for a detailed, three-dimensional evaluation of the GU tract.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is not commonly utilized as the first imaging modality for the diagnosis of kidney disorders. This modality can give much of the same information as a CT scan, with far more detail and information about specific tissues and structures. The cost, time investment, and, to a lesser extent, patient comfort prohibit this modality from becoming mainstream in kidney disease evaluation. Furthermore, the contrast medium used for magnetic resonance angiography (MRA) is gadolinium based. Gadolinium has been linked as a cause of a progressive skin fibrosis called nephrogenic systemic fibrosis (NSF), which is seen exclusively in patients with advanced kidney disease (GFR <30 mL/min/1.73 m^2) or who are on dialysis. This condition carries a high morbidity and mortality burden; therefore, the gadolinium-based contrast medium is generally not administered when the patient's GFR is <30 mL/min/1.73 m^2. Recent data indicate that NSF is exceedingly uncommon when macrocyclic or newer linear gadolinium compounds are used in patients with GFR <30 mL/min/1.73 m^2. This knowledge will improve access to gadolinium-based enhanced MRI when medical benefits clearly outweigh a very small risk.

The primary kidney-related indications for utilizing MRI/MRA is either the evaluation of the renal vasculature if significant renal artery stenosis is suspected, or evaluation of a mass, solid or cystic, when radiocontrast cannot be used with a CT scan.

Intravenous Pyelography

Prior to ultrasonography and CT, IV pyelography was the most commonly used and relied upon radiologic examination of the kidneys. Following the IV injection of a contrast medium, a plain-film abdominal radiograph is taken. Further films are exposed every minute for the first 5 minutes, followed by a film exposed at 15 minutes and a final film exposed at 45 minutes. Since various diseases of the kidney alter its ability to concentrate and excrete the dye, the extent of renal damage can be assessed. The location and distribution of the dye itself give information regarding the position, size, and shape of the kidneys. This examination has limited application, particularly in patients with severe azotemia (the building up of nitrogenous waste products in the blood)—that is, those whose BUN >70 mg/dL); for them this test is deferred because there is sufficiently low glomerular filtration to prevent the excretion of the dye, rendering information about the kidney nondiagnostic.

Nuclear Medicine (Radionuclide Scintigraphy)

While the aforementioned imaging modalities can provide structural information, radionuclide scintigraphy can provide qualitative and quantitative functional information about the kidneys. Using radiolabeled tracers, information can be garnered about renal blood flow, glomerular filtration, or urinary excretion. Several compounds are available that incorporate technetium-99 as the radioactive isotope; these include diethylenetriamine pentaacetic acid, mercaptoacetyl triglycine, and ^{131}I-o-iodohippurate (^{131}I-OIH). Measurement of these radiolabeled substances can be used to calculate true GFR or the presence/absence of renal blood flow. They can also be combined with captopril to investigate possible renal artery stenosis or furosemide to uncover unilateral urinary obstruction. Radionuclide scintigraphy is the modality of choice to accurately measure GFR in patients who have undergone a spinal injury, as serum creatinine is linked to muscle mass, which may be disproportionately lower in this patient population. This modality is frequently used in kidney transplant (KT) evaluation, as IV radiocontrast may be contraindicated and renal ultrasound may be equivocal.

Kidney Biopsy

The development and growing use of renal biopsy have considerably advanced the knowledge of the natural history of kidney diseases. Percutaneous needle biopsy guided by ultrasonography or CT can usually be performed by nephrologists, with the patient lying in a prone position with one to two firm pillows. Approximately 25% of cardiac output flows to the kidney; hence, intrarenal and perirenal bleeding may be common sequelae, with serious postprocedural bleeding and hematuria occurring in 5% of cases. The incidence of postprocedural bleeding also depends on needle size. When a 16G or 18G needle is used, 0.5% of patients require blood transfusion, as opposed to 2% with the use of a 14G needle. Careful assessment of the risk–benefit ratio is required before performing a kidney biopsy. Patients are placed on bed rest for at least 6 hours following the procedure while vital signs and abdominal changes are monitored. Safe conditions for performing kidney biopsy include hemoglobin >9 g/dL, platelets >100,000 × 10^9/L, normal coagulation profile (prothrombin time or PT/partial thromboplastin time or PTT), blood pressure preferably <160/90 mm Hg, and no active urine infection. Single kidney, atrophic kidneys with thin cortex, difficult anatomy with multiple kidney cysts, uncontrolled hypertension, and active pyelonephritis (infection) are relative contraindications of kidney biopsy.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is defined by a rapid increase in serum creatinine, a decrease in urine output, or both. AKI occurs in approximately 10%–15% of patients admitted to hospital, while its incidence in intensive care has been reported in more than 50% of patients. Complete recovery following AKI may not occur predisposing patients with residual kidney damage resulting in CKD. AKI is not a single disease, but rather a loose collection of diverse syndromes such as sepsis, cardiorenal syndrome, and urinary tract obstruction. Serum creatinine and urine output can be used to stage AKI based on AKI Network (AKIN) criteria (Table 16-3).

Sepsis, shock, medications, surgery, pregnancy-related complications, and trauma are the most common causes of AKI (Table 16-4). Unlike patients who develop CKD, patients with AKI usually have normal baseline renal function, yet mortality from AKI even with medical intervention, including dialysis, remains high. The causes of AKI are often divided into three diagnostic categories: prerenal failure, postrenal failure, and acute intrinsic renal failure.

Table 16-3 Staging Acute Kidney Injury (AKI) based on AKI Network criteria.

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline *or* ≥0.3 mg/dL (≥26.5 μM/L) increase	<0.5 mL/kg/hr for 6–12 hrs
2	2.0–2.9 times baseline	<0.5 mL/kg/h for 12 hrs
3	3.0 times baseline *or* Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 μM/L) *or* Initiation of renal replacement therapy *or* In patients <18 years, decrease in eGFR to <35 mL/min/1.73m^2	<0.3 mL/kg/h for ≥24 hrs OR Anuria for ≥12 hrs

eGRF, estimated glomerular filtration rate.
Source: Modified from Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet*. 2012;380(9843):756–766.

Such denominations are increasingly becoming arbitrary, as significant overlap exists between prerenal AKI and acute intrinsic AKI (acute tubular necrosis, or ATN).

Prerenal Acute Kidney Injury or Prerenal Azotemia

Prerenal AKI is by definition caused by inadequate blood flow to the kidneys without significant structural damage, and therefore is rapidly reversible following volume expansion (volume-responsive prerenal AKI) and treatment of the underlying cause that results in volume depletion. Septic shock due to decreased effective circulating volume from endotoxin-mediated vasodilation and loss of extracellular volume from diarrhea, vomiting, blood loss from trauma, and so on are frequent causes of prerenal AKI. Prerenal AKI represents hypoperfusion of kidneys from events occurring "outside" the kidneys. Decreased effective circulating volume is sensed by protective mechanisms such as activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), resulting in increased sodium reabsorption in the kidneys (Table 16-4).

Prerenal AKI can be diagnosed with urine indices such as low fractional excretion of sodium (FeNa) or low fractional excretion of urea (FeUrea) in the presence of low urine output (oliguria; urine output <400 mL/24 hrs). Etiologies such as heart failure, cirrhosis of liver, radiocontrast exposure, and bilateral renal artery stenosis can result in low FeNa due to

Table 16-4 Pathophysiology and mechanism of injury in select clinical conditions resulting in acute kidney injury.

Mechanism of Injury	Pathophysiology
Renal hypoperfusion Renal hypoperfusion activates sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS). Failure of renal autoregulation and resultant renal hypoperfusion lead to ATP depletion that activates epithelial cellular injury and death via necrosis or apoptosis	• Volume depletion (from diarrhea, vomiting, diuretic use, etc.) • Systemic vasodilatation • Increased vascular resistance (inotrope use in ICU, RAS, HTN, etc.) **Result:** Endothelial injury and intrinsic AKI or ATN
Acute worsening of cardiac function	• Reduced effective circulation fluid volume or an increase in central venous pressure **Result:** Cardiorenal syndrome (kidney dysfunction from acute worsening of cardiac function)
Nephrotoxin exposure Nephrotoxic drugs (e.g., antibiotics, contrast media, NSAIDs), and endogenous toxins (e.g., myoglobin, uric acid among others)	• Direct cytotoxic effect on renal tubular epithelial or endothelial cells • Impaired intrarenal hemodynamics • Precipitation of metabolites or crystals, among others **Result:** Acute tubular necrosis
Sepsis and septic shock Capillary microthrombi generation, decreased tissue perfusion, and imbalance in nitric oxide production	• Endothelial damage leading to increased vascular permeability • Suppression of cardiac function **Result**: Increased interstitial edema, redistribution of intrarenal perfusion, inflammation and septic cardiomyopathy leading to ischemic ATN
Major surgery Blood loss, third spacing of fluids, peripheral vasodilation, myocardial depression	• Effect of anesthesia and medications • Increased level of circulating cytokines and reactive oxygen species • Endotoxin load from gut and tissue hypoperfusion **Result:** Impaired renal perfusion and ischemia-reperfusion injury leading to prerenal and intrinsic AKI
Intraabdominal hypertension Sustained intraabdominal pressure >12 mm Hg (volume overload, ascites or interstitial edema of bowel loops)	• Reduced arterial inflow and venous outflow • Elevated hydrostatic pressure in Bowman's space (area of the nephron where filtrate enters after passing through filtration slits, also known as capsular space or urinary space) **Result:** Decreased renal hypoperfusion leading to prerenal AKI and if left uncorrected intrinsic ATN

AKI, acute kidney injury; ATN, acute tubular necrosis; HTN, hypertension; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; RAS, renal artery stenosis.
Source: Based on Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet*. 2012;380(9843):756–766.

perceived decrease in effective circulating volume sensed by the kidneys. In theory, a detailed history, clinical examination of accurate volume status, and, in carefully selected cases, invasive monitoring of volume status may help establish the correct diagnosis. Medications such as diuretics, blockers of the RAAS system, and nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently implicated in prerenal AKI. Newer urinary biomarkers may help in the diagnosis of AKI before the elevation of serum creatinine.[4] When prerenal AKI persists for a long time, continued hypoperfusion of kidneys will lead to ischemia and ATN or intrinsic AKI.

Intrinsic Acute Kidney Injury

Intrinsic AKI or ATN is characterized by the presence of structural damage to the kidneys, which is not rapidly reversible by correcting underlying or causal conditions. The outer medullary parenchymal region of the kidney is metabolically very active with high energy demands, but due to the anatomic arrangement of the renal vasculature, oxygen supply in this area is limited, making it highly susceptible to cellular kidney injury with prolonged ischemia. Firmly establishing cellular damage clinically is difficult. Most clinicians consider prerenal AKI and intrinsic AKI as a continuum, as both often coexist with patchy areas of structural cellular damage (ATN, intrinsic AKI) interspersed with areas of hypoperfusion that may still be structurally intact and upon receiving reperfusion (volume expansion) can rapidly resume normal nephron filtration function (prerenal AKI).

Glomerular disease, vascular disease, and tubulointerstitial disease comprise the three additional causes of acute intrinsic

renal failure and describe the sites of pathology. Glomerulonephritis is an uncommon cause of AKI and usually follows a more subacute or chronic course. However, when fulminant enough to cause AKI, it is associated with active urinary sediment (dysmorphic red blood cells [RBCs], acanthocyturia, RBC casts), oliguria, and rapid deterioration of renal function. Prominent clinical and laboratory findings include hypertension, proteinuria, microscopic hematuria, and RBC casts. Postinfectious, membranoproliferative, and rapidly progressive glomerulonephritis, as well as glomerulonephritis associated with endocarditis, are the most common glomerular diseases to cause a sudden renal deterioration. The pathogenesis of glomerulonephritis appears to be related to the immunocomplex and complement-mediated damage to the kidney.[4]

Vascular diseases that induce AKI cover the spectrum of vessel size from large (renal artery and vein) to microscopic (afferent and efferent arterioles of the glomerulus). Large vessel occlusive processes such as renal arterial or venous thromboses present as a classic triad of severe and sudden lower back pain, severe oliguria, and macroscopic hematuria. Medium- to small-vasculature AKI is often caused by autoimmune vasculitides, thrombotic microangiopathies, or cholesterol crystal embolization.

By far the most common causes of acute intrinsic failure are tubulointerstitial disorders (>75% of cases), including interstitial nephritis and ATN. Infiltrative diseases (such as lymphoma or sarcoidosis), infections (such as syphilis and toxoplasmosis), and medications are the leading causes of interstitial nephritis. With drug-induced interstitial nephritis, there are accompanying systemic signs of a hypersensitivity reaction, and the presence of eosinophils is a common finding in the urine. Although renal function usually returns to normal with the discontinuation of the offending drug, recovery may be hastened with corticosteroid therapy. ATN is a renal lesion that forms in response to prolonged ischemia or exposure to nephrotoxin, among other causes. ATN remains more of a clinical diagnosis of exclusion than a pathologic diagnosis. The period of renal failure associated with ATN can range from weeks to months, and the major complications of this transient failure are imbalances in fluid and electrolytes, as well as uremia. Serum levels of BUN and creatinine peak, plateau, and slowly fall, accompanied by a return of renal function over 10–14 days in most cases.[4]

Sudden renal failure in hospitalized patients is often very apparent from either oliguria or an increase in BUN and creatinine levels. However, renal dysfunction in the outpatient population is frequently more subtle. A patient can present to the dental office with vague complaints of lethargy and fatigue or entirely without symptoms. These patients can go undiagnosed but for abnormal results on routine urinalysis, the most common test for screening for renal disease.

Postrenal Failure

Postrenal causes of failure are less common (<5% of patients) than prerenal causes. Postrenal failure refers to conditions that obstruct the flow of urine from the kidneys at any level of the urinary tract, and that subsequently decrease the GFR. Postrenal failure can cause almost total anuria, with complete obstruction or polyuria. Renal ultrasonography often shows a dilated collecting system (hydronephrosis). Obstructive uropathy is, most commonly, seen in older men as a result of the enlargement of the prostate gland. If present in females, a thorough pelvic examination is warranted to elicit the cause of the obstruction. Although postrenal failure is the least common cause of AKI, it remains the most treatable.[4]

CHRONIC KIDNEY DISEASE

Epidemiology and Progression

The prevalence of kidney diseases worldwide is estimated to be between 8% and 16%.[5] In the United States, over 30 million people or approximately 15% of US adults are estimated to have CKD and are at risk for progression of their renal disease (Figure 16-4).[6] Based on Medicare data assessing patients older than 65 years, the prevalence of recognized CKD in the United States has steadily risen year after year across all stages of CKD. From 2016 to 2017, the proportion of Medicare patients with recognized CKD increased from 13.8% to 14.5%, and these patients used 7.2% of total Medicare expenditure for less than 2% of the eligible Medicare patient population. As a result, CKD remained the ninth leading cause of death in the United States in 2017.

CKD is classified according to the GFR (Table 16-5).[7]

Diabetes and hypertension are major disease processes that lead to CKD and ESRD. The burden of CKD may be examined in several ways, including individual or societal costs, attributable or excess mortality, years of life lost (YLL), and disability-adjusted life years (DALYs). DALYs include YLLs plus years of poor health or disability. Elevated fasting plasma glucose levels, overweight, obesity, diets high in sodium, sugar-sweetened beverages, and elevated systolic BP account for significant healthcare cost burden in CKD progression.[8] Globally, CKD incidence increased by 89% and CKD-attributable deaths swelled by 98%, according to data from the Global Burden of Disease Study, which incorporated kidney disease data from 1990 to 2016.[9] Strong disparities in race, sex, and socioeconomic status continue in the United States and worldwide in the ESRD population. The lifetime risk of ESRD is more than twofold higher among non-Hispanic black and Hispanic men compared

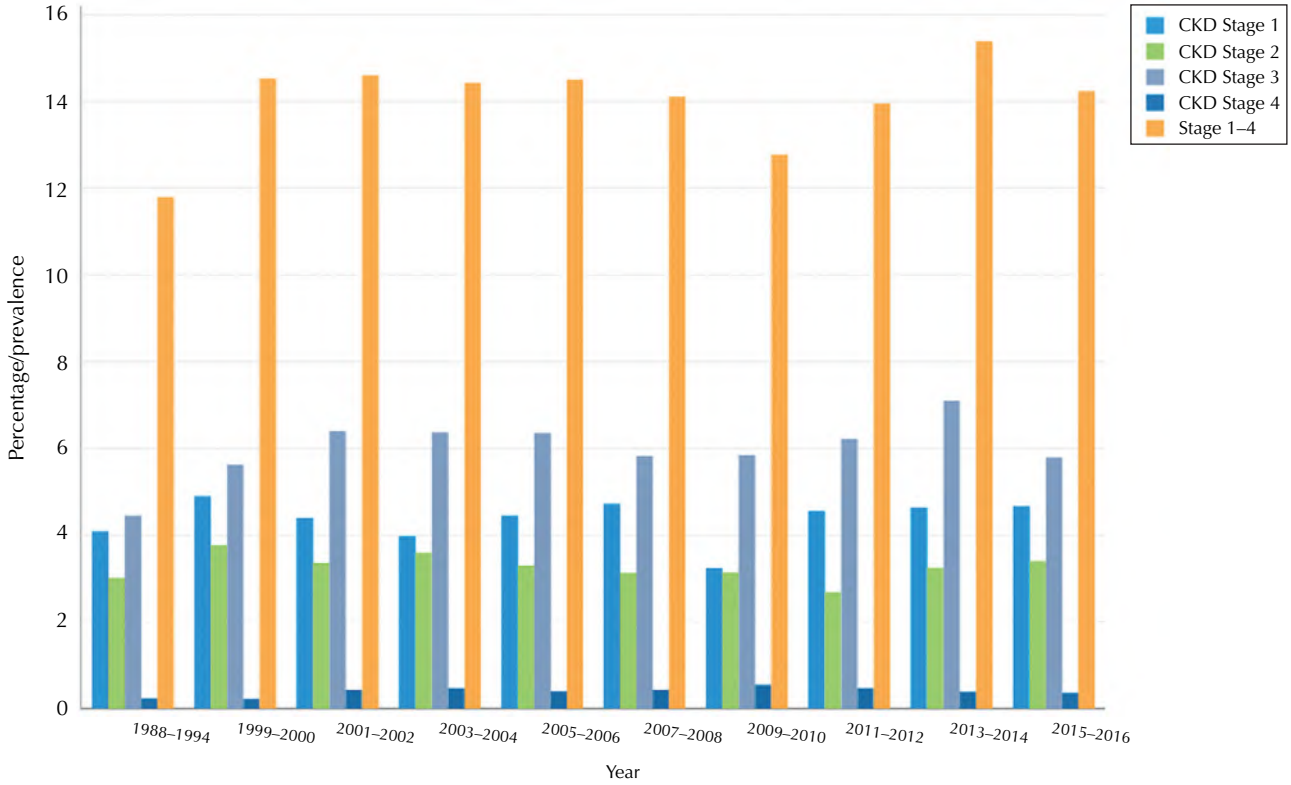

Figure 16-4 Prevalence of CKD Stages 1–4 by Year: Data from the National Health and Nutrition Examination Survey. *Source:* Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System website. https://nccd.cdc.gov/CKD. Accessed May 1, 2019.

Table 16-5 Classification of Chronic Kidney Disease (CKD) based on Glomerular Filtration Rate (GFR).

Stage of CKD	Definition	GFR (mL/min/1.73 m^2)
Stage 1	Kidney damage with normal GFR	≥90
Stage 2	Kidney damage with mild decrease in GFR	60–89
Stage 3A	Mild to moderate decrease in GFR	45–59
Stage 3B	Moderate to severe decrease in GFR	30–44
Stage 4	Severe decrease in GFR	15–29
Stage 5	End-stage renal disease (ESRD)	<15
Stage 6	ESRD on dialysis therapy	<15 with symptoms requiring dialysis therapy

Source: Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *New England Journal of Medicine.* 2014;371(1):58–66. © 2014, Massachusetts Medical Society.

with Caucasian men. In recent years, studies have started to examine the role of recreational drug use in CKD progression.[10] Past or present marijuana use is not proven to be associated with an increased risk of kidney disease; however, persistent smoking, heroin, cocaine, or methamphetamine use is associated with increased risk of CKD progression and increased mortality among adults with established CKD. Given the rising incidence of CKD, screening for kidney disease with urinary albumin excretion has been attempted at a population level. Unfortunately, widespread population-based screening models have not proved to be cost-effective except in targeted high-risk individuals with hypertension and DM. Urinary albumin excretion above 300 mg/g of creatinine is associated with a high risk of progression to ESRD and increased cardiovascular mortality.[4]

Some medications such as cimetidine, trimethoprim, corticosteroids, pyrimethamine, salicylates, and active vitamin D metabolites have been reported to increase plasma creatinine without influencing its glomerular filtration via inhibiting the distal secretion of creatinine. Patients may present

with worsening serum creatinine but preserved renal function while taking the above-listed medications. Low thyroid function is associated with decreased GFR by decreasing renal blood flow, but not increased rates of kidney disease progression and ESRD.[11]

Diet and Chronic Kidney Disease

High sodium intake may exacerbate HTN and CKD progression. Motivated patients frequently ask about advice with regard to their fluid intake and diet. A recent study showed that drinking at least two cups of coffee per day was associated with a significantly lower risk of progression to ESRD.[12] The renal benefits of coffee consumption may, in part, be secondary to chlorogenic acids that replenish glutathione and prevent oxidative injury to proximal tubular cells.[12] In contrast, in patients with polycystic kidney disease (autosomal dominant kidney diseases with progressive bilateral kidney cysts and progression to ESRD) a reduction in caffeine intake has been recommended, because caffeine induces cyclic adenosine monophosphate, which is involved with cyst growth and disease progression. Diets low in animal protein and red meat may help preserve kidney function, provided nutritional parameters are carefully monitored and malnutrition is avoided. Increasing water intake has not been shown to reduce the risk of kidney function decline.[13] Patients with kidney stones are advised to drink a sufficient amount of water to maintain urine output in the vicinity of 2.5–3.0 L, in order to minimize recurrent stone formation. For the general population, benefits of prescribed water intake in slowing the progression of CKD have not been identified. Sugar-sweetened and artificially sweetened beverage intake is associated with higher risks of non-dialysis-dependent CKD, and their intake should be minimized.[14] Control of diabetes and HTN will certainly help in slowing the progression of CKD.

Uremic Toxins, the Microbiome, and Chronic Kidney Disease

The term "microbiota" refers to the ensemble of microorganisms (composed of bacteria, bacteriophage, fungi, protozoa, and viruses) that live in or on the human body. The microbiome is the collective genome of the microbes. The interplay between the oral and colonic microbiome and ESRD is an active area of research.

A significant adaptation of gut function can assist in the excretion of solutes and water when kidney function is impaired. The gut assumes a progressively larger role in nitrogen waste excretion and potassium homeostasis that compensates, to a certain extent, for the loss of renal excretory function. Diarrhea was induced to treat uremia when dialysis was unavailable to physicians. Gut dialysis has been successfully used in animal and human renal failure.[15] In addition to its role in salt and water absorption, potassium excretion, and feces propulsion, the colon plays a vital role in protein and energy metabolism in close synergy with the resident colonic microbiome. The gut microbiome has been shown to play a pivotal role in the metabolic derangements seen in patients with CKD.[16]

Chronic Kidney Disease, End-Stage Renal Disease, and Cardiovascular Mortality

Although it is often perceived that standard dialysis treatment has been mostly unchanged for years, the outcomes in patients with ESRD have steadily improved. Even with this improvement, the five-year hemodialysis (HD) survival rate across different nations ranges from 39% in the United States to 60% in Japan.[17] The percentage of deaths in patients undergoing dialysis that can be attributed to cardiac arrest approaches 40%. The rate of sudden cardiac death is nearly 20-fold higher in the dialysis population than in the general population. In patients undergoing dialysis, longer interdialytic interval, coexisting electrolyte abnormalities, mainly hyperkalemia, and massive fluctuation of volume status between dialysis days are all associated risk factors, resulting in higher cardiovascular mortality. Atrial fibrillation may act as a precipitator of heart failure and other dysrhythmias.[18] Patients with CKD and ESRD have a higher incidence of atrial fibrillation and stroke, requiring treatment with Coumadin or one of the newer direct thrombin inhibitors. These patients, on the other hand, also have higher bleeding risk from anticoagulation, requiring careful evaluation of the risk–benefit ratio.

The natural history, progression, and outcomes of associated complications of chronic kidney disease are outlined in Table 16-6.

Renal Replacement Therapy in End-Stage Renal Disease

The human kidney is responsible for the composition of plasma. In addition to its excretory and synthetic functions (production of erythropoietin, activation of vitamin D, and others), the kidney's role as a regulator of immune function is also being recognized. There are well-established communication networks between the heart, brain, liver, gut, endocrine

Table 16-6 Natural history, progression, and outcomes of associated complications of chronic kidney disease.

CKD- and ESRD-Related Complications	Natural History and Progression	Treatments and Outcome
Salt and water retention and HTN	• Progressively worsens HTN and results in concentric left ventricular hypertrophy • Contributes to higher incidences of atrial fibrillation and diastolic heart failure • With the progression of CKD, adherence to a low salt diet is pivotal in maintaining acceptable volume status	• Systolic BP <120 mm Hg can be a target in patients with a high degree of protein loss in urine[19] • Loop diuretics are frequently required to control BP in patients with volume overload and edema; they have no effect on cardiovascular system outcomes
Anemia of CKD and ESRD[20]	• EPO deficiency from progressive CKD • Iron deficiency frequently coexists and can make EPO response suboptimal • Normalization of hemoglobin with supplemental EPO does not improve disease progression and mortality	• Optimal dose of EPO or IV iron not established • Oral iron poorly absorbed in advanced CKD and ESRD • Outcome limited to symptom improvement
CKD-mineral bone disease[21]	• Spectrum includes biochemical abnormalities, renal osteodystrophy, and soft tissue calcifications • Secondary and tertiary hyperparathyroidism ensues if phosphorous control remains suboptimal	• High blood phosphate levels, deficiency in vitamin D, and secondary hyperparathyroidism should be monitored and treated with phosphate binders, nutritional vitamin D, and analogs of 1,25-dihydroxyvitamin D
Metabolic acidosis and electrolyte abnormalities[22]	• In the early stages of CKD, there is a positive acid balance without low plasma bicarbonate due to buffering and renal adaptation • In later stages of CKD and ESRD, chronic metabolic acidosis contributes to skeletal muscle catabolism, insensitivity to endocrine hormones, and bone disease • In advanced stages of CKD and ESRD, hyperkalemia becomes progressively worse	• Alkali therapy with sodium bicarbonate may be required to correct acidosis • Stopping of angiotensin-converting enzyme inhibitors and gut binding of potassium may be required • Intractable metabolic acidosis and hyperkalemia frequently require initiation of dialysis

BP, blood pressure; CKD, chronic kidney disease; EPO, erythropoietin; ESRD, end-stage renal disease; HTN, hypertension; IV, intravenous.

system, and kidneys. With the progression of kidney disease, eventually renal replacement therapy (RRT) may be required. RRT does barely replenish 10%–15% of normal renal function. There are no uniform criteria based on the percentage of kidney function loss that absolutely necessitates the onset of dialysis therapy. Need for dialysis is frequently based on advanced uremic symptoms such as nausea, vomiting, metallic taste, loss of appetite or failure to thrive, intractable volume overload or metabolic acidosis, and life-threatening electrolyte abnormalities such as hyperkalemia.[23] Occasionally, anemia that fails to respond to a maximum allowable dose of erythropoietin (EPO) or uremic bleeding diathesis may require initiation of RRT. Uremic encephalopathy, uremic pericarditis, and pericardial effusion are also acceptable indications to start RRT. RRT includes hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT). For eligible patients, KT remains the best and most cost-effective form of RRT. Unfortunately, over the last few decades the number of patients waiting for KT has steadily increased, but the number of cadaveric and live kidney donations has lagged behind, making transplant waitlist time progressively longer for all waitlisted patients. Human artificial kidney transplantation and xenotransplantation remain exciting future innovations, but are still far from day-to-day clinical application. While these advances are very promising, existing patients have to make a choice between various forms of dialysis therapy while waiting on a transplant list, or pursue symptoms-guided conservative medical therapy. In elderly patients with significant medical comorbidities and frailty, dialysis seldom adds to a meaningful quality of life. Conservative medical therapy and hospice therapy are the most underdiscussed options of RRT. Home-based dialysis therapy, mainly PD and home HD, remains a very attractive option for working and self-caring patients. Despite these facts, acceptance of home therapy is lower in the United States compared to other industrialized countries.

In-center HD sessions comprise 3–4-hour dialysis treatment, three times a week. Almost 80% of all dialysis patients in the United States undergo in-center hemodialysis as opposed to home-based therapies like peritoneal dialysis or home hemodialysis. Patients undergoing in-center HD frequently describe a feeling of being "wiped out," and almost

40% of patients will take 2–6 hours post dialysis to recover to their usual state of health.[24] Many of these patients have never been offered a formal CKD education program that helps them make an informed decision about dialysis modality choice. For-profit dialysis providers and greater comorbidities of in-center patients undergoing dialysis result in the lowest KT rate in in-center HD patients as opposed to other dialysis modalities.[25] Compared to in-center dialysis, frequent home hemodialysis (HHD) therapy results in fewer episodes of low BP, intradialytic hypotension, and better control of salt and water balance, with fewer BP medications. Advances in HHD and the ability to remotely monitor HHD sessions have reassured many patients, and there appears to be a steady and slow uptake of the HHD modality among patients with ESRD. PD is easy to learn and does not involve contact with blood or self-cannulation of vascular access, and hence remains the most acceptable form of home-based RRT. In the PD modality, dialysis is performed repeatedly via a PD catheter using the osmotic force of sugar water solution. Here, the peritoneal membrane acts as a filter and performs the removal of uremic toxins. PD can be performed with the help of a cycler at night, giving some patients the ability and freedom to control their time during the day when they do not need to perform PD exchanges. PD patients preserve their residual renal function for a longer period of time compared to HD. Regulatory authorities have identified home-based therapy as a preferred dialysis therapy and are putting in place financial and educational incentives to promote better uptake of home-based dialysis therapy.

ORAL CONDITIONS IN PATIENTS WITH RENAL DISEASE

Patients with CKD, those undergoing in-center HD and PD, and those receiving KT can be commonly seen and managed by various oral care professionals. These medical conditions are associated with a broad range of clinical manifestations and lesions affecting soft and hard tissues of the oral and maxillofacial area.[26] These oral conditions can be directly associated with renal impairment or indirectly associated either with medications used in the treatment of renal conditions or various systemic comorbidities.[5] We have categorized all oral clinical conditions into symptoms (subjective abnormalities perceived by a patient) and signs (objective abnormalities observed by a patient and examiner); see Table 16-7.

Table 16-7 Oral symptoms and signs in patients with renal disease.

Oral Symptoms	Oral Signs
• Xerostomia • Altered taste perception • Halitosis • Other oral manifestations	A. Soft tissue lesions 01 Oral mucosa lesions • Uremic stomatitis • Purpura • Fungal infections • Oral mucosal ulcers • Oral malignancies • Other oral mucosa conditions 02 Tongue conditions • Saburral tongue • Dialysis-related amyloidosis • Oral hairy leukoplakia • Other tongue conditions 03 Periodontal conditions • Medication-induced gingival enlargements • Periodontitis • Other periodontal conditions B. Hard tissue lesions 01 Tooth conditions • Dental caries • Edentulism • Tooth periapical lesions • Other tooth conditions 02 Bone conditions • Renal osteodystrophy • Primary hyperoxaluria • Other bone conditions

Oral Symptoms

Epidemiology

Up to 69% of patients with CKD,[27,28] 68% of patients undergoing in-center HD,[29] and 6% of patients received KT[28] displayed oral manifestations, compared to up to 10% in control individuals without renal disease.[30] The data on the prevalence of oral manifestations in patients undergoing PD are missing. These results demonstrate that patients with CKD and those undergoing HD have an increased prevalence of oral manifestations, whereas patients who received KT may have reduced or comparable prevalence compared to control individuals without renal disease.

Xerostomia (ICD-10-CM Diagnosis Code K11.7)

This is a sensation of dry mouth with (objective) or without (subjective) a noticeable decrease in saliva production (Figure 16-5).[31]

- *Patients with CKD (prior to undergoing in-center HD).* Smaller-scale studies on patients with CKD prior to undergoing in-center HD have shown that ~28%–69% of them presented with signs of xerostomia,[27,28] which positively correlated with the increased age and stage of CKD.[32]
- *Patients undergoing in-center HD.* The large-scale prospective multinational ORAL Diseases in Hemodialysis study has

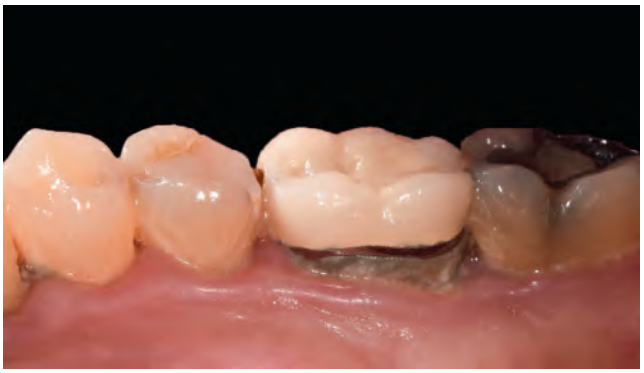

Figure 16-5 Xerostomia (ICD-10-CM Diagnosis Code K11.7).

shown that 45% of dentate patients undergoing in-center HD presented with signs of xerostomia.[33] These findings also correlated with those in smaller-scale studies reporting the prevalence of xerostomia to range from 33% to 56%, compared to 0%–29% in control individuals without renal disease.[29,34–36] However, compared to predialysis levels, the salivary flow rate (SFR) increased after the initiation of HD[37] and PD.[30] No studies reporting the prevalence of oral symptoms in patients undergoing PD have been identified.

- *Patients receiving KT*. In these patients, the SFR improved compared to patients with CKD and those undergoing in-center HD, but was still significantly lower compared to control individuals without renal disease.[38–40] A recent study has shown that the prevalence of xerostomia in KT patients was 35% 24 hours before the transplantation, and significantly decreased to 10.7% and 8.2% 15–20 and 45–60 days after the procedure, respectively.[41]

Etiology and Pathogenesis

- *Xerostomia-inducing medications*. Over 500 medications, including anticholinergic drugs, antihistamines, antihypertensive drugs, tranquilizers, and skeletal muscle relaxants, can affect SFR and induce xerostomia.[31,42–46]
- *Decreased fluid intake and polyuria*. Many patients with renal disease are elderly and naturally tend to drink less fluid. Combined with the reduced ability of the kidneys to reabsorb sodium and subsequent polyuria,[28] this reduced intake of fluids can contribute to fluid loss and xerostomia.[42]
- *Stress and depression*. Both stress and depression can reduce salivary gland activity in patients with CKD and those undergoing in-center HD.[47,48]
- *Subjective xerostomia*. A study that involved patients undergoing in-center HD has shown that signs of xerostomia were reported by 68% of patients with decreased SFR and by 59% of those with normal SFR.[35]
- *Other mechanisms contributing to xerostomia/reduced SFR*. Several other factors, including changes in salivary chemical composition,[49] fibrosis and atrophy of minor salivary glands,[35] and damage to salivary gland cells,[50] have been proposed to contribute to xerostomia/reduced SFR. However, the large difference in the amounts of unstimulated and stimulated saliva (~3.4–3.6 times) suggests that the renal disease did not damage the structure of the salivary glands, but rather affected their functional activity.[51]

Significance

- *Functional impairment*. Significantly more patients undergoing in-center HD and displaying a reduced SFR experienced speech difficulty compared to control individuals without renal disease (22% vs. 15%).[28,31,34,52] In patients undergoing in-center HD, xerostomia was significantly associated with difficulty in chewing (odds ratio [OR] 2.7; 95% confidence interval [CI] 1.7–4.3; $P < .001$) and swallowing (OR 2.3; 95% CI 1.5–3.4; $P < .001$) and consequent avoidance of food intake (32% vs. 18% in nonxerostomic controls; OR 2.1; 95% CI 1.4–3.2; $P < .001$).[53]
- *Intraoral lesions*. Xerostomia is associated with glossitis, fissured lips, and candidiasis.[54]
- *Systemic concerns*. Xerostomia is significantly associated with hypertension (OR 5.24; 95% CI 1.11–24.89; $P = .03$);[46] however, a wide confidence interval in this study should be noted.

Altered Taste Perception (ICD-10-CM Diagnosis Codes R43.8 and R43.9)

These conditions can be categorized into dysgeusia (altered taste perception), hypogeusia (reduced taste perception), and ageusia (absent taste perception).[55]

- *Patients with CKD (prior to undergoing in-center HD)*. There seems to be a significantly higher prevalence of dysgeusia among patients prior to dialysis compared with individuals without renal disease.[56] A questionnaire study of patients with CKD suggested that 31% of them perceived a metallic taste (vs. 0% in the control group without renal disease) and 53% of them felt a taste alteration (vs. 9% in the control group without CKD). These findings did not correlate with the disease duration, but were primarily encountered in elderly patients (88% of all cases).[57]
- *Patients undergoing in-center HD*. A large-scale study has shown that 13.4% of patients undergoing in-center HD had signs of dysgeusia,[33] whereas smaller-scale studies reported its prevalence to be 28%.[28] No studies reporting the prevalence of oral lesions in patients undergoing PD have been identified.
- *Patients receiving KT*. The prevalence of patients with KT and who experienced a metallic taste was lower compared to that in patients undergoing in-center HD (6% vs. 28%), but higher than in control individuals without renal disease (0%).[28]

Etiology and pathogenesis

The proposed mechanisms include changes in salivary flow, pH, and chemical composition,[58] thick tongue coating,[36] and genetic ability to taste thiourea at low thresholds.[59]

Significance

Taste alterations in patients with renal disease can lead to impaired quality of life.

Halitosis (ICD-10-CM Diagnosis Code R19.6)

Halitosis is a perceived malodor with an intensity beyond a socially acceptable level.[60] Six types of halitosis can be distinguished, depending on the mechanisms and origin of its development (physiologic, oral, airway, gastroesophageal, blood-borne, and subjective halitosis).[60] In patients undergoing in-center HD, halitosis was one of the most common observations, with a prevalence of 30%–49% (vs. 0% in controls with normal renal function).[30,36,61] No studies examining the prevalence of halitosis in patients with CKD (prior to undergoing in-center HD), those undergoing PD, and those receiving KT have been identified.

Etiology and pathogenesis

- *Breakdown of organic compounds*. In general, halitosis is attributed to the presence of various volatile organic compounds present in saliva and tongue coating, including volatile sulfur compounds (VSCs).[62,63] These products are enzymatically generated by intraoral bacteria, including periodontal pathogens (*Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, and *Prevotella intermedia*),[62,64,65] and a positive association between poor periodontal health and the levels of VSCs has been demonstrated.[66]
- *Reduced rinsing property of saliva*. In patients with CKD who exhibit a reduced SFR, halitosis could be associated with the accumulated biofilm, bacteria, and desquamative epithelial cells from the tongue. However, no scientific evidence supporting this hypothesis has been shown.
- *Other reasons*. Up to 42% of the general population have signs of subjective halitosis,[67,68] which is a psychologic sensation, but not the objective presence, of halitosis.[62] Since the presence of halitosis in several studies was determined using a questionnaire, its prevalence could be overestimated. Therefore, a series of questions for more objective differentiation between objective and subjective types of halitosis has been developed.[60]

Significance

Halitosis in patients with renal conditions can lead to impaired quality of life.

Other Oral Manifestations

Patients with CKD, especially those exhibiting oral candidiasis and anemia,[69] could also display glossodynia, a chronic debilitating oral condition characterized by the presence of a burning sensation of the oral mucosa,[29,70–72] tongue,[30] and gingiva.[73]

Oral Signs

(A) Soft Tissue Lesions: (1) Oral Mucosa Lesions

Epidemiology

- *Patients with CKD (prior to undergoing in-center HD)*. Sex- and age-adjusted regression analysis has shown that predialysis patients with CKD had a significantly higher likelihood of developing clinically observable oral symptoms compared to controls with normal renal function (OR 153.3; 95% CI 40.1–584.8; $P < .001$)[74]; however, an extremely wide CI makes the interpretation of these results challenging. These patients were also reported to have a significantly higher prevalence of oral manifestations compared to control individuals without renal disease (66% vs. 37%; OR 3.3; 95% CI 1.9–5.6; $P < .001$).[30]
- *Patients undergoing in-center HD*. Smaller-scale studies have shown that the prevalence of oral lesions in patients undergoing in-center HD varied substantially, ranging from 9% to 94%.[28,39,75] A large-scale study has shown that the overall prevalence of oral lesions was 40%,[76] with HD duration (<12 or >12 months) not affecting their prevalence.[28] These patients also had a statistically higher risk of the development of various combinations of oral lesions with oral manifestations, with ORs ranging from 2.6 to 14.0.[30] No studies reporting the prevalence of oral lesions in patients undergoing PD have been identified.
- *Patients receiving KT*. These patients had a higher prevalence of oral lesions compared to control individuals without renal disease (32%–96 vs. 57%)[28,39,77–79] and patients undergoing in-center HD (32% vs. 9%).[39] A recent study has also shown that 24 hours prior to KT, oral lesions were observed in 3.7% of patients, and their prevalence increased substantially, reaching 23.7% and 25.7% 15–20 and 45–60 days after KT, respectively.[41] Their prevalence was not related to post-transplant period duration[28] or patient age.[41]

Uremic Stomatitis (ICD-10-CM Diagnosis Code K12.1)

Inflammation of the oral mucosa (stomatitis) is associated with impaired renal function and urea accumulation. Due to a slow rate of disease progression over a period of years, its incidence is estimated as low, but this has not been confirmed in epidemiologic studies. There are four variants of uremic stomatitis:[80,81]

- *Ulcerative stomatitis* is the most common presentation, characterized by extremely painful ulcerations on the tongue, cheeks, lips, and palate with indefinite margins, often covered by a thick, adherent, yellowish covering on the tongue. Other symptoms include xerostomia, metallic taste, mouth burning sensation, erythematous lingual and palatal mucosa, and fissuring and bleeding at the corner of

the mouth. Tissue biopsy is needed to perform differential diagnosis with vesiculobullous diseases.[81]

- *Erythematosus membranous stomatitis* is characterized by the formation of gray pseudomembranes that consist of a thick, sticky exudate on the erythematous mucosa and overlay painful erythema patches.
- *Hemorrhagic stomatitis* is characterized by the presence of bleeding of the gingival or oral mucosa. In combination with immune deficiency, bacterial infection can cause extremely painful ulcerations and pseudomembranes, often on the ventral surface of the tongue.
- *Hyperparakeratotic stomatitis* occurs rarely and is characterized by hyperkeratosis, sometimes in combination with ulcerations.[82]

Etiology and Pathogenesis

The precise mechanisms of the development and progression of uremic stomatitis remain unclear; however, it has long been associated with higher levels of caustic salivary ammonia, causing a slowly developing "chemical burn."[83] Indirect evidence of the association between salivary urea and stomatitis can be observed in patients with acute necrotic pseudomembranous gingivostomatitis, which develops within a short period of time as a response to rapidly elevated BUN levels.[84] Predisposing factors could be local bleeding, infectious environment, and compromised immune condition.[85] In addition, patients with ESRD may present with white patches intraorally (tongue, mucosa of the floor of the mouth),[86,87] as well as on the skin of the face and lips.[88] These patches represent crystals of urea deposited after the evaporation of saliva or sweat and occur when the blood urea concentration >200 mg/dL.[89] However, direct evidence of the adverse effects of ammonia, causing the "chemical burn" of the oral mucosa, and the role of uremic patches in this process have not been demonstrated.

Significance

Due to painful intraoral lesions, patients with ulcerative stomatitis may have a loss of appetite, dehydration, and weight loss. They can also develop generalized gastrointestinal changes, suggesting that the oral manifestations are local manifestations of generalized mucosal breakdown.[84] Hemorrhagic stomatitis can impair the intactness of the oral mucosa of these patients and contribute to bacterial infection.

Purpura (ICD-10-CM Diagnosis Code D69)

This is the development of extravascular red- or purple-colored spots on the oral mucosa. Depending on the size of the spots, purpura can be classified into petechiae (pinpoint size) and ecchymoses (larger than pinpoint size).[90]

- *Patients with CKD (prior to undergoing in-center HD).* These patients had a significantly higher prevalence of mucosal petechiae compared to control individuals without renal disease (15.1% vs. 0.8%; OR 23.0; 95% CI 3–178; $P < .001$);[30] however a very wide confidence interval should be noted.
- *Patients undergoing in-center HD.* A large-scale study has shown that the prevalence of petechiae in these patients was 7.9%,[76] and a smaller-scale study reported the prevalence of petechiae and/or ecchymoses to be 12%.[36] No studies reporting the prevalence of purpura in patients undergoing PD have been identified.
- *Patients receiving KT.* No studies have been identified.

Etiology and Pathogenesis

The proposed mechanisms include trauma (e.g., physical impact, biting) and platelet dysfunction.[90]

Significance

The purpura might be suggestive of platelet dysfunction or the use of anticoagulants, which are commonly encountered in patients undergoing in-center HD and will be discussed in the Dental Considerations and Multidisciplinary Management section of this chapter.

Fungal Infections (ICD-10-CM Diagnosis Codes B37.0 and B37.9)

These are opportunistic conditions, which can be signs of systemic conditions, side effects of medications (antibiotics, steroids), and local factors (poorly maintained dental dentures, the use of steroid inhalers, and reduced SFR).[91]

- *Patients with CKD (prior to undergoing in-center HD).* A single study reported that significantly more of these patients had oral yeast infections compared to control individuals without renal disease (32% vs. 11%).[92]
- *Patients undergoing in-center HD.* A large-scale study has shown that the prevalence of oral candidiasis in these patients was 4.6%.[76] Smaller-scale studies have shown that the prevalence of yeast infection was markedly higher in these patients compared to control individuals without renal disease (40%–54% vs. 18%–31%),[93–96], especially in those >45 years of age,[97] and with a majority of yeast lesions (23.3%) being chronic erythematous candidiasis.[93] Dorsal tongue coating with yeasts was a common finding in HD patients (78%), with *Candida albicans* and *C. parapsilosis* being the most common yeast species.[75] In PD patients, the prevalence of yeast infections was slightly higher compared to control individuals without renal disease (21% vs. 18%).[96]
- *Patients receiving KT.* These patients have a significantly higher risk (adjusted OR 3.49; 95% CI 1.27–9.18; $P < .05$)[98] and prevalence of yeast infections compared to control individuals without renal disease (10%–32% vs. 0%–2.5%).[41,77,99,100] Erythematous candidiasis was the most prevalent form of yeast

infection (3.8%–13.3%)[77,99] and *C. albicans* was the most common yeast (61.9%). A case of *Histoplasma capsulatum*–associated histoplasmosis in a long-term immunosuppressed patient with KT and a history of maxillary tooth extractions and development of oro-antral communication with maxillary sinus has also been described.[101]

Etiology and Pathogenesis

- *Dental prostheses*. Oral candidiasis in patients undergoing in-center HD was significantly associated with wearing a dental prosthesis (OR 4.5; 95% CI 1.6–12.7; $P = .004$).[94,96] No association between the signs of yeast infection and the number of missing teeth, smoking status, HD duration, KT duration, and antibiotic use was observed.[96]
- *Xerostomia*. In patients with ESRD and those undergoing in-center HD, the prevalence of oral fungal infections was significantly higher when xerostomia was self-reported compared to nonxerostomic patients.[92]
- *Systemic factors*. Aging, endocrine disorders, and broad-spectrum antibiotic therapy have been associated with yeast infection.[102] A recent study has also demonstrated the significant positive correlation between oral candidiasis and the immunosuppressant drug azathioprine.[41]

Significance

- *Oral cavity*. Yeast infections can be associated with denture stomatitis[103] and glossodynia.[104] Although older studies have suggested the association between oral yeast infections and mouth burning, the recent evidence did not establish this association.[105]
- *Systemic health*. While oral candidiasis did not seem to be associated with all-cause mortality (adjusted hazard ratio [HR] 1.37; 95% CI 1.0–1.86), it was significantly associated with cardiovascular mortality (adjusted HR 1.64; 95% CI 1.09–2.46) after adjusting for several critical cofounders.[76] Similarly, the increased prevalence of oral candidiasis (OR 3.1; 95% CI 1.0–9.4; $P = .04$) and wearing dental prostheses (OR 4.1; 95% CI 1.2–13.9; $P = .03$) were associated with a higher risk for advanced coronary artery disease.[94] In both these studies, low lower limits of the CIs should be noted.

Oral Mucosal Ulcers (ICD-10-CM Diagnosis Codes K12 and K13.7)

These are painful lesions in the oral cavity, which can be chronic or acute depending on the underlying mechanisms of their development.[106] In patients undergoing in-center HD, the prevalence of intraoral mucosal ulcers was 1.2%–1.7%.[36,76] However, no studies reporting the prevalence of intraoral ulcers in patients with CKD (prior to undergoing in-center HD) and those receiving KT have been identified.

Etiology and Pathogenesis

Oral ulcers can be a sign of ulcerative uremic stomatitis (see the earlier section on Uremic Stomatitis).

- *Other renal conditions*. Oral ulcers can be associated with the development of lupus nephritis in patients with systemic lupus erythematosus (SLE) affecting kidney functions (rapidly developing glomerulonephritis) and predict their activity.[107,108] Also, oral ulcers can often be presented in patients with Behçet disease[109] associated with rapidly progressive glomerulonephritis.[108]
- *Cytomegalovirus (CMV) treatment*. Oral ulcers can develop secondary to CMV treatment, such as the use of everolimus.[41,73] The presence of ulcers on the oral mucosa, hard and soft palate, and tongue were observed in KT patients who developed CMV infection within the first three years after transplantation.[110]
- *Medications*. Limited evidence suggests that in patients with KT, oral ulcers could be associated with immunosuppressant medications, such as sirolimus or mycophenolate mofetil.[111,112]

Significance

Painful oral ulcers can result in discomfort during meal intake, leading to malnutrition.

Oral Malignancies

The prevalence of intraoral neoplasms in patients undergoing in-center HD was 2%,[76] whereas it was up to 5% in those receiving KT.[78,113] The development of spindle cell carcinoma in the lower lip[78] and squamous cell carcinoma of the tongue after KT[114] have also been described. However, no studies examining the prevalence of intraoral malignancies in patients with CKD (prior to undergoing in-center dialysis) have been identified.

Etiology and Pathogenesis

Longstanding postallograft immunosuppression may predispose patients receiving KT to human herpesvirus 8 (HHV-8) and associated Kaposi's sarcoma.[115,116] Shedding of HHV-8 into the oral cavity was observed after the transplantation of a seropositive HHV-8 kidney.[117] Therefore, intraoral malignancies are likely to be associated with the immunocompromised conditions of these patients.[118–120] During the past two decades, the use of various antiviral medications has reduced the incidence of viral infections substantially.[119,121–124] However, studies examining the association between the reduced viral load and the prevalence of intraoral malignancies in patients with CKD and those on in-center HD are missing.

Other Oral Mucosa Conditions

Patients undergoing in-center HD and those receiving KT might also present with rare cases of other oral mucosa lesions, such as pyogenic granuloma.[28,99] In addition, various

types of viruses, including intraoral herpes simplex (0.5%–7.8% of cases),[33,41,76–78,125] Epstein–Barr virus, cytomegalovirus, and varicella zoster virus, were observed in patients prior to and those undergoing in-center HD, especially in patients with severe periodontal destruction.[126] Studies have shown that patients with CKD might also display a higher prevalence of pale oral mucosa compared to control individuals without renal disease (40% vs. 12%).[30] This could likely be due to the impaired absorption of dietary iron and functional iron deficiency,[127,128] impaired EPO synthesis,[30] and malnutrition.[127,129] A recent large cohort study has shown that anemic conditions positively correlated with the stage of CKD (44%, 64%, and 73% for stages 3, 4, and 5, respectively).[130] Cases of fibroma in patients undergoing in-center HD can also be encountered (Figure 16-6).

(2) Tongue Conditions

Saburral (Coated) Tongue (ICD-10-CM Diagnosis Code K14.9)

This is a yellowish-white, thrush-like coating on the back of the tongue, representing large amounts of normal desquamated epithelial cells and bacterial colonies (more commonly *Staphylococci*), without the presence of yeasts[131] and coexisting with elongated (<3 mm) filiform papillae.[77] Its development is commonly associated with poor oral hygiene;[132] however, the precise mechanisms are still unclear. Initially, these lesions were described in patients during episodes of acute rejection following KT and after treatment with high doses of steroids,[131] but later studies have described their development in other patients with CKD as well.

- *Patients with CKD (prior to undergoing in-center HD).* A series of studies have shown that these patients had a significantly higher prevalence (12%–37% vs. 3%)[28,30,36] and risk for saburral tongue compared to control individuals without renal disease (OR 7.0; 95% CI 2.3–21.4; $P < 0.001$);[30] however, a wide confidence interval makes the interpretation of these results challenging.
- *Patients undergoing in-center HD.* No studies have been identified.
- *Patients receiving KT.* Studies have shown that 22%–42% of patients with KT developed saburral tongue, especially within the first year after the transplantation.[28,77]

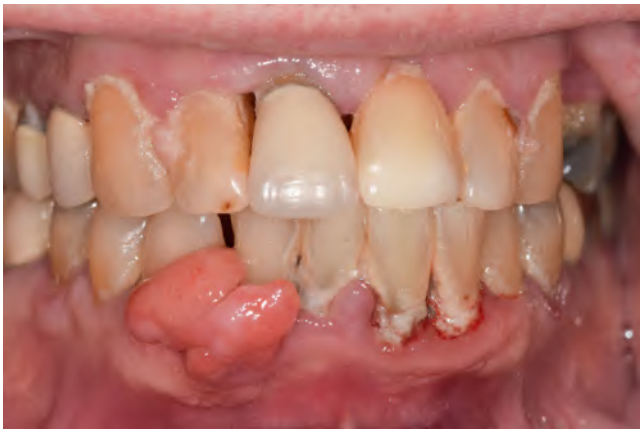

Figure 16-6 Other oral mucosa conditions.

Etiology and Pathogenesis

The precise mechanisms of the development of saburral tongue in patients with renal disease are unclear. Patients with renal disease prior to in-center HD (especially those >50 years) displayed a thick tongue coating, which, however, had no significant association with changes in blood levels of urea, creatinine, and albumin.[133] It is likely that similar to individuals without renal disease,[132] the development of saburral tongue in patients with renal disease is associated with poor oral hygiene. However, systemic disturbances, especially those resulting from immunosuppressive medications, should also be considered.

Significance

Patients with saburral tongue may have a compromised taste perception and a risk for biting the tongue due to its enlargement.

Dialysis-Related Amyloidosis (ICD-10-CM Diagnosis Code E85.4)

This is a rare and late complication of long-term HD,[134,135] characterized by multiple soft, painful, whitish-to-yellow nodules of various sizes >1 mm and with a cobblestone appearance on the dorsum and lateral borders of the tongue, causing macroglossia.[136] However, cases of HD-related amyloidosis with asymptomatic nodules have also been described.[134,137] The nodules gradually enlarge over time, consistent with HD-related amyloidosis,[137–139] which is not degraded in patients undergoing in-center HD and cannot pass through a dialysis membrane.[140] Depending on the intraoral location and extent, two types are described, lateral and diffuse, with no differences in the HD duration between them.[135]

- *Patients with CKD (prior to undergoing in-center HD).* An older large-scale study that included 236 patients with CKD (prior to undergoing in-center HD) with systemic amyloidosis showed that macroglossia was the most common intraoral sign, observed in 17% of these patients.[141] A recent case report study described a case of lingual amyloidosis in an 82-year-old patient with CKD (prior to undergoing in-center HD).[142]
- *Patients undergoing in-center HD.* Older studies have reported that some patients undergoing in-center HD

have a sensation of an enlarged tongue associated with amyloidosis.[36,143,144] In patients undergoing long-term (>10 years) in-center HD, the prevalence of tongue amyloidosis was 1.7% compared to 0% in control individuals without renal disease.[135] Rare cases of amyloid-associated macroglossia in the HD patient with Fabry disease (inherited lysosomal storage disease due to α-galactosidase A deficiency)[145] and combined β_2-microglobulin and light chain deposits in a patient undergoing long-term (18 years) HD have recently been reported.[146]

- *Patients receiving KT*. A recent study has reported that 28% of patients with KT had macroglossia compared to 22% of patients undergoing in-center HD; however, it is unknown whether or not this was associated with amyloidosis.[147]

Etiology and Pathogenesis

In patients undergoing in-center HD, polyphosphate released from the activated platelets can induce precipitation of β_2-microglobulin, leading to the formation of amyloid.[148]

Significance

Dialysis-related amyloidosis can lead to significant speech, taste, and swallowing difficulty.[135,139,142,145] Macroglossia can be the first sign of amyloid-associated renal dysfunction.[149] Studies also suggest that the presence of macroglossia and progressive renal failure may be indicative of systemic amyloidosis with multiple myeloma.[149]

Oral Hairy Leukoplakia (ICD-10-CM Diagnosis Code K13.3)

This is a painless white patch with an irregular surface and prominent folds and projections, which cannot be scraped off. It can be unilateral or bilateral and typically involves the lateral and dorsolateral tongue.[99]

- *Patients with CKD (prior to undergoing in-center HD)*. No studies have been identified.
- *Patients undergoing in-center HD*. No studies have been identified.
- *Patients receiving KT*. In these patients, oral hairy leukoplakia (OHL) was the second most common oral lesion, with a prevalence of 6.8%–12.2% compared to a lack of cases in control individuals without renal disease.[77,99,150]

Etiology and Pathogenesis

OHL is probably caused by drug-induced reactivation of the Epstein–Barr virus (EBV) in the basal layers of the oral epithelium.[82] It is often observed in patients undergoing cyclosporine A (CsA) therapy, including patients receiving KT.[99] A single OHL case on the lateral borders of the tongue in a patient with KT was associated with EBV.[151]

Significance

In some cases, OHL can be mimicked by uremic stomatitis with white tongue coating,[82] and therefore can represent a diagnostic challenge.

Other Tongue Conditions

In patients undergoing in-center HD, the prevalence of fissured tongue and geographic tongue was 10.7% and 4.9%, respectively.[76] Patients receiving KT also presented with various tongue conditions (fissured tongue, geographic tongue, and black hairy tongue[28,99]); however, their prevalence has not been reported, except geographic tongue (11.1% vs. 5.6% compared to patients undergoing in-center HD).[147]

(3) Periodontal Conditions

Medication-Induced Gingival Enlargements (ICD-10-CM Diagnosis Code K06)

This is a subcategory of gingival diseases associated with medications that can induce overgrowth of gingival tissues.[152] Clinically, medication-induced gingival enlargement (MIGE) is characterized by enlarged gingiva with an irregular gingival margin, shorter clinical crowns, and periodontal pseudopockets (pockets with an increased probing depth [PPD] but without clinical attachment loss [CAL]).

- *Patients with CKD (prior to undergoing in-center HD)*. No studies have been identified.
- *Patients undergoing in-center HD*. A recent study has shown that MIGE was observed in 17% of these patients.[153] Another study has demonstrated that in these patients, MIGE was observed only after the failure of KT and not prior to the KT procedure.[154]
- *Patients receiving KT*. The prevalence of MIGE in these patients ranged from 22% to 67.5%, thus making it their most common oral lesion, typically in the area of anterior teeth.[77,78,99,125,153,155,156] The prevalence of gingival overgrowth is approximately similar between patients taking calcium-channel blockers (e.g., nifedipine, amlodipine, felodipine; up to 34% of patients)[157] and those receiving immunosuppressants (e.g., CsA, tacrolimus; up to 33% of patients).[158] Some studies have reported that the intake of more than one medication has a cumulative effect;[29,78] however, other studies could not establish that correlation.[99]

Etiology and Pathogenesis

In patients undergoing in-center HD, MIGE was related to calcium-channel blockers (e.g., amlodipine, nifedipine, verapamil) used as antihypertensive medications.[154] In patients receiving KT, MIGE was associated with immunosuppressive therapy aimed to prevent allograft rejection following KT (e.g., using CsA, tacrolimus, azathioprine,

cyclophosphamide, prednisone).[154] Among patients who received KT, 55% took mycophenolate, 42% took glucocorticoids, 36% took CsA, and 34% took tacrolimus,[159] thus predisposing a large cohort of them to MIGE. The severity and extent of gingival overgrowth in these patients were positively associated with the dosage of CsA, but not with the duration of its intake.[160] In patients who received KT, there was a positive association of CsA-induced MIGE with IL-1α polymorphism[161] and red complex microbiota.[162]

There are controversies surrounding the role of dental biofilm in MIGE. Some studies showed that the higher prevalence of gingival overgrowth significantly correlated with poor oral hygiene,[77,163] whereas others observed gingival overgrowth even in the presence of meticulous oral hygiene.[164] A double-blinded randomized control study showed that 67.5% of CsA-treated patients receiving KT developed MIGE, and a 7-day course with metronidazole or azithromycin had no significant effects on gingival overgrowth,[155] suggesting that overgrowth was primarily due to medications and not bacterial colonization of periodontal pockets.

Significance

MIGE conditions can impair the quality of a patient's life by affecting their functional and esthetic demands.

Periodontitis (ICD-10-CM Diagnosis Code K05—Multiple Codes)

This is a polymicrobial multifactorial inflammatory disease of tooth-supporting tissues (periodontium)[165] and is one of the most common human infectious diseases, estimated at 42% in dentate US adults.[166]

- *Patients with CKD (prior to undergoing in-center HD).* A recent 10-year large-scale study showed that CKD was not associated with severe (interproximal CAL ≥5 mm) periodontal breakdown (adjusted OR 1.01; 95% CI 1.005–1.015).[167] Similar findings were reported in smaller-scale studies.[168] Other studies, however, have shown that patients with CKD (prior to undergoing in-center HD) had a significantly greater extent of CAL (a surrogate measure of periodontitis) and higher risk for tooth-specific progression of total (slight, moderate, and severe) CAL, compared to control individuals without renal disease (OR 1.73; 95% CI 1.15–2.60; $P < .05$).[169] A recent study has also shown that the risk of severe periodontitis was significantly associated with the advanced stages of CKD.[170]
- *Patients undergoing in-center HD.* Similar to studies on patients with CKD (prior to undergoing in-center dialysis), studies on patients undergoing in-center HD also report controversial findings on the prevalence of periodontitis. A recent study has shown that these patients had significantly greater mean CAL (1.8 mm vs. 1.2 mm), deeper mean PPD (2.3 mm vs. 1.8 mm), and prevalence of periodontitis (slight, moderate, and severe).[34] Gingival index, plaque index, and PPD (but not CAL) were positively associated with the duration of HD (especially after 10 years).[171] Other studies, however, have shown that the prevalence of periodontitis was similar between these patients and control individuals without renal disease. Periodontitis was observed in 41% of patients undergoing in-center HD; however, average PPD of 1 mm questions the validity of the periodontal exam and periodontal status of these patients;[33] in addition, the prevalence of periodontitis in this patient cohort was similar to that reported by a recent National Health and Nutrition Examination Survey (NHANES) III–based study (42%).[166] Long-term (11 years), large-scale,[172] and smaller-scale[173] studies have also shown no significant association between CKD and periodontitis.
- *Patients receiving KT.* Studies on the prevalence of periodontitis in these patients were controversial and included both a positive association[159] and the lack of it.[40]

Etiology and Pathogenesis

Poor oral hygiene. Periodontitis is developed as a result of dysbiosis of the commensal microflora (present in dental biofilm/plaque) in a susceptible host organism.[174,175] Studies have shown that significantly more patients with CKD,[92,168,176,177] those undergoing in-center HD,[178] and those receiving KT[179] had poor oral hygiene compared to control individuals without renal disease. It has been shown that only 8.2% of HD patients use dental floss, 30% had a dental appointment within the past 6 months, 66% brush teeth twice a day, 21% were edentulous, and 42% had dental prostheses.[33] Another study has shown that greater numbers of patients undergoing in-center HD[180] and those receiving KT[179] wore dentures that could alleviate plaque retention and periodontal inflammation. Discrepancies between their compromised dental conditions and oral health–related quality of life might also suggest that patients undergoing in-center HD did not realize their worse oral hygiene condition and therefore did not seek to see a dentist.[181] Finally, due to their significantly lower income, these patients might not be able to afford dental treatment to the same extent as control individuals without renal disease.[72,182,183] A recent review study has also summarized the current evidence for the kidney damage induced by oral microorganisms, primarily *Streptococci*; however, a majority of the included studies are extremely outdated.[184]

- *Increased salivary pH.* Selected periodontal pathogens such as *P. gingivalis*, *P. intermedia*, and *Fusobacterium nucleatum* show optimal growth in alkaline pH.[185] Urea

can be hydrolyzed to alkaline ammonia by oral bacteria's ureases, thus resulting in the increased pH levels.[56,186–189] Studies have shown that patients with CKD had significant and stage-dependent increases in salivary pH compared to control individuals without renal disease.[56,190] Similarly, patients undergoing in-center HD also had significantly higher salivary pH compared to control individuals without renal disease,[36,56,187] which positively correlated with the duration of HD.[191] Interestingly, patients with severe periodontitis had significantly increased salivary urea concentrations,[192] further supporting the role of urea in dysbiosis of periodontal microflora. Therefore, increased salivary pH in patients with CKD and those undergoing in-center HD can lead to conditions providing more favorable growth of periodontal pathogens.

- *Systemic effects of urea*. Uremia alters host response by several mechanisms, including functional abnormalities of neutrophils, monocytes/macrophages, and dendritic cells,[193–196] abnormal neutrophil activity,[197] impaired maturation of T-helper cells,[198] and increased oxidative stress.[199,200] Since periodontitis develops in a susceptible host environment, impaired immune responses will favor its development.

Significance

In patients with ESRD, periodontitis was associated with poorer quality of life, including physical and physiologic impairment.[201]

Other Periodontal Conditions

The limited and inconclusive evidence of the presence of gingival diseases other than MIGE (non-dental biofilm-induced gingival diseases[30,40] and necrotizing gingivitis[202]) in patients with ESRD has been reported in the literature. Recent case series studies have reported that the prevalence of biofilm-induced gingivitis was observed in 17%–61% of patients undergoing in-center HD compared to 61%–75% of those who received KT.[147,153]

(B) Hard Tissue Lesions: (1) Tooth Conditions

Dental Caries (ICD-10-CM Diagnosis Code K02—Multiple Codes)

To quantify the prevalence of dental caries and characterize it further, DMF (missing teeth, and teeth with fillings), DMFS (dental caries, missing, and filled tooth surfaces), and DMFT (dental caries, missing teeth, teeth with fillings, and tooth loss) indices/scores are commonly used (Figure 16-7.)[203]

- *Patients with CKD (prior to undergoing in-center HD)*. The impact of CKD on the prevalence of dental caries remains controversial, as studies have shown that CKD was associated with a decreased, increased, or unchanged prevalence of dental caries. A recent systematic review with a meta-analysis of 14 studies has shown no significant differences in the number of decayed (mean difference −0.18; 95% CI −1.52–1.17; $P > .05$) and filled (mean difference −0.47; 95% CI −2.84–3.78; $P > .05$) teeth or the DMFT score (mean difference −3.17; 95% CI −0.83–7.18; $P > .05$) between patients with CKD and those undergoing in-center HD compared to control individuals without renal disease; however, the large heterogeneity in the studies makes interpretation of their results challenging.[204]
- *Patients undergoing in-center HD*. Although these patients displayed significantly greater amounts of dental biofilm and calculus[173] and a prevalence of cariogenic bacteria (*Streptococcus mutans*, *Lactobacillus salivarius*, *L. fermentum*, *L. vaginalis*, *Scardovia wiggsiae*, and *Actinomyces. naeslundii*) in dental biofilm,[205] the prevalence of dental caries was similar to that in control individuals without renal disease.[173]
- *Patients receiving KT*. These patients had a higher but statistically nonsignificant prevalence of dental caries (DMFS or DMFT score) compared to control individuals without renal disease (5.3% vs. 1.4%).[40,206] However, these patients had a significantly higher DMFT score compared to patients with other organ transplants (liver and lungs).[159]

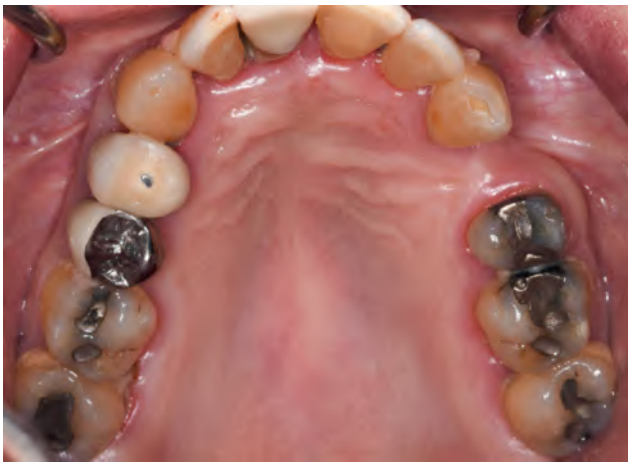

Figure 16-7 Dental caries (ICD-10-CM Diagnosis Code K02 – multiple codes).

Etiology and Pathogenesis

Caries resistance is associated with higher concentrations of ammonia due to the higher urease activity.[207,208] Increases in salivary urea resulted in elevated pH and increased amounts of dental calculus (this will be discussed in more detail in the Periodontitis section of this chapter). At the same time, this environment neutralizes the acidic environment associated with tooth demineralization and caries development.[209] In

addition, the similarities in the prevalence of dental caries in renal patients and control individuals without renal disease due to the high degree of heterogeneity of various studies implies that the differences could be masked by various other factors (e.g., differences in patient selection and their renal disease status, the presence or absence of other systemic conditions).

Significance

A two-year large multinational cohort study that included 4205 patients undergoing in-center HD has shown that complete edentulism (adjusted HR 1.29; 95% CI 1.10–1.51; $P < .001$) and DMF score ≥14 (adjusted HR 1.70; 95% CI 1.33–2.17; $P = .04$) were associated with higher all-cause mortality.[210] These observations suggest that the low prevalence of dental caries can serve as a plausible preventive determinant of clinical outcomes in these patients.

Edentulism (ICD-10-CM Code K08—Multiple Codes)

This is a loss of one or several teeth (partial edentulism) or all teeth (complete edentulism) due to various reasons, most commonly periodontitis and dental caries.

- *Patients with CKD (prior to undergoing in-center HD).* A recent systematic review with a meta-analysis showed that these patients lost significantly more teeth compared to control individuals without renal disease (mean difference 3.84; 95% CI 1.10–6.57; $P \leq .05$).[204] The increased tooth loss was significantly associated with the increased levels of cystatin C used as a surrogate estimate of decreased renal function (OR 7.70; 95% CI 1.24–47.84; $P = .03$), but not with age, CAL ≥4 mm, or body mass index (BMI);[211] however, a large CI should be noted.
- *Patients undergoing in-center HD.* A systematic review of observational studies showed that 21% of patients with CKD undergoing in-center HD were edentulous; however, no data on control individuals without renal disease were reported.[212] A smaller-scale study demonstrated that significantly more patients undergoing in-center HD were completely edentulous compared to control individuals without renal disease (13.6% vs. 2.2%), and dentate ones lost more teeth compared to control individuals without renal disease (14 vs. 10 teeth).[30]
- *Patients receiving KT.* No studies have been identified.

Etiology and Pathogenesis

Since several studies have shown that the prevalence of dental caries in patients with CKD (prior to undergoing in-center HD) and control individuals without renal disease was similar, dental biofilm–associated periodontitis is the most feasible etiology of edentulism in these patients. In addition, a severe periodontal breakdown could lead to tooth loss in rare cases of primary hyperoxaluria.

Significance

- *Masticatory dysfunction.* Tooth loss may result in compromised masticatory function of renal patients, which consequently leads to impaired quality of life. A large-scale NHANES III–based study of patients with CKD (prior to undergoing in-center HD) showed that the confounder-adjusted tooth loss was significantly associated with malnutrition in these patients.[213]
- *Esthetic concerns.* Tooth loss may result in esthetic concerns in renal patients.
- *Systemic dysfunction.* A study that involved patients with CKD (prior to undergoing in-center HD) and control individuals without renal disease (both cohorts presented with signs of carotid artery calcification) found that tooth loss was significantly more prevalent in patients with CKD. This study suggested that the combination of edentulism with calcification of the carotid artery might help in early diagnosis of renal diseases.[214] Also, a recent study showed that the association between the number of lost teeth and the incidence of death was statistically (but likely not clinically) significant (HR 0.95; 95% CI 0.92–0.98; $P = .002$);[215] which, however, could also be associated with the increased age of the participants.

Tooth Periapical Lesions (ICD-10-CM Diagnosis Code K04.90)

These are pathologic lesions associated with the apices of teeth and radiographically presented as radiolucencies. Periapical lesions can have odontogenic (periapical granulomas and radicular cysts) and, more rarely, nonodontogenic (periapical cemental osseous dysplasia) origin.

- *Patients with CKD (prior to undergoing in-center HD).* These patients had a significantly higher prevalence of apical periodontitis (OR 3.95; 95% CI 1.54–6.32; $P < .004$), but not the number of endodontically treated teeth (OR 2.54; 95% CI 0.9–5.32; $P > .05$), compared to control individuals without renal disease. The number of teeth with apical periodontitis significantly correlated with increased serum urea levels.[216]
- *Patients undergoing in-center HD.* Significantly more of these patients had periapical radiolucencies compared to patients with CKD (prior to undergoing in-center HD).[217]
- *Patients receiving KT.* A case of periapical radiolucency associated with odontogenic infection and no complications 7 years after its endodontic management was described in these patients.[218]

Etiology and Pathogenesis

A study that included patients with hypophosphatemic rickets due to the excessive loss of renal phosphate has shown that they have an increasing trend to develop endodontic infections, especially in the population >40 years.[219] Dental manifestations in patients with hypophosphatemic rickets

also include dental abscesses.[220] In patients with CKD (prior to and undergoing in-center HD), nonodontogenic periapical lesions could represent radiolucencies associated with brown tumor (see the section on Renal Osteodystrophy later in this chapter) and not odontogenic periapical lesions, especially if these teeth were vital and therefore did not require root canal therapy.[221]

Other Tooth Conditions

A large-scale study has shown that 47% and 2.7% of patients undergoing in-center HD presented with dental erosion and enamel hypoplasia, respectively.[33] A smaller-scale study has demonstrated that 3.7% of HD patients had enamel hypoplasia.[36] A recent systematic review with a meta-analysis of five studies found no significant differences in the prevalence of developmental enamel defects (mean difference 0.73; 95% CI 0.33–1.64; $P > .05$) in patients with CKD (prior to in-center HD) and those undergoing in-center HD compared to control individuals without renal disease;[204] however, the large heterogeneity in this study makes interpretation of its results challenging. These conditions were primarily associated with extrinsic factors associated with decreased SFR and various electrolyte imbalances ($P \leq .05$), including significantly decreased salivary (but not serum) Ca^{2+}, increased salivary and serum phosphorus, and markedly increased parathyroid hormone (PTH) levels ($P \leq .01$ for all comparisons).[222] Tooth hypercementosis has also been reported.[223]

Several studies have also shown that patients with CKD had an increased prevalence of pulpal stones compared to control individuals without renal disease.[224,225] A recent systematic review with a meta-analysis of seven studies has demonstrated a significant association between pulpal and kidney stones (OR 1.97; 95% CI 1.21–3.18]; $P < .05$),[226] which became even more pronounced in patients with ≥3 teeth with pulpal stones (OR 5.78; 95% CI 2.013–16.592; $P < .05$). Studies suggest that pulpal stones may predict undiagnosed kidney stones, and since kidney stones were significantly associated with the development of CKD (HR 1.46; 95% CI 1.2–1.77; $P < .05$), pulpal stones may have a diagnostic value for CKD as well.[227]

(2) Bone Conditions

Renal Osteodystrophy (ICD-10-CM Diagnosis Code N25.0)

CKD-mineral and bone disorder (CKD-MBD) is a systemic mineral and bone condition associated with CKD and presented with abnormalities in appendicular skeleton and craniofacial bones.[228] Among these conditions, a spectrum of pathologic alterations of bone morphology in patients with renal disease is classified under the term "renal osteodystrophy" (RO). Studies have shown that 70% of patients undergoing in-center HD for more than 3 years had signs of RO, evidenced by generalized calcification and bone resorption.[229] A systematic review of 205 publications has demonstrated that the average age of RO patients was 30 years, with women being affected 1.7 times more often than men[230] and with the highest prevalence in African Americans and lowest prevalence in those of Hispanic origin.[231]

Based on the rate of bone turnover and levels of circulating PTH, four types of RO can be distinguished: osteitis fibrosa (also called hyperparathyroidism bone disease, osteitis fibrosa cystica, leontiasis ossea, and von Recklinghausen's disease), osteomalacia, adynamic bone disease, and mixed disease.[232,233] In a cohort of patients with ESRD, 50% of them presented with osteitis fibrosa, 27% with adynamic bone disease, 7% with osteomalacia, and 15% with mixed disease; patients with adynamic bone disease were significantly older compared to those with osteitis fibrosa and mixed disease (56 vs. 41 vs. 39 years).[233]

Clinically, RO is characterized by painless or painful swelling masses of the jaw, causing facial deformity,[234] which is observed in the mandible (41%), maxilla (29%), and both jaws (30%).[230] This makes jaw hypertrophy the most common observation in RO, affecting up to 78% of patients.[230] Up to 62% of patients diagnosed with CKD-MBD had the severe form of RO called brown tumor;[235] in these patients, jaws were affected in 62% of cases,[236] with a higher prevalence in the mandible than maxilla (54 vs. 46%),[235] thus making them the most frequent skeletal location. Despite its name, the brown tumor does not have any neoplastic characteristics, but rather reflects the expanding masses within the jaw.[237] The higher prevalence of brown tumor in the mandible is thought to be due to circulating PTH stimulating osteoclastic activity in cortical bone, which makes brown tumor one of the earliest diagnostic signs of hyperparathyroidism.[237] Due to early diagnosis and improved therapy, the incidence of brown tumors is low;[229] however, it is three times more prevalent in women than in men and is more common in the third and fourth decades of life.[237] Other forms of RO are also rare, with the continuously decreasing prevalence due to the improved early diagnosis using biochemical parameters and the withdrawal from aluminum-containing dialysis fluids.[238]

Jaw hypertrophy can be accompanied by severe periodontitis,[239] increased tooth mobility, pathologic tooth migration, diastemas (spaces between teeth),[234] increased palatal size, and flattening of the nasal bridge due to the widening of the nares;[240] however, the gingival covering of the expansive bone mass was normal.[239] Clicking of the

temporomandibular joint associated with pain around it and surrounding tissues has also been reported.[241,242] Other clinical features may include delayed tooth eruption, hypoplastic enamel, and dental erosion.[234] Various functional changes (e.g., masticatory dysfunction, nasal obstruction, epiphora, and diplopia) have also been reported.[237,243] Whether RO-associated periodontal breakdown is related to inflammation-associated periodontitis is unclear, as the periodontal status of these patients was not described in detail. According to the 2017 classification of periodontal diseases and conditions by the American Academy of Periodontology and European Federation of Periodontology, periodontal changes secondary to hyperparathyroidism should be classified under the category of "systemic diseases or conditions affecting periodontal supporting tissues" and not under the general "periodontitis" category.[244]

Radiographic Features

Radiographic changes are among the earliest signs of RO, which become more pronounced with disease progression.[234] In the most common type of RO, osteitis fibrosa, they have a diagnostic value in 47%[231] and include the partial or complete loss of lamina dura of the tooth sockets (creating a characteristic "floating teeth" appearance[245]), loss of cortical bone in maxillary sinus walls and mandibular canal, generalized diffuse bone porosity, and widening of the periodontal ligament (PDL) space (suggesting an increased osteoclastic activity).[234,237,246–249] In contrast to control individuals without renal disease who presented with heterogeneous and dense trabecular bone, the bone pattern in patients with CKD had a "ground-glass" appearance due to a finely meshed pattern of bone resorption[237,250–253] and a "salt and pepper" pattern of the skull bones on cone-beam computed tomography (CBCT).[254–256] Well-demarcated unifocal or multifocal bony lesions can be observed in patients with brown tumor.[231,237,243] Multiple periapical lesions around the root apices (sometimes coalescent into a single multilocular radiolucent lesion) could also be seen, but contrary to periapical lesions of odontogenic origin, tooth vitality was not affected.[241,246,248]

Etiology and Pathogenesis

The development and progression of RO are associated with impaired hydroxylation of 1-hydroxycholecalciferol to the active form of vitamin D (1,25-dihydroxycholecalciferol, or calcitriol) and impaired Ca^{2+} balance (due to its decreased retention in renal tubules, reduced absorption in the gastrointestinal tract, and secondary hyperparathyroidism leading to increased Ca^{2+} release from bone to blood).[229,257,258]

Significance

- *Bone fracture*. The decreased bone resistance in patients with RO may predispose them to a higher fracture risk;[233,259,260] however, bone healing following tooth extraction appears to be unaffected.[261]
- *Functional impairment*. Due to the expansive growth of the bone in patients with osteitis fibrosa, patients may have difficulty in swallowing and chewing and this may lead to airway obstruction, which can predictably be addressed by surgical therapy.[223,262]
- *Cardiovascular and anemia-related conditions*. Patients with RO can have compromised erythropoiesis and poorer response to EPO therapy, which have been associated with the mean serum PTH, the extent of the peritrabecular and marrow fibrosis, and the percentages of eroded bone surfaces.[263] As mentioned in the section on renal replacement therapy in end-stage renal disease, failure in production of EPO by the kidney is an underlying mechanism of anemia progression in renal disease patients.[258] Also, PTH levels represent the main biochemical marker of RO and have been shown to be associated with the development of cardiovascular diseases.[264]

Primary Hyperoxaluria (ICD-10-CM Diagnosis Code R82.992)

This is a rare, inherited, autosomal recessive disorder of glyoxylate metabolism characterized by an accumulation of oxalate due to its excessive production and impaired excretion (systemic oxalosis).[265–268] It is commonly observed in patients with CKD stages 4 and 5,[265] and although during CKD and early dialysis treatment the disease appears to be rather mild and not to affect the patient's health substantially, it becomes much more severe after as short as 2 years of dialysis, likely due to the inefficiency of dialysis treatment to reduce oxalate load.[265]

Clinical Signs

The disease is characterized by the presence of needle- or star-like crystals in virtually all tissues (systemic oxalosis), including alveolar bone, periodontium, dental pulp, and salivary glands. The degree to which the disease affects quality of life and life expectancy depends on the extent and rate of oxalate deposition in the tissues.[266] The reported dental cases include patients in their 20–30s, suggesting a rapid progression of dental conditions.[269–271] Oral findings include poor oral hygiene, vital teeth,[271] generalized gingival inflammation, external root resorption due to increased osteoclastic activity, increased tooth mobility due to severe periodontal breakdown and alveolar bone loss, and masticatory dysfunction.[269–271]

Radiographic Findings

Radiographically, diffuse deposition of radiopaque oxalate crystals within various soft (oral mucosa, PDL, dental pulp) and hard tissues (dentin, alveolar bone, and cementum) was observed.[269,270,272] Widened PDL[273] and well-demarcated bony lesions resembling cysts[269] could also be observed.

Etiology and Pathogenesis

The oxalate crystal deposition can be alleviated by the increased permeability of blood vessels in periodontitis, thus leading to a greater extent of periodontal breakdown.[274] However, it is unclear whether periodontal changes are associated with the deposit of crystals alone or aggravated by the inflammatory events of periodontitis. Since the 2017 classification of periodontal and peri-implant conditions does not list primary hyperoxaluria among the systemic conditions affecting the periodontium,[275,276] these conditions might be classified as periodontal abscesses associated with foreign bodies (oxalate crystals).

Significance

- *Local effects*. Hyperoxaluria-associated adverse effects could contribute to increased tooth mobility, tooth loss, and subsequent compromised chewing. However, the long-term outcomes of dental management of oral lesions, especially in patients after KT and liver transplantation, have not been reported.[274]
- *Systemic effects*. In addition to functional impairment of multiple tissues and organs, deposition of crystals in bone leads to an inflammatory reaction, activation of bone remodeling, and hyperparathyroidism.[265] Progressive renal fibrosis induced by chronic inflammation leads to the deterioration of glomerular filtration, causing systemic oxalosis, primarily in the bones, causing pain, spontaneous fractures, and EPO-resistant anemia, and radiographically presented with "bone-within-bone" and diffuse demineralization.[277]

Other Bone Conditions

A few cases of ossifying fibroma have been reported in patients undergoing in-center HD with poorly controlled secondary hyperparathyroidism, radiographically presenting with osteolytic bone and displaced roots of the teeth.[278,279] Also, aneurysmal bone cyst in a patient undergoing in-center HD and presenting with hyperparathyroidism has been described.[280] A more advanced stage of bisphosphonate-related osteonecrosis of the jaw is significantly associated with eGFR[281] and a poorer degree of response to therapy, especially in older individuals.[282] Also, a case of extensive osteonecrosis of both maxilla and mandible (not related to bisphosphonate use) of a patient who received KT (15 years after transplantation) has been recently described.[283]

DENTAL CONSIDERATIONS AND MULTIDISCIPLINARY MANAGEMENT

As already discussed, patients with renal disease present with various oral manifestations and pathologic lesions of soft and hard tissues and teeth. At the same time, the presence of oral lesions even in individuals without renal disease is associated with a statistically significant reduction in mean GFR compared to the respective controls without oral lesions (49.7 vs. 109.5 mL/min).[74] These findings suggest that observation of oral lesions can serve as an early indicator of reduced GFR flow and a predictor of future renal diseases; however, long-term follow-up studies are needed to determine whether patients with oral signs and reduced GFR eventually develop renal disease. Due to the compromised systemic condition of patients with renal diseases, dental professionals must establish close multidisciplinary collaboration with the patient's nephrologist team to ensure the patient's safety, minimize the risk of complications, and provide the best possible care. At the same time, nephrologists need to understand the importance of dental care in the systemic health of their patients and ensure that all acute or chronic loci of dental infections are eliminated prior to renal treatment, which is especially relevant for patients receiving KT.[284] Limited evidence suggests that the efficiency of this collaboration, however, appears to be inadequate. An older questionnaire study showed that 81% of dentists were aware of the kidney status of their patients with CKD and only 71% of patients had complete medical records;[29] nevertheless, whether the use of modern electronic health records has improved this statistic remains unexplored. At the same time, only ~30% of Brazilian nephrologists referred their patients for dental consultations,[285] although whether or not these data can be extrapolated to other countries is still uninvestigated. The importance of these gaps in patient management should not be overlooked.

Those who are not nephrologists frequently encounter issues with antibiotic dosing and electrolyte abnormalities in patients undergoing HD. Excellent volume control is necessary for certain tests or procedures so that patients can lie in the supine position for the duration of the test or procedure. Most dialysis units can accommodate longer or extra treatments before procedures that optimize acid–base and volume status prior to major procedures requiring general anesthesia.

Based on the available literature evidence, we have summarized the current knowledge on the dental management of patients with renal conditions.

Up to 70% of KT candidates require dental therapy prior to transplant surgery.[286] The multidisciplinary dental management of patients receiving KT is similar to that for patients with CKD and those undergoing in-center HD. However, patients receiving KT commonly present with more compromised immune conditions, which require special consideration. Ongoing dental infections (dental caries or periodontal breakdown) in these patients can contribute to fever, cough, and jaw pain, which are alleviated after addressing the respective dental conditions.[287] Therefore, the United Network of Organ Sharing has published guidelines for patients anticipating organ transplants (including patients with renal diseases) that outline the process of preparation for transplantation and include a "dental exam clearance" communication form, which should be completed by a dentist and returned to the transplantation team before a patient can be "listed" for transplantation. Since most US kidney pre-transplant patients have Medicare, their dental treatment preceding transplantation may not be covered (except for selective tooth extractions).[288] This poses a higher risk of delaying KT procedures. Therefore, nephrologists should establish close communication with dentists regarding the schedule for KT and the patient's dental needs.

Hematologic Conditions

The anemia and hypertension commonly seen in patients with renal disease as well as various anticoagulants used in HD therapy and vascular access maintenance[258] pose a significant risk of increased bleeding. Up to 50% of patients with CKD and those undergoing in-center HD had an increased tendency for systemic preoperative bleeding[289] and a significantly higher perioperative risk of blood transfusion.[290] A case report study of patients undergoing in-center HD who displayed medication-induced gingival overgrowth reported extensive (1650 mL) bleeding during gingivectomy and extensive tooth extraction (19 teeth), even despite normal blood tests (bleeding time and upper limits of PTT and PT).[291]

The mechanisms of the increased bleeding in patients with CKD prior to undergoing in-center HD commonly include an impaired coagulation cascade and fibrinolytic system, platelet dysfunction, vasodilation with increased fragility of the blood vessel wall, impaired platelet–vessel wall interaction, and inflammation (see Table 16-8).[127,258,289] In select patients undergoing in-center HD (typically three 3-5-hour courses of dialysis weekly), increased bleeding can be associated with the use of anticoagulants (commonly heparin, but danaparoid, lepirudin, and argatroban can also be used as alternatives[292]) prior to each procedure.[258] Older studies have proposed performing dental procedures before dialysis, since any medications given by a dentist and their metabolites will be removed during subsequent dialysis.[293] Currently, it is recommended that dental procedures be performed on alternate days to dialysis to avoid anticoagulant-induced bleeding and the adverse effects of uremic metabolites, which may otherwise put the patient at hemorrhagic and/or cardiovascular risk, and to avoid conflicts in the dialysis and dental appointment schedule.[258,294,295] Heparin dose in hemodialysis is very low and it is safe to treat patients after 6 hours from a coagulation point of view; however, logistically it may be better to do more invasive procedures after dialysis day. Caution needs to be exercised when doing invasive procedures in patients who are taking direct oral anticoagulants. These include antithrombotic agents such as acetylsalicylic acid and clopidogrel, anticoagulants (unfractionated heparin, low molecular weight heparin, fondaparinux), direct thrombin inhibitors (such as dabigatran), and direct factor Xa inhibitors (such as rivaroxaban or apixaban). Patients with advanced CKD (stages 4 and 5) and ESRD may experience higher bleeding risk than the general population, and this needs to be addressed when planning invasive dental procedures.

Patients undergoing PD use their peritoneum as a filter, and routine use of anticoagulation is not required during PD; hence, clotting of blood in the extracorporeal system is not a potential complication.

Nevertheless, dentists who plan invasive dental procedures and expect greater than minor bleeding should still

Table 16-8 Mechanisms of increased bleeding in patients with renal disease.

- Impaired coagulation cascade and fibrinolytic system
- Platelet dysfunction (disturbance of the platelet α-granules; impaired intracellular calcium flux; impaired synthesis and/or release of thromboxane A_2 and a subsequent reduction in platelet adhesion and aggregation; deregulated metabolism of arachidonic acid and prostaglandins; intake of medications affecting platelet function)
- Vasodilation with increased fragility of the blood vessel wall
- Impaired platelet–vessel wall interaction (due to the decreased expression of platelet glycoprotein Ib, and impaired binding of von Willebrand factor and fibrinogen to activated platelets)
- Inflammation (indirectly, due to increased tissue fragility)

Sources: Babitt JL, Lin HY. Mechanisms of anemia in CKD. *JASN*. 2012;23(10):1631–1634; Greenwood M, Meechan JG, Bryant DG. General medicine and surgery for dental practitioners. Part 7: renal disorders. *Br Dent J*. 2003;195(4):181–184; Lutz J, Menke J, Sollinger D, et al. Haemostasis in chronic kidney disease. *Nephrol Dial Transplant*. 2014;29(1):29–40.

communicate with nephrologists to discuss the possible risk of excessive bleeding. In addition, they should be ready to use various local hemostatic agents (e.g., oxidized regenerated cellulose, Gelfoam with activated thrombin, tranexamic acid [Cyklokapron, 500 mg/5mL], and cellulose sponges),[291,296] especially in patients with thrombocytopenia and platelet dysfunction (see Table 16-9). Appropriate flap management and suturing techniques were required to minimize the risk of excessive bleeding[297] and provide optimal healing of intraoral soft tissues.[298]

In an emergency, various systemic aids, including heparin antagonist protamine sulfate and desmopressin, antifibrinolytic drugs (tranexamic acid, epsilon aminocaproic acid), fresh frozen plasma, and platelet transfusion can also be performed in the appropriate settings (see Table 16-10).[291,296]

If a patient receives warfarin to maintain shunt patency, International Normalized Ratio (INR) values prior to the procedure need to be obtained. Minor invasive procedures, such as isolated tooth extraction, can be safely performed with INR <3.5, whereas higher INR values require a nephrologist consultation.[305] For a comprehensive review of bleeding disorders and their dental management, refer to the Bleeding and Clotting Disorders chapter of this textbook.

Medications

A non-nephrologist frequently encounters issues with antibiotic dosing and electrolyte abnormalities in patients undergoing dialysis. Excellent volume control is necessary for certain tests or procedures so that patients can lie in a supine position for the duration of the test or procedure. Most dialysis units can accommodate longer or extra treatment before the procedure to optimize acid–base and volume status prior to major procedures requiring general anesthesia. Hyperkalemia, hyperphosphatemia, and hypocalcemia were the most commonly encountered electrolyte abnormalities in patients undergoing in-center HD. Drugs that prolong the QT interval should be carefully prescribed in patients with ESRD (a noninclusive list is shown in

Table 16-9 Local hemostatic agents used during invasive dental procedures.

Name	Mode of Action	Mode of Delivery
Oxidized regenerated cellulose	Stimulates denaturation of blood proteins, activates platelet aggregation, and induces blood clot formation[299,300]	Local application to the wound area
Gelfoam with activated thrombin	Gelfoam acts as a spongy carrier that can be soaked with thrombin that induces the formation of fibrin from fibrinogen[301]	Local application to the wound area
Cyklokapron (tranexamic acid)	Antifibrinolytic; reduces the binding of plasminogen to fibrin[302]	• Oral rinse (15 mL) 4×/day for 10 days • Soaking a piece of gauze and biting on it for 15–20 min
Sutures	Mechanically approximate wound tissue margins	Placed during the surgical invasion

Table 16-10 Systemic hemostatic agents used during invasive dental procedures.

Name	Mode of Action	Effects
Protamine sulfate	Heparin antagonist	If emergency treatment has to be performed on a heparinized patient, protamine sulfate can be used to antagonize the anticoagulant effect of heparin[294,295]
Desmopressin	Stimulates the release of von Willebrand factor from endothelial cells (effects last for up to 4 hours[258,297,303])	If prolonged bleeding time and low platelet aggregation tests are observed, 0.3 μg/kg of desmopressin can be administered subcutaneously or intravenously.[304] Preferably perform the procedures in one visit to avoid the use of another dose of desmopressin

Sources: Nishide N, Nishikawa T, Kanamura N. Extensive bleeding during surgical treatment for gingival overgrowth in a patient on haemodialysis—a case report and review of the literature. *Aust Dent J*. 2005;50(4):276–281; Abed H, Burke M, Shaheen F. The integrated care pathway of nephrology and dental teams to manage complex renal and postkidney transplant patients in dentistry: a holistic approach. *Saudi J Kidney Dis Transpl*. 2018;29(4):766–774.

Table 16-11 The use of drugs prolonging QT interval in patients with renal disease.

Category	Drugs
Antiarrhythmics	Amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotolol
Antidepressants	Amitryptyline, fluoxetine, sertraline, venlafaxine
Antimicrobials	Azithromycin, clarithromycin, erythromycin, levofloxacin (fluoroquinolones), fluconazole (azole antifungals), pentamidine
Antipsychotics	Chlorpromazine, clozapine, haloperidol, quetiapine, risperidone, ziprasidone
Miscellaneous	Methadone, ranolazine, sumatriptan, zolmetriptan

Table 16-11). Communication with dialysis units and nephrologists is key to delivering optimal care to medically complex patients undergoing in-center HD.

As a general rule, clinicians should avoid prescribing any medications that are nephrotoxic or become nephrotoxic due to accumulation and prolonged plasma levels in patients with renal disease (see the detailed examples that follow).[258,284] In these patients, other mechanisms of impaired pharmacokinetics of the drugs may include hypoalbuminemia (which limits the amount of proteins available to bind the drugs) and elevated urea levels (inhibiting the binding of proteins to plasma albumin), leading to the decreased availability of bound drugs and increased levels of free drugs. As a result, the doses and duration of various medications must be adjusted depending on the stage of renal disease. Therefore, it is essential to understand the pharmacokinetics of various drugs in patients with renal disease, taking into consideration their compromised health and increased risks for the development of infections.

Antibiotics

Bacteremia is a common sequela of impaired renal function, often leading to the development of infective endocarditis (IE),[306,307] Even while undergoing in-center HD, patients have a significantly higher risk of IE (1.4% vs. 0.3% at 1 year, 2.2% vs. 0.6% at 3 years, and 3.9 vs. 0.9% at 5 years),[308] which is a frequent cause of all-cause mortality of these patients.[309] Antibiotics were commonly used in the management of impaired renal function to prevent or minimize the risk of adverse complications associated with bacteremia.[310] Since many of them were excreted by the kidneys,[310] assessment of the functional activities of the kidneys is essential for choosing the optimal dose (see Table 16-12). Several papers provide guidelines on the choice and dose of antibiotics depending on eGFR (see Table 16-13).[258,284,304,311–313]

To minimize the possible risk of IE after invasive dental procedures, US dentists use prophylaxis antibiotics according to the American Heart Association (AHA) and American College of Cardiology guidelines.[314] Clinicians in Europe follow similar recommendations outlined by the European Society of Cardiology.[315] However, since these guidelines do not address the need for prophylactic antibiotics prior to dental procedures in patients with renal disease and those who have received KT, some dentists have raised concern about this need. It has been argued that cessation of antibiotic prophylaxis, as recommended by the UK National Institute for Health and Care Excellence, has resulted in an increased incidence of IE.[316] Although antibiotic prophylaxis appears to be safe and cost-effective,[298,316,317] 81% of antibiotic prophylaxis prescriptions prior to dental procedures were made to patients not at high cardiac risk, thus not following the AHA guidelines.[318] In patients receiving KT, antibiotic prophylaxis is recommended,[284,319] and some authors suggest it for at least 2 years after KT.[258] However, a retrospective study of patients receiving KT has shown that antibiotic prophylaxis prior to extraction procedures had no effect on the outcome of the procedure, and no difference in post-healing events were found compared to patients receiving no antibiotic prophylaxis.[261] Therefore, best practice remains discussion with the patient's nephrologist to evaluate the indication for antibiotic prophylaxis in each individual case.[294]

Nonsteroidal Anti-inflammatory Drugs

NSAIDs are commonly used to minimize inflammatory changes and reduce pain after invasive dental procedures. Extensive overviews of their use in dental patients with renal disease are available.[311,320] In a healthy, well-hydrated patient, the use of NSAIDs does not pose an increased nephrotoxic effect. However, in patients with impaired renal function, NSAIDs, especially those used for an extensive period of time or at high doses, can exert nephrotoxic effects, including the induction of hyperkalemia and hypertension, retention of sodium and fluids, and production of acidosis, and therefore they deteriorate already compromised renal function and contribute to the progression of CKD.[312,321,322]

Patients undergoing in-center HD with reasonable residual renal function (urine output >200–300 mL/24 hrs) may want to avoid long-term NSAIDs to preserve renal function. It is generally recommended to avoid NSAIDs, especially in patients with GFR <10 mL/min.[296,311] In patients with eGFR 10–50 mL/min, aspirin can be used no more often than every 6 hours; however, it is recommended to avoid it due to increased platelet dysfunction, impaired renal blood flow, commonly observed gastrointestinal ulcers, increase in gastrointestinal bleeding, and deterioration in renal function.[294,312] For postoperative

Table 16-12 Antibiotics.

Antibiotic	Can It Be Used in Renal Patients? (Y/N)	Recommended Dose
Tetracycline	Y	250–500 mg every 6 hrs
Doxycycline	Y	No dose adjustment necessary
Minocycline	Y	Do not exceed 200 mg/day
Doxycycline and minocycline	Y (excreted via bile)	
Erythromycin (and other macrolides)	• Y (in non-renal-transplant patients) • N (in patients receiving KT and taking CsA since it reduces CsA metabolism and leads to increased toxicity)	• No dose adjustment necessary (stages 1–4) • 50%–75% of the normal dose (maximum 1.5 mg/day) for stage 5 and dialysis • N/A
Amoxicillin (and other penicillins, except potassium penicillins)	Y	• 500 mg (stages 1–4) every 12 hrs • 250 mg (stage 5) every 12 hrs • 250 mg every 24 hrs—dose after dialysis (HD) • Avoid high doses (>500 mg every 12 hrs) due to the possibility of seizures
Clindamycin	Y	No dose adjustment necessary (oral, 600–1800 mg/day in 2–4 divided doses)
Metronidazole	Y	• For CKD stages 1–4, no dose adjustment necessary (500 mg every 8–12 hrs) • For CKD stage 5 and dialysis, dose adjustment is necessary (500 mg every 12 hrs, dialyzable, dose after HD on dialysis days)
Aminoglycosides	N	• IV/IM • Nephrotoxic (AKI and AKI on CKD) • If no alternative, can use regular dose every 48–72 hrs with therapeutic drug level monitoring
Cephalosporins	Y	0.5 mg IV 1 hr prior to procedure[298]

AKI, acute kidney injury; CKD, chronic kidney disease; CsA, cyclosporine A; HD, hemodialysis; IM, intramuscular; IV, intravenous; KT, kidney transplant; N, no; N/A, not applicable; Y, yes.

Table 16-13 Antibiotic doses in patients with various estimated Glomerular Filtration Rates (eGFRs).

eGFR	Antibiotics
10–50 mL/min	Regular dose of antibiotic of choice (e.g., amoxicillin, clindamycin, metronidazole, erythromycin) • Amoxicillin: 500 mg 21 tabs (3×/day for 7 days) • Metronidazole: regular dose every 12 hrs
<10 mL/min	Reduced doses of antibiotics: • Amoxicillin: 250 mg 21 tabs (2–3×/day for 7 days) • Clindamycin: no dose adjustment • Erythromycin: 50–75% of a regular dose (maximum of 1500 mg/day) Metronidazole: regular dose every 12 hrs
Dialysis (hemodialysis and peritoneal dialysis)	Same as with eGFR <10 mL/min

Sources: Greenwood M, Meechan JG, Bryant DG. General medicine and surgery for dental practitioners. Part 7: renal disorders. *Br Dent J*. 2003;195(4):181–184; Vasanthan A, Dallal N. Periodontal treatment considerations for cell transplant and organ transplant patients. *Periodontol 2000*. 2007;44:82–102; Saif I, Adkins A, Kewley V, et al. Routine and emergency management guidelines for the dental patient with renal disease and kidney transplant. Part 2. Dental update. 2011;38(4):245–248,250–251; Brockmann W, Badr M. Chronic kidney disease: pharmacological considerations for the dentist. *J Am Dent Assoc*. 2010;141(11):1330–1339; Svirsky JA, Nunley J, Dent CD, Yeatts D. Dental and medical considerations of patients with renal disease. *J Calif Dent Assoc*. 1998;26(10):761,763–770; Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. Am Fam Physician. 2007;75(10):1487–1496.

pain management, acetaminophen is generally more recommended, since it does not cause bleeding and is tolerated better (every 6 hours if GFR 10–50 mL/min and every 8 hours if GFR <10 mL/min).[294,311] However, chronic administration of acetaminophen should be avoided, since it can form phenacetin with nephrotoxic effects.[312] NSAIDs with weaker effects on renal prostaglandins (e.g., nabumetone, etodolac, and sulindac)[320] and nonacetylated salicylates (e.g., diflunisal, salsalate, magnesium choline salicylate, or salicyl salicylate)[311] can also be considered in patients with ESRD.

Benzodiazepines and Opioid Drugs (Narcotics)

Many long-lasting benzodiazepines (e.g., diazepam, clorazepate, and flurazepam) are excreted renally and produce toxic active metabolites with long half-lives that accumulate in patients with renal impairment (see Table 16-14).[311,312]

A recent review study has summarized various aspects of opioid use in older patients with CKD and suggested that opioids should only be used when absolutely necessary.[323] Buprenorphine, fentanyl, ketamine, and hydromorphone form inactive metabolites and therefore are the safest opioids to use (Table 16-15). In contrast, hydrocodone, oxycodone, and methadone form active metabolites, which may accumulate due to reduced renal function and induce toxicity (Table 16-15). Due to greatly reduced clearance with renal impairment and possible enhancement of drug effects, codeine, morphine, and meperidine should also not be used in nondialysis renal patients (Table 16-15).[295,297,311,312,323] However, even safe and short-lasting opioids delivered repeatedly can substantially prolong the elimination of the drug and its metabolites. Also, due to the anemia commonly seen in patients with renal disease, narcotics should be used with caution due to their respiratory depressant effects.[61]

Table 16-14 Metabolites formed by benzodiazepines.

Benzodiazepines	Effects
Chloral hydrate	Reduced excretion of its active metabolite 2,2,2-trichloroethanol leads to its accumulation owing to a long half-life (>10 hours) and excessive and prolonged sedation; avoid its use if GFR <50 mL/min
Meprobamate	Eliminated via renal route almost entirely unchanged; unmetabolized meprobamate (10%–12% of total concentration) accumulates with repeated dosing due to long half-life (>10 hours), resulting in excessive sedation; double the dosing interval when GFR is 10–50 mL/min and triple it when GFR <10 mL/min
Chlordiazepoxide, diazepam, clorazepate, flurazepam	Active metabolites with long half-lives; avoid multiple doses (as multiple dosing greatly increases the half-life and prolongs sedation); reduce doses by 33%–50% if GFR >30 mL/min

Sources: Brockmann W, Badr M. Chronic kidney disease: pharmacological considerations for the dentist. *J Am Dent Assoc*. 2010;141(11):1330–1339; Svirsky JA, Nunley J, Dent CD, Yeatts D. Dental and medical considerations of patients with renal disease. *J Calif Dent Assoc*. 1998;26(10):761,763–770.

Oral Sedatives

Patients with renal disease may require long-term glucocorticoid therapy, which can result in an adrenal crisis during stressful events (such as dental treatment).[258,294] Therefore, these patients should be treated in a quiet, stress-free environment, as exogenous steroids can reduce

Table 16-15 Opioid drugs (Narcotics).

Opioid Drug	Effects
Buprenorphine, fentanyl, ketamine, hydromorphone	Do not form active metabolites (relatively safe to use)
Hydrocodone, oxycodone, methadone	Form active metabolites (should not be used in patients prior to undergoing in-center HD; should be used judiciously in patients undergoing in-center HD and those who have received KT)
Codeine	Forms an active metabolite, morphine-6-glucuronide
Meperidine	Forms an active metabolite, normeperidine (neurotoxic central nervous system stimulant and convulsant)
Propoxyphene	Forms an active metabolite, norpropoxyphene, which accumulates due to its long half-life (>36 hours) and causes cardiotoxic and seizure activity. Avoid its use in GFR <10 mL/min
Tramadol	Forms an active metabolite, O-desmethyltramadol, which accumulates and causes seizures and respiratory depression)

GFR, glomerular filtration rate; HD, hemodialysis; KT, kidney transplant.Sources: Alamo S, Esteve C, Pérez M. Dental considerations for the patient with renal disease. *J Clin Experiment Dent*. 2011;3(2):112–119; Ziccardi VB, Saini J, Demas PN, Braun TW. Management of the oral and maxillofacial surgery patient with end-stage renal disease. *J Oral Maxillofac Surg*. 1992;50(11):1207–1212; Brockmann W, Badr M. Chronic kidney disease: pharmacological considerations for the dentist. *J Am Dent Assoc*. 2010;141(11):1330–1339; Svirsky JA, Nunley J, Dent CD, Yeatts D. Dental and medical considerations of patients with renal disease. *J Calif Dent Assoc*. 1998;26(10):761,763–770; Owsiany MT, Hawley CE, Triantafylidis LK, Paik JM. Opioid management in older adults with chronic kidney disease: a review. *Am J Med*. 2019;132(12):1386–1393.

the adrenal function to produce cortisol in response to stress, thus posing an increased risk for hypotension.[324] When this is not possible, oral sedatives may provide an excellent level of sedation and patient comfort. Similar to various other medications, sedatives are affected by compromised renal function. A comprehensive review of the use of oral sedatives in renal patients has been published.[311] Chlordiazepoxide, diazepam, clorazepate, and flurazepam produce active metabolites; therefore their dose should be reduced by 33%–50% if GFR >30 mL/min, and multiple doses should be avoided (as multiple dosing greatly increases the half-life and prolongs sedation). Chloral hydrate can be accumulated in the form of its active metabolite, 2,2,2-trichloroethanol, resulting in excessive sedation; therefore chloral hydrate should be avoided in GFR <50 mL/min. Meprobamate is eliminated via the renal route almost entirely unchanged; unmetabolized meprobamate accumulates with repeated dosing due to its long half-life (>10 hours), resulting in excessive sedation; its dosing interval should be doubled in GFR 10–50 mL/min and tripled in GFR <10 mL/min.

Intravenous Sedation

A large cohort study that involved patients undergoing in-center HD and conscious sedation by nephrologists has shown that midazolam alone was used in 95% of cases (mean dose of 3.4 mg); fentanyl alone in 1% of cases (mean dose 79 μg); and their combination in 4% of cases (mean doses 3.3 mg and 60 μg for midazolam and fentanyl, respectively). The study has concluded that both drugs were safe to use even in high-risk patients, although in decreased doses.[325] Another study has shown that compared to diazepam, midazolam was preferable because of the lower risk of thrombophlebitis.[326]

Local Anesthetics

Local anesthetics (administered during infiltration or nerve block anesthesia) have a hepatic route of elimination, and therefore they can be safely used in patients with renal disease at a regular dose (300–500 mg to 14 cartridges).[258,284,297,311,312] Due to an increased prevalence of hypertension, epinephrine-containing anesthetics should be used judiciously.[312]

Cardiovascular Considerations

Hypertension is a common etiologic factor, and at the same time a consequence of renal disease, which should be monitored pre- and postoperatively.[258,295] In addition, some medications, such as NSAIDs, can produce hypertension.[295] Due to the elevated blood potassium levels, renal patients may also present with increased neuromuscular excitability, potentially leading to life-threatening ventricular arrhythmias and cardiac arrest.[327] It is important to remember to protect dialysis access during dental procedures[61,304,312] by avoiding the arm with vascular access for the measurement of blood pressure (as well as delivering IV medications or drawing blood),[295,297,312] as its accidental damage can cause torrential hemorrhage.[258] Patients should be kept in comfortable positions in the dental chair and allowed to take breaks as needed to minimize the risk of access obstruction.[61] These patients should be treated sitting upright to minimize the risk of pulmonary edema and congestive heart failure.[258] A recent study has shown that patients undergoing in-center HD might have a higher prevalence of carotid artery calcifications identified in dental panoramic radiographs compared to patients with ESRD and CKD (26 vs. 22 vs. 16%).[328] Therefore, a dentist may be the first healthcare specialist to observe these signs and refer the patient to a nephrologist or another medical specialist.

Box 16-1 Protocol for Dental Management of Patients with Chronic Kidney Disease and Those Undergoing In-Center Hemodialysis[208,329–331]

Prior to Dental Treatment

- Implementation of a multidisciplinary, patient-centered dental plan tailored to their individual needs upon communication with the nephrologist. This communication should include (a) any systemic concerns (e.g., stage of renal disease, most recent blood tests, presence of systemic comorbidities, risk of excessive bleeding); (b) choice/dose/duration of current medications and medications suggested (and contraindicated) prior to, during, and after dental procedures (including the need for antibiotic prophylaxis); and (c) proposed duration and timing of treatment, anticipated results, time frame of healing, and post-therapeutic complications that could possibly develop.
- Implementation of a stress reduction protocol that includes morning dental appointments, a quiet calm environment to minimize the risk of stressful changes, and possible conscious sedation.
- Comprehensive intra- and extraoral examination, including hard tissue charting, periodontal examination, and intraoral pathology screening. Full-mouth radiographs and/or panoramic radiograph should be obtained to properly evaluate tooth hard tissue conditions and possible alveolar bone changes.

- A patient-centered oral hygiene care plan, including patient education, demonstration of stained biofilm, calculation of plaque, and evaluation of brushing and interdental flossing efficiency, should be developed and implemented. Daily use of antibacterial mouth rinses with essential oils or 0.12% chlorhexidine is recommended to minimize the risk of a fungal infection or in patients who are unable to follow a recommended oral hygiene protocol. Evaluate the need for topical fluoride therapy in patients with high caries risk, but remember that systemic delivery of fluoride for caries prophylaxis should be minimized due to its nephrotoxicity for patients with compromised renal function.[319] Identify local risk factors for the development or progression of oral infections (such as dentures). In patients with xerostomia, chewing gum or artificial saliva can be used to alleviate xerostomia symptoms.[52,332,333] Salivary substitutes should be alcohol free, and contain xylitol and carboxymethylcellulose (or hydroxyethyl cellulose). Adjust the frequency of professional cleaning appointments, if needed.
- In patients presenting with halitosis, mechanical removal of dental biofilm, tongue coating, and bacteria,[62,65,334] mouthwashes (containing cetylpyridinium chloride, zinc, triclosan, H_2O_2, and 0.12% chlorhexidine),[335-337] and patient education on proper oral hygiene[338] should be used. In cases of pseudo-halitosis, a referral to a psychologist may be necessary.
- In patients presenting with a reduced salivary flow rate, the following approaches should be considered: (a) patient education emphasizing the importance of exercising oral hygiene and smoking cessation; (b) management of systemic diseases and medications associated with their treatment; (c) preventive measures to reduce oral diseases, and pharmacologic treatment with sialagogues (e.g., pilocarpine, cevimeline, sugar-free chewing gums); and (d) blood tests and biopsy of minor salivary glands to identify systemic contribution.[31] Although pilocarpine appears to be a medication of choice for patients with xerostomia,[339] it should be used with caution in patients receiving beta-blockers.[31] Although various saliva stimulants are available and beneficial,[332] there is no strong evidence to support their particular choice.[340] It is also important to remember that artificial saliva substitution agents do not exert the protective properties of natural saliva.[31]
- If an invasive dental procedure is planned, a dentist should anticipate excessive bleeding during the procedure. Obtain a complete blood count (white blood cell count, absolute neutrophil count, platelet count) and coagulation tests prior to any invasive dental treatment and ensure the availability of local and systemic hemostatic agents in the dental office. Although tooth extractions are not contraindicated in patients with renal disease, they can present with weakened jawbones due to renal osteodystrophy. In addition, postextraction healing events may differ from those in control individuals without renal disease.[250] For patients considering dental implants, general guidelines have been described recently,[341] and implant placement appears to be safe to consider.[342]
- If a patient is hypertensive, a dentist should consider the proper choice of local anesthesia agent or sedation (oral or intravenous [IV]) prior to the procedure. Ensure you use the correct arm to deliver IV medications and take blood pressure measurements.

During Dental Treatment

- The dentist should follow medication recommendations (including antibiotic prophylaxis) received from the patient's nephrologist. If the patient is on warfarin, International Normalized Ratio values should be obtained <1 hour prior to the procedure.
- In patients prior to undergoing in-center dialysis who need to have IV sedation or drug administration, the cephalic vein should not be used, since the arteriovenous fistula established through this vein is the first choice for permanent dialysis access.[343] Therefore it should be preserved in case the patient needs to be placed on dialysis in the future.[344] In hemodialysis patients with limited peripheral IV access, IV antibiotic prophylaxis at the end of the dialysis session and prior to the dental appointment may be needed and should be discussed with the nephrologist.[344] Patients who receive antibiotic prophylaxis and schedule multiple dental appointments should allow for an interval of 1–2 weeks between these appointments, and may need to use antibiotics from a different class to avoid resistance to it.
- If a patient presents with signs of chronic or active infection (e.g., dental caries, periodontal disease, abscesses, endodontic infection), these need to be addressed as soon as possible.
- If a flap needs to be raised, conservative flap management and hemostatic agents are encouraged.

After Dental Treatment

- Follow the post-therapeutic schedule appropriate for the dental procedure performed.
- Reinforcement of patient education on home oral hygiene and smoking cessation (if the patient is a smoker) should be undertaken. Patients should be advised to have professional dental cleanings.
- Ensure you have an updated list of medications and medical procedures performed during this period.
- Communicate with the nephrologist regarding the post-therapeutic outcomes, especially if there are complications or side effects of the medications used.

Box 16-2 Protocol for Dental Management of Patients Who Have Received Kidney Transplant[284,294,329,331,345–348]

Prior to Transplantation

This period is characterized by a high risk of the development of oral infections due to the concurrent immunocompromised status of these patients. Therefore, the goal of dental treatment is to perform aggressive elimination of the existing infectious foci *prior to* transplantation, and ensure that the patient has reached an acceptable oral hygiene and dental status for transplant candidacy.

Initial Patient Visit

- Whenever possible, the patient needs to be treated in a quiet environment, especially if they are receiving long-term glucocorticoid therapy. In these cases, it is also important to remember that the use of glucocorticoids can be associated with hypertension and hyperglycemia, which should be considered by the dentist.
- Obtain and review the most recent medical history, including the presence and status of systemic comorbidities (cardiovascular conditions, diabetes, hepatitis, etc.). Update the list of medications and be familiar with the side effects of these medications and their combination. Ensure the use of protective equipment and universal precautions.
- Although cancer screening is a mandatory part of dental examinations and standard of care, patients who have received a kidney transplant may have an increased prevalence of intraoral malignancies due to their immunocompromised conditions. Therefore, dentists should be especially thorough in performing oral cancer screening of these patients.
- Update the dental history and full mouth series (FMS), if needed.
- If the dentist is not aware that the patient requires antibiotic prophylaxis prior to a dental visit, perform a noninvasive (without periodontal probing) dental examination.
- Reinforcement of oral hygiene via patient education, motivation for home care (toothbrushing, using interdental floss or brushes, use of antibacterial mouth rinses), and professional visits.
- Discuss the findings with the patient and propose a treatment plan.

Consultation with the Patient's Nephrologist

- Is the proposed dental treatment feasible considering the patient's renal and other systemic conditions?
- What is the desired time frame for dental procedures considering the expected date of the transplantation surgery?
- Does the patient need to have antibiotic prophylaxis prior to the dental procedures?
- Are medications proposed during the dental treatment recommended or not? If yes, do these medications require dose adjustment?
- If the patient receives prolonged corticosteroid therapy, are supplemental doses of corticosteroids recommended prior to the dental procedure to avoid an adrenal crisis?
- If the patient presents with signs of medication-induced gingival enlargements, can alternative medications be used?

Dental Treatment

- Perform comprehensive hard tissue, periodontal evaluation, and oral pathology screening.
- Initiate the proposed dental treatment after receiving approval from the patient's nephrologist.
- The dentist should address all dental concerns, including but not limited to treatment of active (progressive) periodontal disease, operative treatment of dental caries, extraction of hopeless or impacted teeth, endodontic treatment, elimination of all sources of active infection (fistulas, abscesses, pericoronitis) or necrotic tissue, adjustment of existing or fabrication of new dental dentures, and removal of orthodontic appliances. Consider the use of 0.12% chlorhexidine irrigation throughout the dental visit and its prescription to reduce the risk of dental caries and biofilm-induced gingival inflammation due to poor oral hygiene.[284]
- During prophylaxis (dental cleaning), a limited number of teeth may be instrumented during the same appointment.
- No implant therapy or periodontal procedures that require a long healing period (such as maxillary sinus elevation and guided tissue regeneration using particulate bone graft material) should be performed at this point.
- Reinforce patient education on oral hygiene and home care. Perform smoking cessation counseling, if needed.

- In the case of intraoral fungal infections, it is important to remember that antifungal medications can interact with immunosuppressive medications, inhibit their metabolism, and increase their blood concentration.[349] Therefore, their use requires close monitoring and a possible dose reduction of immunosuppressive medications.[304] In addition, some antifungal medications (e.g., clotrimazole and terbinafine) are poorly (if at all) absorbed by the oral mucosa,[304] especially in patients with xerostomia,[31] and thus cannot enter the systemic circulation. Therefore their choice should be justified depending on both systemic and intraoral patient conditions.

Months 0–6 after Transplantation

During this period, patients receive intense immunosuppressive therapy.

- Only emergency dental procedures, in the hospital environment and after the nephrologist is informed and has consented to this treatment, should be performed.
- Follow the recommended steps described for pretransplantation patients (see above).

Months 6+ after Transplantation

During this period, graft healing is expected to stabilize.

No Transplant Rejection

- The patient should be observed to reveal any intraoral lesions secondary to the transplant procedure or medications (yeast infection, gingival overgrowth, and possible malignancies). Any updates on the patient's dental status should be reported to a nephrologist.
- Selective dental procedures can be performed. Dental implants appear to be safe and predictable to perform.[350]
- All new emergency cases should be addressed as soon as possible. Report their occurrence to the patient's nephrologist.
- Follow the recommended steps described for pretransplantation patients (see above).

Transplant Rejection

Only emergency dental treatment should be done, preferably in the hospital environment.

CONCLUSIONS

Patients with compromised renal conditions present with a wide variety of oral manifestations and lesions, which are often challenging to recognize and interpret for medical professionals. Therefore, nephrologists should consider referring patients to an oral healthcare professional for comprehensive evaluation and treatment. Considering the increased prevalence of renal disease in the United States and worldwide, it is expected that oral healthcare professionals will see increasing numbers of these patients. Therefore, the ability to observe, differentiate, and diagnose oral conditions can be important in the early diagnosis of renal disease and evaluation of their progression. Not only will the proper management of oral conditions improve the quality of dental conditions and quality of life of the patient, it also will contribute to improved outcomes of renal treatment. It is important to note that patients with renal disease can be treated safely and appropriately in ambulatory dental settings as long as proper communication with the patient's primary care provider and/or nephrologist has been undertaken prior to, during, and after the course of renal therapy.

Limitations to the Current Literature Evidence

- As mentioned throughout the chapter, literature evidence is lacking for the presence and severity of various oral symptoms and signs in patients with renal disease.
- The vast majority of studies represent case reports, case series, and studies that are retrospective in nature, with their inherent study design limitations. In addition, since a majority of studies are case-control studies, the only estimates we have are odds ratios (OR) and not relative risk (RR). This poses a risk of overestimating the extent of the association or intervention effect and erroneously presenting the results as clinically substantial and justified.
- Several studies evaluated dental conditions without having a dentist as an author. In these and other studies, only limited periodontal evaluation was performed.
- Several studies showed the presence/absence and prevalence of oral symptoms and signs only in patients with renal disease, without comparison with control individuals without renal disease. Therefore, it is challenging to interpret these findings and assess the impact of renal conditions on oral symptoms and signs.

- Several studies did not conduct multiple regression analysis to adjust for confounding factors (such as systemic comorbidities, duration of HD, ethnicity, etc.)
- Only a few studies evaluated the effects of renal therapy on the prevalence and severity of oral symptoms and signs. Similarly, only a few studies have examined the impact of dental therapy on renal function.
- We question the statistical analysis in several studies (e.g., demonstrating statistical significance with lower or upper limits of the 95% CI being ~1.0). In other instances, OR were statistically significant, but their clinical significance is inconclusive due to a small OR value (up to 1.5), which was not addressed in the studies.

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17

Hematologic Diseases

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HEMATOPOIESIS

Hematopoiesis is the process of production of blood cells and platelets, which continues throughout life. This lifelong supply is derived from a rare population of multipotent hematopoietic stem cells (HSCs). Hematopoiesis has long been thought of as a hierarchal linear process where multi-, oligo-, and unipotent progenitors develop into mature hematopoietic cells. In the older model, long-term hematopoietic stem cells (LT-HSCs) located in the adult bone marrow are pluripotent, can self-replicate, and are the progenitors from which all blood cell lineages arise. They are usually quiescent, but they become activated when exposed to a stress stimulus. Short-term HSCs (ST-HSCs) are derived from LT-HSCs, can rapidly restore the hematopoietic system, and differentiate into multipotent progenitors (MMPs) with no detectible self-renewal ability. MMPs further differentiate into lineage-committed oligopotent progenitors: the common lymphoid progenitor (CLP) that only possesses lymphoid-restricted ability, and the common myeloid progenitor (CMP), which further differentiates into megakaryocyte–erythrocyte progenitor (MEP) and granulocyte–monocyte progenitor (GMP). MEPs give rise to megakaryocytes that mature to platelets, erythroid cells that mature to red blood cells (RBCs), and GMPs that give rise to eosinophils, neutrophils, basophils, and macrophages. CLPs give rise to B lymphocytes, T lymphocytes, and natural killer and dendritic cells.[1]

It is now acknowledged through single-cell transcriptome, epigenetic, and transplantation analysis, along with barcoding and in vitro clonal functional assays, that the process of lineage commitment is not strictly unidirectional, but more plastic and flexible, and lacks boundaries at the different hierarchical levels.[2] In the revised hierarchical roadmap, the MMPs are divided into four subgroups (MMP1, MMP2, MMP3, and MMP4/LMPP). LT-HSCs, intermediate-term HSCS (IT-HSCs), and ST-HSC/MMP1s give rise to MMP2, MMP3, and MMP4/lymphoid-primed multipotent progenitors (LMPPs). MMP2 and MMP3 mainly give rise to CMPs and MMP4/LMPP predominantly generate lymphoid lineages. The CMPs produce mature hematopoietic cells similar to the MEPs and GMPs of the old model, and the

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

CLPs yield mature lymphocytes. Megakaryocyte differentiation can bypass the states of MMPs, CMPs, and MEPs coming directly from the HSCs (Figure 17-1).[1]

Hematopoiesis is continuous, adaptive, and capable of responding to metabolic, infectious, and inflammatory challenges. Perturbations of the system lead to disease. Regulation of hematopoiesis is complex and only partially understood. It entails signaling through external factors such as cytokines and intracellular factors such as transcriptional signaling factors and microRNAs.[3] While LT-HSCs undergo several intermediate steps to produce mature blood cells, megakaryocyte lineage segregation occurs early during differentiation. The primary cytokines governing erythrocyte, platelet, and granulocyte production have been identified and are erythropoietin, thrombopoietin, and granulocyte colony-stimulation factor (G-CSF), respectively. Additional factors positively regulating erythropoiesis include insulin, insulin-like growth factor, activin, and angiotensin II. Factors negatively regulating erythropoiesis include transforming growth factor beta- and alpha-related ligand, growth and differentiation factor 11, inflammatory cytokines such as c-interferon, tumor necrosis factor (TNF) alpha, and tumor necrosis factor-related apoptosis-inducing ligand.[4]

The healthy human produces approximately 10^9 RBCs, 10^8 white blood cells, and 4 billion platelets every hour. Different cell types have different normal lifespans (e.g., 120 days for erythrocytes, 5–10 days for platelets, 6–8 hours for neutrophils, day to years for lymphocytes). Senescent or otherwise damaged erythrocytes are recognized and removed by the reticuloendothelial system. At least half of senescent RBCs are destroyed in the spleen by splenic macrophages and the remaining RBCs are destroyed in the liver, bone marrow, or other sites of the mononuclear phagocyte system. Aging platelets are also sequestered in the spleen and are subject to phagocytosis by macrophages. The death and removal of neutrophils and lymphocytes are less well understood.

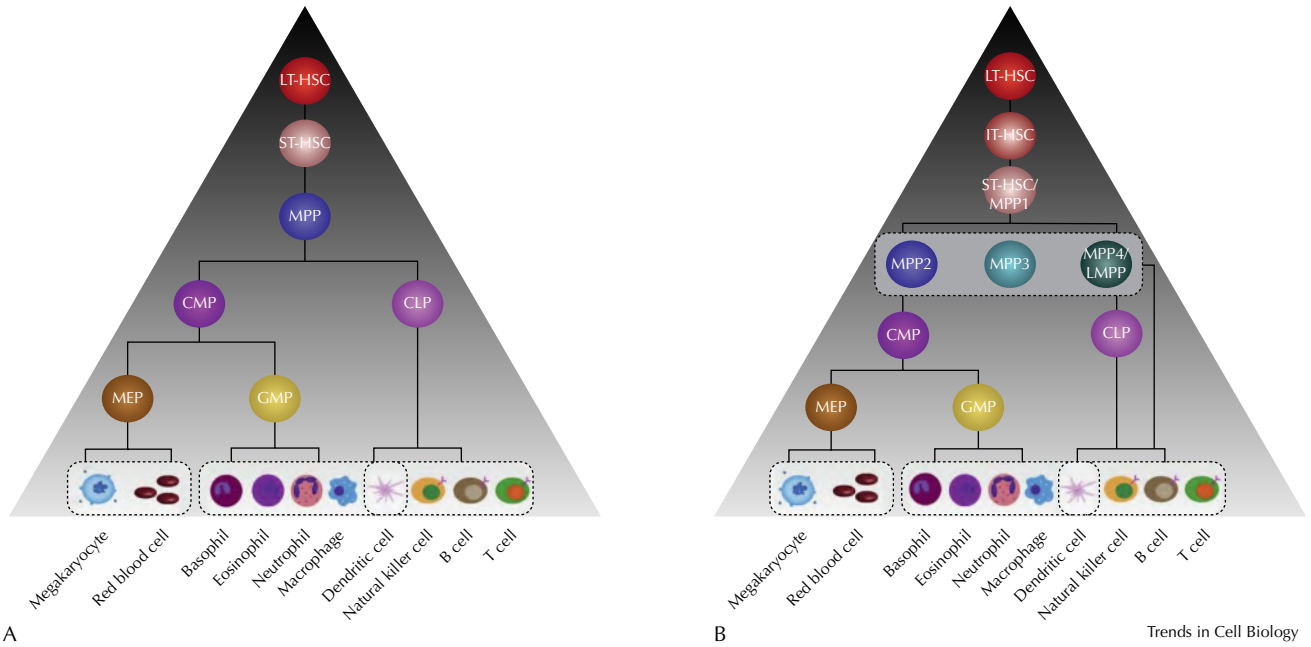

Figure 17-1 Classical and revised roadmap of hematopoietic hierarchy. (a) In the classical hierarchy roadmap, LT-HSCs and ST-HSCs are both multipotent, but sit at different hierarchical levels owing to their distinct self-renewal abilities. The HSCs give rise to the MPPs with an accompanying reduction of self-renewal ability. Next there emerges a myeloid/lymphoid lineage segregation downstream of MPP. CLPs can produce lymphocytes. CMPs diverge into MEPs and GMPs. MEPs yield megakaryocytes and erythrocytes. GMPs generate granulocytes, macrophages, and dendritic cells. (B) In the revised hierarchy roadmap, LT-HSCs, IT-HSCs, and ST-HSCs/MPP1 cells are all multipotent, but differ in their self-renewal ability. In the branching trees, the HSCs differentiate into MPPs, which consist of MPP2, MPP3, and MPP4/LMPP subpopulations. MPP2 and MPP3 cells mainly give rise to CMPs, whereas MPP4/LMPP cells predominantly generate lymphoid lineages. Next, CMPs can produce mature hematopoietic cells via MEP and GMP stages. CLPs can yield mature lymphocytes, which also can derive from MPP4/LMPP cells directly. CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte/macrophage progenitor; IT-HSC, intermediate-term hematopoietic stem cell; LMPP, lymphoid-primed multipotent progenitor; LT-HSC, long-term hematopoietic stem call; MEP, megakaryocyte/erythrocyte progenitor; MPP, multipotent progenitor; ST-HSC, short-term hematopoietic stem cell. *Source:* Zhang Y, Gao S, Xia J, Liu F. Hematopoietic Hierarchy – An Updated Roadmap. *Trends Cell Biol.* 2018;28(12):976–986. doi:10.1016/j.tcb.2018.06.001. © 2018, Elsevier.

RBCs are made up mostly of hemoglobin, a metalloprotein composed of heme (the iron-containing portion that binds oxygen) and globin (amino acid chains that form a protein) groups. Normal hemoglobin types include adult hemoglobin A (HgbA; about 95%–98%) containing two alpha globulin chains and two beta globulin chains; $HgbA_2$ (2%–3%) containing two alpha and two delta chains; and fetal hemoglobin (HgbF, up to 2%). HgbF has two alpha and two gamma chains. HgbF is the primary hemoglobin produced by the fetus during gestation. Its production usually falls to a low level shortly after birth.

Hemoglobinopathies occur when point mutations or deletions in the globin genes cause changes in the amino acids that make up the globin protein, resulting in abnormal forms of hemoglobin. The structure of hemoglobin may be abnormal in its behavior, production rate, and/or stability. Several hundred hemoglobin variants have been documented; however, only a few are common and clinically significant. The majority of these are beta chain variants that are inherited in an autosomal recessive fashion. Since a person inherits one copy of each beta-globin gene from each parent, if one normal beta gene and one abnormal beta gene are inherited, the person is said to be a carrier or heterozygous for the abnormal hemoglobin. The abnormal gene can be passed on to offspring, but does not cause symptoms or disease in the carrier. If two abnormal beta genes of the same type are inherited, the person is considered to have the disease and is homozygous for the abnormal hemoglobin.

The initial laboratory test to assess hematopoietic health is a complete blood count (CBC) with differential (see Table 17-1). When necessary, more specific testing to include a peripheral blood smear, bone marrow biopsy, molecular/cytogenetic analysis, and functional assessments may be ordered to further assess the patient.

RED BLOOD CELL DISORDERS

Erythrocytosis

Erythrocytosis is suspected when elevated hemoglobin (Hb) levels (>185 mg/dL for males, >165 mg/dL for females) or elevated packed RBCs (hematocrit [HCT]; >52% for males, >48% for females) is seen. As Hb and HCT are surrogate indicators of true red cell mass, absolute or true erythrocytosis is confirmed when the red cell mass exceeds 125% of the predicted value for body mass using specialized nuclear medicine tests (e.g., radioisotope RBC studies).[5] Once an absolute erythrocytosis has been confirmed, it is desirable to identify the underlying etiology, which may be classified as either primary or secondary. Apparent erythrocytosis occurs in the presence of elevated venous HCT but RBC mass below 125% of predicted value. Relative erythrocytosis is when the RBC mass is in the normal reference range, but the plasma volume is decreased. This generally occurs with significant dehydration (e.g., from diuretics, persistent diarrhea, excessive use of alcohol, or burns).

Primary erythrocytosis is a condition in which the erythropoietic compartment of the bone marrow leads to increased red cell production. The predominant form of primary erythrocytosis is polycythemia vera (PV), discussed in detail below. Other causes of erythrocytosis include primary familial and congenital polycythemia, a rare primary form of erythrocytosis caused by mutations of the erythropoietin (EPO) receptor gene resulting in increased RBC mass and low EPO levels, tumors such as cerebellar hemangiomas or parathyroid adenomas causing increased EPO secretions, and rare genetic mutations to oxygen-sensing pathways resulting in dysregulation of EPO synthesis.[6]

Secondary erythrocytosis is characterized by increased red cell production in response to something external to the

Table 17-1 Red blood cell indices.

Test Name	Normal Range (SI units)	Increased	Decreased
Red Blood Cell (RBC)	Adult male: 4.5–9.0 x $10^6/\mu$ Adult female: 4.5–5.1 x $10^6/\mu$	Polycythemia; erythrocytosis; fluid loss due to dehydration, diuretics, diarrhea, burns	Anemia
RBC Indices			
Mean corpuscular volume	Adult: 80–93 μm^2	Vitamin B_{12} and folate deficiency	Iron deficiency anemia; thalassemia
Mean corpuscular hemoglobin	27.5–33.2 pg	Hyperchromia	Hypochromic anemia
Mean corpuscular hemoglobin concentration	33.4%–35.5% (concentration fraction 0.334–0.355)	Hyperchromia	Hypochromic anemia
Hemoglobin	Adult male: 13–14.2 g/dL Adult female: 11.6–12.3 g/dL	Same as RBC results	Same as RBC results
Hematocrit	Adult male: 41.5%–50.4% Adult female: 35.9%–44.6%	Same as RBC results	Same as RBC results

bone marrow that causes tissue hypoxia, inappropriately increased erythropoietin production, or increased sensitivity to erythropoietin. Common causes of hypoxia include chronic lung disease, right to left cardiopulmonary vascular shunts, CO_2 poisoning, high-altitude habitat, smoking, and renal artery stenosis. Less common causes include EPO receptor mutations, Chuvash polycythemia (in which a mutation in the *VHL* gene affects the hypoxia-sensing pathway), right to left arteriovenous shunts in the lungs, and proline hydroxylase 2 and hypoxia-inducible factor 2 alpha (*HIF-2α*) mutations. Secondary erythrocytosis may be congenital (high oxygen-affinity Hb, EPO receptor-mediated dysfunction, 2,3-bisphosphogycerate mutase deficiency), or acquired. Acquired erythrocytosis may be due to central EPO-mediated hypoxia driven, local EPO-mediated hypoxia driven (end-stage renal disease [ESRD], renal cysts), or pathologic EPO production (tumors or drugs).[7] The term idiopathic erythrocytosis (IE) is reserved for cases in which all primary and secondary causes of increased red cell mass have been ruled out. As a consequence of increased recognition of primary and secondary causes of erythrocytosis, patients classified as having IE are on the decline.[6]

PV is a myeloproliferative neoplasm, a panmyelopathy with an estimated incidence of 1.9–2.3 cases per 100,000 persons/year and a slight male predominance. It is often caused by more than one genetic event in a single hematopoietic progenitor that results in clonal myeloid of pluripotent stem cell (expansion of red cell production). PV is characterized by an acquired Janus kinase 2 (*JAK2*) V617F mutation. JAK/STAT signaling plays a role in cellular proliferation and cell survival. The *JAK2* V617F mutation accounts for 95%–97% of PV cases, while a similar mutation of *JAK2* in exon 12 accounts for 3% of PV cases. The *JAK2* V617F mutation is associated with dysregulation of tyrosine kinase receptor binding, resulting in increased RBC, platelet, and granulocyte production; mutation of *JAK2* exon 12 results in increased RBCs only.[8] PV shares several features with two other forms of myeloproliferative neoplasia: essential thrombocytosis (ET) and primary myelofibrosis (PMF). Collectively, these three conditions exhibit relatively normal cellular maturation, phenotypic and genotypic mimicry, *JAK2* gene mutations, and a tendency to evolve into each other or develop myelofibrosis. There is growing evidence from studies in patients with sporadic PV as well as familial myeloproliferative neoplasms that the *JAK2* V617F mutation is not the PV-originating somatic mutation, but rather represents a late secondary change occurring in a clone initiated by as yet unidentified genetic change(s).[9]

The diagnostic criteria for PV were updated by the World Health Organization in 2016 and consist of both major and minor criteria. Major criteria are (1) Hb >16.5 g/dL in men, >16.0 g/dL in women, or HCT >49% in men, >48% in women, or increased red cell mass >25% above mean normal predicted value; (2) bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size); (3) presence of *JAK2* V617F or *JAK2* exon 12 mutation. Minor criterion: subnormal serum erythropoietin level. The presence of all three major criteria or the first two major plus the minor criterion is required for the diagnosis (see Table 17-2).[10]

Clinical and Oral Manifestations

PV is usually asymptomatic and often only discovered incidentally. Its clinical course is measured in decades. It can be acquired at any age, but is rarely seen in children and increases exponentially in those aged >60 years.[11] PV should be suspected in patients with elevated hemoglobin or HCT levels, splenomegaly, or portal venous thrombosis. When symptoms occur, they may include pruritis, vertigo, gastrointestinal (GI) pain, headache, paresthesias, burning pain in the feet and hands, fatigue, weakness, visual disturbances, tinnitus, and facial plethora. Pruritis following a bath or shower is often the predominant complaint and has been suggested to be due to mast cell degranulation.[12]

Major complications of PV (e.g., stroke, venous thromboembolism) are attributable to blood hyperviscosity and the qualitative and quantitative platelet alterations observed in the disease. Other complications include ocular migraine, transient ischemic attacks, thrombosis, leukocytosis, hyperuricemia, and splenomegaly. PV is an indolent disease with a lifespan that can exceed 40 years.[11]

PV can manifest intraorally with erythema (red-purple color) of mucosa, glossitis, and erythematous, edematous gingiva.[13] Spontaneous gingival bleeding can occur because the principal sites for hemorrhage, although rare, are reported to be the skin, mucous membranes, and gastrointestinal tract.

Treatment

Contemporary PV therapy is focused on reducing vascular risks and tailored to the thrombotic risk stratification of the

Table 17-2 Polycythemia vera diagnostic criteria.

Major Criteria	Minor Criterion
Hb >16.5 g/dL in men >16.0 g/dL in women	Subnormal serum erythropoietin level
Bone marrow biopsy: panmyelosis, prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes	
JAK2 V617F or *JAK2* exon 12 mutation	

patient. Low-risk PV patients or intermediate-risk PV patients with a high HCT level are treated with phlebotomies to reduce the HCT (<0.45% for males and <42% for females) plus low-dose aspirin, if no contraindications are present. Poorly compliant patients or those who manifest progressive myeloproliferation warrant myelosuppressive therapy. Hydroxyurea is the primary drug of choice, with anagrelide or peginterferon-alpha as alternatives. All of these agents have potential side effects. Hydroxyurea is a ribonucleotide reductase inhibitor and an effective agent in managing PV and is the drug of choice. It is important to remember that there is risk for leukemic transformation, so it is usually not recommended in young patients. Current nonmyelotoxic therapy is ruxolitinib, which targets *JAK2* kinase.[11] Busulfan has been shown to induce durable hematologic response in patients unable to tolerate hydroxyurea.[14] Radioactive phosphorus (^{32}P) has been used in the past, with a success rate of 80%–90%; however, its association with an increased incidence of acute leukemic transformation severely restricts its usefulness to patients >75 years of age.

Oral Health Considerations

There are no established guidelines addressing the delivery of dental care for the PV patient. The delivery of routine dental care for the well-controlled PV patient likely incurs minimal risk. Low-dose aspirin is rarely associated with hemorrhagic complications from dental extractions. Poorly controlled patients are at an increased risk for both thrombotic and hemorrhagic complications due to blood hyperviscosity and concurrent qualitative and quantitative platelet alterations.[15,16] It is important to know that inappropriately high HCT can lead to spuriously high prothrombin time values.[11]

Anemia

Anemia is defined as a reduction in the quantity of the oxygen-carrying pigment (Hb) in the blood. The normal range for hemoglobin is 13–14.2 g/dL for men and 11.6–12.3 g/dL for women.[17] Data from large population studies suggest that hemoglobin levels for African Americans tend to be 0.8–0.7 g/dL lower, perhaps owing to the high frequency of alpha-thalassemia in this population. Another important factor is the trend of hemoglobin. For example, a patient with previous hemoglobin values at the higher end of the normal range, who presents with a hemoglobin concentration at the lower end of the normal range, can now be considered anemic.[17]

The signs and symptoms of anemia occur as a consequence of the hypoxia and compensatory physiologic responses. Typical symptoms include fatigue and dizziness. The classic sign of anemia is pallor, which may be observed in the conjunctivae, face, nail beds, tongue, and palmar creases. Analysis of National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2012 shows that 5.6% (95% confidence interval [CI]: 5.1–6.1%) of the US population had anemia.[18] In the elderly, anemia is associated with decreased physical performance of daily activities, cognitive impairment, depression, diminished quality of life, greater hospital admissions, and impaired survival.[19]

The initial laboratory tests used to assess suspected anemia are the CBC and the blood smear. The blood smear is used to morphologically characterize the red cells (e.g., macrocytic, normocytic, microcytic, normocytic, hypocytic). Once discovered, it is essential to determine the underlying cause of the anemia. There are several broad causes of anemias, which can be due to impaired production of the RBC (EPO deficiencies, hypoproliferation, impaired maturation of the RBC, impaired heme or globin production), accelerated destruction, consumption or loss of RBCs due to morphologic changes (sickle cell, cell membrane defects, enzymopathies), reduced protein stability, and factors extrinsic to the RBC.

Anemias Due to Impaired Production

Erythropoietin Deficiency

EPO is a hormone secreted by the liver in fetal development and then primarily by peritubular fibroblasts in the renal cortex of the kidneys in response to hypoxia or low O_2 tension (hemorrhage, hemolysis, etc.). It circulates in the plasma and binds to receptors on erythroid progenitor cells in the bone marrow to promote proliferation and differentiation of erythroid precursors to increase RBC production in a dose-dependent manner. EPO mRNA is also detectable in liver, spleen, bone marrow, lung, and the brain, where it may play a paracrine role. Renal function impairment (i.e., chronic kidney disease) leads to insufficient EPO production in the kidney, either from direct damage to the EPO-producing cells of the kidney or from suppression of EPO production by inflammatory cytokines in a patient with inflammatory disorders such as rheumatoid arthritis, cancer, or acquired immunodeficiency syndrome (AIDS).[20]

Impaired Hemoglobin Production

Hb, the protein in the RBC responsible for transporting oxygen, is made up of four subgroups, each containing a heme group with an iron atom. If there is no iron within the heme group (due to insufficient iron or inefficient delivery of iron), a defect in the synthesis of the heme group and resulting ability to bind, or lack of globin production (thalassemia), the RBC is smaller than normal. The term for this is microcytic anemia. To understand microcytic anemias, it is crucial to understand iron metabolism and homeostasis. The lifespan of a normal RBC is

~120 days, when senescent erythrocytes are removed from circulation by macrophages of the spleen. Most of the iron contained in the Hb is stored in macrophages or transported to the blood plasma bound to transferrin back to the myeloid tissue and used in the production of Hb for the new RBC. Hepcidin is a regulatory hormone produced by hepatocytes and functions to decrease plasma stores of iron. It does this by acting on enterocytes of the small intestine to inhibit the iron-exporting activity of ferroportin, thereby promoting cellular storage of iron and lowering plasma iron concentration. Plasma iron levels are maintained at a range of 10–30 μM and whole-body stores of 0.3–1 g. The following section describes microcytic anemias.

Iron Deficiency Anemia

Iron deficiency anemia (IDA) is the most common type of anemia worldwide. It is defined as a reduction in total body iron to an extent that iron stores are fully exhausted, and some degree of tissue iron deficiency is present in the presence of anemia. Iron deficiency affects approximately 40% of preschool children, 30% of menstruating females, and 38% of pregnant women. The most common cause of iron deficiency in children is malnutrition; in adult males, postmenopausal women, and the elderly, the cause is bleeding (cancers, GI bleed); and in women of childbearing age, menstruation, pregnancy, and, minimally, lactation. First, menstrual iron loss exceeds dietary intake. Second, dietary intake is insufficient to meet the demands of fetal development in the gravid or lactating female. Pathologic causes of IDA are more commonly observed in older adults and include gastritis, peptic ulcer disease, ulcerative colitis, GI carcinoma, achlorhydria, and celiac disease.

Iron resistance are disorders of the GI tract such as partial or total gastrectomy, *Helicobacter pylori* infection, celiac disease, and gluten sensitivity, another common cause of IDA. IDA affects up to 45% of people, particularly women, who have undergone gastric bypass, as the procedure removes active iron absorption from the gut and caloric intake is severely restricted.[21]

Plummer–Vinson syndrome, also called Paterson–Kelly syndrome, is rare and characterized by the classic triad of dysphagia, IDA, and upper esophageal webs or strictures.[22,23] It usually affects middle-aged white women in the fourth to seventh decades of life, but has also been described in children and adolescents. The dysphagia may be intermittent or progressive over the years, is usually painless and limited to solids, and may be associated with weight loss. Symptoms resulting from anemia (weakness, pallor, fatigue, tachycardia) dominate the clinical picture. Other potential findings include glossitis, glossopyrosis, glossodynia, angular cheilitis, koilonychia, fragility, thinning of nails, and brittle hair. Radiologic examination of the pharynx shows the presence of webs.[24] The etiopathogenesis is unknown, but it is postulated that iron deficiency adversely affects iron-dependent enzymes in the epithelium of the upper GI tract, increasing free radical stress, DNA damage, and malignant transformation.[22]

Iron deficiency anemias can often be treated effectively with iron supplementation. In cases of significant obstruction of the esophageal lumen by esophageal webs/strictures with persistent dysphagia in Plummer–Vinson anemia, rupture and mechanical dilation of the web may be required. Since Plummer–Vinson syndrome is associated with an increased risk of squamous cell carcinoma of the pharynx and the esophagus, these patients are monitored closely.[22]

Anemia of Inflammation/Chronic Disease

Anemia of inflammation (AI), also known as anemia of chronic disease (ACD), is the second most prevalent anemia and the most common type of anemia seen in hospitalized or chronically ill patients. It affects up to 77% of the elderly. The most common associated diseases include infections, cancer, autoimmune diseases, chronic kidney disease, and rejection after solid organ transplant.[25]

The body needs 20 mg of iron per day. Only 1–2 mg is absorbed from the intestine; the rest is obtained from recycling senescent RBCs or iron stores in hepatocytes and macrophages, as it is not excreted from the body. One of the main processes that are associated with anemias of inflammation are those that affect iron metabolism via hepcidin. Hepcidin is the main iron-regulatory hormone responsible for controlling the actions of ferroportin, a major iron export protein located on cell surfaces (enterocytes, macrophages, and hepatocytes) that release iron into the plasma. Hepcidin directly binds to ferroportin to decrease its functional activity. During iron overload, hepcidin synthesis increases and functions to shut down iron absorption by enterocytes, decrease recycling by macrophages, and increase storage into the hepatocytes.

Inflammation (acute, chronic, autoimmune conditions, and malignancy) acts as a potent stimulus for hepcidin production through JAK-STAT signaling through proinflammatory cytokines (interleukin (IL)-6, IL-1, TNF-alpha). Increased hepcidin results in increased stored iron into marrow, splenic, and hepatic macrophages and lowered serum iron levels, but not a true iron deficiency and otherwise known as a disorder of iron distribution. Increased cytokines produced in systemic inflammation also push hematopoiesis more toward myeloid production instead of erythroid production and activate erythrophagocytosis by macrophages, shortening the lifespan of erythrocytes by approximately 25%.[26] IL-6 is one of the most important cytokines involved in AI/ACD. It does this by inhibiting TNF-alpha and inducing transcription of ferritin, which increases retention of iron and storage within

reticuloendothelial cells, and inhibits erythropoiesis and hemoglobin synthesis.[25–28]

Sideroblastic Anemia

Sideroblastic anemias are inherited or acquired bone marrow disorders. Heme is assembled from iron and protoporphyrin IX in mitochondria by ferrochelatase. Iron within the mitochondria is also required to generate iron–sulfur clusters that regulate cellular iron uptake, heme synthesis, and iron storage. In sideroblastic anemia, there is pathologic iron accumulation in the mitochondria of erythroid precursors, which appear as coarse granules occurring in a perinuclear distribution that stains with Prussian blue. Iron metabolism is altered, leading to ineffective erythropoiesis to generate a systemic iron overload state that suppresses hepcidin to increase intestinal absorption of iron. Treatment consists of repeated transfusions for severe anemia, which adds to iron burden and then iron depletion preformed via phlebotomy or iron chelation. Pharmacotherapeutics include deferoxamine (Desferal), deferasirox (Exjade), and deferiprone (Ferriprox).[29,30]

Diagnosis

It is often difficult to serologically differentiate between IDA and ACD. IDA has three stages: the first stage exhibits iron depletion with decreased iron stores without decrease in serum iron levels or Hb concentration and low serum ferritin; the second phase exhibits abnormal iron serologies (reduced transferrin saturation, increased total iron-binding capacity, and increased zinc protoporphyrin); and in the third phase there is Hb concentration of less than the lower limit of the normal range.[17]

ACD presents as a normocytic/normochromic anemia that changes with time to become hypochromic and microcytic. Less than 25% of cases will present as microcytic hypochromic anemia. There is decreased serum iron, total iron-binding capacity, and transferrin saturation and an increase in serum ferritin and bone marrow iron stores. Table 17-3 shows the differences between ACD and IDA.[26] To complicate matters, the two conditions can coexist.

Diagnosis of ACD is made in the presence of systemic inflammation, iron restriction not caused by systemic iron deficiency (low serum iron, low transferrin saturation, and low ferritin), and symptoms such as fatigue, exercise intolerance, and dyspnea. Indeed, a patient with an inflammatory condition such as inflammatory bowel disease (IBD) may manifest both IDA and ACD. However, patients with ACD have normal transferrin receptor levels and high hepcidin levels, while patients with IDA have high transferrin receptor levels and normal or low hepcidin levels. Iron stores are usually adequate, but there is impaired iron delivery and EPO production is usually suppressed. When the diagnosis remains ambiguous, further testing including a bone marrow biopsy may be necessary.[17]

Sideroblastic anemias can be congenital or acquired. The distinction between the two may not be apparent until adulthood. The clinical laboratory findings include microcytosis, hypochromia, increased red cell distribution width, and absence of evidence for common causes of microcytic anemia such as iron deficiency and thalassemia. Definitive diagnosis is based on showing a genetic defect by mutational analysis.

Clinical and Oral Manifestations

The most important clinical symptom of anemia is chronic fatigue. Outward signs may be subtle and may include pallor of the conjunctivae, lips, and oral mucosa; brittle nails with spooning, cracking, and splitting of nail beds; and palmar creases. This has traditionally been used by physicians in the diagnosis of anemia. Among 50 prospectively examined patients, a statistically significant correlation was noted

Table 17-3 Differences in laboratory measures in iron deficiency anemia and anemia of inflammation.

Laboratory Measure	Iron Deficiency Anemia	Anemia of Inflammation
MCV	Low	Normal
MCH	Low	Normal
Reticulocyte hemoglobin	Low	Normal
% Hypochromic erythrocytes	High	Low
Serum transferrin	High	Low
Serum transferrin receptor	High	Normal
Serum ferritin	Low	High
Serum hepcidin	Low	High

MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume.
Source: Ganz T. Anemia of inflammation. Longo DL, ed. *N Engl J Med*. 2019;381(12):1148–1157. doi:10.1056/NEJMra1804281. © 2019, Massachusetts Medical Society.

between hemoglobin concentration and the following: color tint of the lower eyelid conjunctiva, nail-bed rubor, nail-bed blanching, and palmar crease rubor.[31] Other findings may include palpitations, shortness of breath, numbness and tingling in fingers and toes, and bone pain.

Glossitis and stomatitis are recognized oral manifestations of anemia. In a study of 12 patients, oral signs and symptoms of anemia included angular cheilitis (58%), glossitis with different degrees of atrophy of fungiform and filiform papillae (42%), pale oral mucosa (33%), oral candidiasis (25%), recurrent aphthous stomatitis (8%), erythematous mucositis (8%), and burning mouth (8%) for several months to 1 year's duration.[32] IDA or ACI should be suspected in every case of glossitis, glossodynia, angular cheilitis, erythematous mucositis, oral candidiasis, recurrent oral ulcers, and burning mouth when no other obvious causes are identified.[33–35] These findings are believed to be caused by impaired cellular immunity, deficient bactericidal activity of polymorphonuclear leukocytes, inadequate antibody response, and epithelial abnormalities attributed to lack of iron.[36] Clinically evident atrophic changes of the tongue, giving a smooth red tongue appearance, in patients with IDA have been associated with a significant reduction in the mean epithelial thickness of the buccal mucosa as determined histologically.[37]

Treatment

Treatment is usually focused on treating the underlying disease (infection, autoimmune disorder, cancer), but most AI disorders and malignancies are chronic conditions. Otherwise, the goal is to improve the oxygen-carrying capacity of blood. This is achieved through iron supplementation, blood transfusions, erythropoiesis-stimulating agents, and downregulating the production of TNF-alpha and IL-6. Novel agents include hepcidin antagonists (monoclonal antibodies, siRNA, antisense oligonucleotides, hepcidin-binding proteins, and aptamers) are in development. Vitamin D deficiency has also been associated with increased prevalence of ACD, so vitamin D supplementation is also a consideration.[27,28]

For IDA, oral iron supplementation is safe, cost-effective, and convenient. The goal is to increase serum hemoglobin by 1–2 g/dL every 2 weeks, and ultimately restore iron stores in in about 3–4 months. Ferrous sulfate and ferrous gluconate have good bioavailability and contain 20% and 12% of elemental iron for absorption, respectively.[38] The recommended dose for both is 325 mg three times per day. Foods and medications that inhibit iron absorption include tea, coffee, phosphate-containing carbonated beverages, antacids, proton pump inhibitors, and H_2-blockers. Adverse effects of oral iron therapy are dose related, can adversely affect compliance, and include nausea, epigastric discomfort, and constipation. For such cases a lower dosage regimen should be attempted.

When oral iron supplementation is ineffective due to poor patient compliance or intolerance, intravenous iron therapy is indicated. Other possible indications for intravenous iron therapy are high iron requirements due to chronic uncorrectable bleeding or chronic hemodialysis; iron malabsorption secondary to a GI condition; IBD with ineffective erythropoiesis, poor iron absorption, and intolerance to oral iron supplementation; and the need for rapid restitution of iron stores (e.g., preoperative).[39] Intravenous iron products are made up of nanoparticles of iron oxyhydroxide gel in colloidal suspension, held within a stabilizing carbohydrate shell.[38] Available products include high molecular weight iron dextran, low molecular weight iron dextran, iron sucrose, ferric gluconate, and ferumoxytol. Serious and potentially life-threatening hypersensitivity reactions may occur, with the highest risk associated with high molecular weight preparations.

Thalassemia

Thalassemias are a group of inherited disorders of hemoglobin synthesis leading to reduced-production of globin chains. Gene clusters on chromosomes 16 and 11 code for alpha- and beta-like globins, respectively. Hemoglobin A, the major hemoglobin component of adult RBCs, is made up of two alpha and two beta chains (Hb A $\alpha_2\ \beta_2$). Defects can occur in either the alpha or beta-hemoglobin chain and these defects yield difficulties in transportation of oxygen. There are over 100 genetic forms of alpha-thalassemias, with phenotypes ranging from asymptomatic to lethal. Clinically relevant forms of alpha-thalassemia usually involve α^0-thalassemia, either coinherited with α^+-thalassemia and resulting in hemoglobin H (HbH) disease, or inherited from both parents and resulting in hemoglobin Bart's hydrops fetalis, which is lethal in utero or soon after birth.[40] Deletion of or mutations in three alpha-chain genes lead to HbH disease, which presents with more prominent anemia.[41] Worldwide, an estimated 5% of the population carry an alpha-thalassemia variant trait.[40] In the United States, the incidence of alpha-thalassemia is 1 in 1,000,000 and the incidence of beta-thalassemia is 1 in 100,000.[42] Historically, alpha-thalassemia is thought to be highly protective against severe malaria, therefore more prevalent in persons of African and Southeast Asian descent, and beta-thalassemia is most common in persons of Mediterranean, African, and Southeast Asian descent. However, human migration greatly blurred these distinctions.[43]

In beta-thalassemia, insufficient beta-globin synthesis results in excess alpha-hemoglobin production. There have been over 200 mutations in the beta-globin gene that cause

disease. Beta-thalassemia has been categorized as minor, major, and intermedia based on alpha-globin or beta-globin chain imbalance, clinical signs, and the severity of anemia. Beta-thalassemia minor trait or carrier manifests as microcytic anemia and is clinically asymptomatic. Beta-thalassemia major presents with severe anemia in infants and is transfusion dependent. Both beta-thalassemia major and beta-thalassemia intermedia result from homozygous or compound heterozygous inheritance of a mutated beta-globin gene. Beta-thalassemia intermedia can also result from increased production of alpha-globin gains.[44]

Clinical and Oral Manifestations

Clinical signs and symptoms of thalassemia are dependent on the severity of the disease and range from none to life-threatening. With regard to alpha-thalassemia, Bart's hydrops fetalis is lethal in utero or shortly after birth due to severe hypoxia. If transfusions are administered intrauterine and after delivery, life expectancy can be extended to 5 years. HbH presents with variable phenotypes with varying severities, ranging from moderate anemia and splenomegaly to a more severe course with episodes of intercurrent infection, severe anemia, and need for transfusions. Other manifestations include jaundice, growth retardation in children, infections, leg ulcers, gall stones, folic acid deficiency, and drug-induced hemolysis.

Patients with beta-thalassemia trait are usually asymptomatic, but may have mild anemia. Patients with beta-thalassemia major develop signs and symptoms as infants, including failure to thrive, pallor, weakness, jaundice, protruding abdomen with enlarged spleen and liver, dark urine, abnormal facial bones, and growth retardation. Compensatory hypertrophy of erythroid marrow with extramedullary erythropoiesis may lead to deformities of the long bones and typical craniofacial changes (see below). Beta-thalassemia intermedia patients manifest variable signs and symptoms of anemia that are milder and occur later in life; however, they are prone to experiencing thrombotic events, especially if splenectomized. Such events include deep vein thrombosis, stroke, portal vein thrombosis, and pulmonary embolism.

Significant oral manifestations related to thalassemia appear to occur more frequently in the beta-thalassemia group and are reflective of the underlying extramedullary erythropoiesis observed in the more severe phenotypes.[45] Characteristic craniofacial deformities include a class II skeletal base relationship with a short mandible, reduced posterior facial height, increased anterior facial proportions, and "chipmunk facies."[46] Other reported potential findings include spike-shaped and short roots, taurodontism, attenuated lamina dura, enlarged bone marrow spaces, small maxillary sinuses, absence of inferior alveolar canal, retained primary teeth, and thin cortex of the mandible.[47] Dental arch morphologic changes include a narrower maxilla, high arched palate, and smaller incisor widths for the maxillary and mandibular arches.[48,49] Consistent with general growth retardation, the dental development of 31 of 39 patients with Cooley's anemia was delayed by a mean of 1.11 years and 0.81 years for boy and girls, respectively.[49]

Individuals with thalassemia appear to experience similar rates of gingivitis and periodontitis to healthy controls.[50,51] An increased caries risk has been reported, which may be attributable to such factors as disease-induced immunologic dysfunction, decreased access to care, and insufficient patient oral hygiene.[50,52] While the parotid salivary flow rates in Cooley's anemia are similar to controls, quantitative changes consisting of reduced levels of phosphorus, immunoglobulin (Ig) A, and urea have been reported.[53,54] Increased oral cavity levels of *Streptococcus mutans* and *Candida* have also been reported.[53,55]

Diagnosis

Thalassemia is diagnosed using a battery of laboratory tests, including a CBC, qualitative and quantitative hemoglobin analysis, and DNA testing. Screening programs are considered for populations where thalassemias are most prevalent.[40] People with thalassemia have microcytic anemia, lowered hemoglobin, and defects in alpha or beta chains of hemoglobin. The clinical signs and symptoms of severe thalassemia usually become apparent within the first 2 years of life.

Treatment

The prognosis for thalassemia patients has improved dramatically over the past decades, but medical management remains complex and multidisciplined. Appropriate genetic counseling and screening should be afforded all patients with thalassemia trait.[40] Patients with alpha- or beta-thalassemia trait generally require no special medical management.

Mild HbH patients may require intermittent transfusion therapy, mainly during intercurrent illness. More severely affected HbH patients may require chronic transfusions, iron chelation therapy, and eventual splenectomy. Management strategies for patients with beta-thalassemia (Cooley's anemia) usually entail periodic lifelong blood transfusions to maintain the hemoglobin level above 90–105 g/L, to prevent growth impairment, organ damage, and bone deformities. Transfusions are given sporadically to patients under acute stress as well. The need for transfusions to manage beta-thalassemia patients is more episodic and dictated by the severity and potential progression of the disease. Splenectomies are traditionally performed as an alternative or adjunct to transfusion.[44]

Regularly transfused patients require iron chelation to resolve the inevitable iron accumulation that leads to dysfunction, primarily involving the heart, liver, and endocrine system. In the United States, there are three Food and Drug Administration (FDA)-approved iron chelators: deferoxamine (Desferal), deferasirox (Exjade), deferiprone (L1) and Ferriprox-L1 (Ferriprox). The most commonly used agent is the oral dispersible agent deferasirox, likely due to its good oral bioavailability and convenient once-a-day dosing. Common side effects include dose-related GI symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain) and mild skin rash. The most serious side effects with deferasirox are potential kidney damage and renal tubular acidosis.[44]

Hemopoietic stem cell transplantation is the only curative treatment for thalassemia. Disease-free survival exceeds 80% with human leukocyte antigen (HLA)-matched sibling donors. Cord blood transplantation may be successful, but there is a 5%–10% mortality from transplant conditioning, graft-versus-host disease, and graft failure. Clinical guidelines are available.[44,56] Future therapeutic strategies involving normal gene transfer via suitable vectors, molecular targeting (i.e., BCL11A) using CRISPR/Cas9, ligand traps (sotatercept and luspatercept) for stimulation of late-stage erythropoiesis, *JAK2* inhibition (in patients who develop myeloproliferative disorders), and agents to stimulate hepcidin production are being investigated.[44]

Infections are major complications and constitute the second most common cause of mortality and a main cause of morbidity in patients with thalassemia. Predisposing factors for infections in thalassemic patients include severe anemia, iron overload, splenectomy, and a range of immune abnormalities.

Oral Health Considerations

There are no contraindications for providing routine dental care for thalassemia patients under proper medical management. Splenectomized patients are more susceptible to developing postsplenectomy sepsis from encapsulated bacteria (e.g., *Streptococcus Pneumoniae, Haemophilus Influenzae*, and *Neisseria Meningitidis*). Prevention of postsplenectomy sepsis includes immunization against the abovementioned bacteria, and early antibiotic treatment for fever and malaise. Additionally, patients with beta-thalassemia intermedia may be on an antithrombotic agent, so one should caution about prolonged bleeding.[57]

Impaired Maturation (Macrocytosis)

The term macrocytosis refers to a blood condition in which RBCs are larger than normal and is reported in terms of mean corpuscular volume (MCV). MCV, the average volume of RBCs, is calculated as HCT × 1,000 divided by RBC (millions/μL). Normal MCV values range from 80 to 100 femtoliters (fL), depending on gender, age, and reference laboratory. Macrocytosis is identified by reviewing peripheral blood smears and/or by automated RBC indices, and is diagnosed when MCV is >100 fL. It is a relatively common finding with a reported incidence ranging from 2% to 4% and about 60% of those who have anemia. Potential causes include alcoholism and B_{12} or folate deficiency. Medications that interfere with DNA synthesis, such as methotrexate, trimethoprim-sulfamethoxazole, nucleic acid analogs (5-fluorouracil, zidovudine), and others (hydroxyurea, pentamidine, phenytoin, pyrimethamine, sulfasalazine, triamterene), may result in macrocytosis. Measures to address the underlying cause often result in normalization of the MCV. Other causes of macrocytosis are variants of associated conditions such as Down syndrome and pregnancy.[58]

B_{12} and Folate Deficiency Anemia

Vitamin B_{12} and folate are cofactors necessary for the enzyme methionine synthase used in the conversion of homocysteine to methionine. As a byproduct of this reaction, methyl-tetrahydrofuran (THF) is converted to THF, which is converted to intermediates used in the synthesis of pyrimidine bases of DNA. In B_{12} deficiency, homocysteine cannot be converted to methionine, and thus methyl-THF cannot be converted to THF and pyrimidine bases cannot be formed, slowing down DNA synthesis and affecting rapidly proliferating cell lines, resulting in a megaloblastic anemia, among other problems.[59] From a hematologic perspective, lack of either B_{12} or folate results in an essentially identical megaloblastic anemia.

B_{12} deficiencies or pernicious anemia can be due to insufficient B_{12} absorption associated with an autoimmune-related atrophy of the gastric mucosa, which reduces the number of parietal cells that produce intrinsic factor (IF). IF is a protein produced by the parietal cells of the fundic mucosa of the stomach that binds B_{12} to allow it to be absorbed through the GI tract. Decreases in IF may be due to gastric disease or surgery (complete or partial gastrectomy or gastric reduction), intake of drugs that affect gastric acid secretion resulting in increased stomach pH and inability for B_{12} to be released from the food matrix, and/or reduced B_{12} consumption (vegetarian/vegan diet, chronic alcoholism). More than 90% of patients with pernicious anemia have serum antibodies against gastric parietal cells and about 50% have antibodies against intrinsic factor.[60] The predominant causes of folate deficiency involve scenarios of inadequate intake, such as malnutrition and alcoholism. The increased physiologic folate and B_{12} requirement associated with pregnancy or lactation and conditions of chronic hemolysis

or hemorrhage may lead to an anemic state. Secretion of intrinsic factor decreases as the stomach acid pH becomes more alkaline, therefore long-term use of proton pump inhibitors may result in pernicious anemia. Vitamin B_{12} deficiency prevalence varies by age range (3% ages 20–39, 4% ages 40–59, 6% ≥60 years), with marginal depletion occurring frequently (>20%) among those 60 years or older.[61]

Clinical and Oral Manifestations

Fatigue, decreased mental concentration, glossitis, and weakness are characteristic of folate or B_{12} deficiency. B_{12} deficiency may present as neurologic symptoms such as clumsiness, unsteady gait, and paresthesia. Prolonged severe B_{12} deficiency, as may be seen in pernicious anemia, may lead to demyelination of the dorsal columns of the spinal cord, resulting in more advanced signs and symptoms such as peripheral neuropathy and ataxia. Severe deficiency shows evidence of bone marrow suppression.[62] Unfortunately, these advanced signs and symptoms are often not reversed with replacement therapy.

Oral signs of folate and B_{12} deficiency are similar to those observed with IDA or ACI and include a beefy red tongue with smooth or patchy areas of erythema. Symptoms include soreness or a burning sensation affecting the tongue, lips, buccal mucosa, and other mucosal sites. Paresthesia and taste alterations have been reported.[63]

Diagnosis

The diagnostic process begins by establishing the presence of vitamin B_{12} (cobalamin) or folate deficiency in the presence of clinical signs. The primary laboratory investigations include total B_{12}, holotranscobalamin, metabolites, methylmalonic acid (MMA), and homocysteine.[64] Serum cobalamin and folate levels are assessed in tandem. To determine differences between pernicious anemia and other causes of low cobalamin, anti-IF antibody assay is the preferred test. Newer assays measure holotranscobalamin II (the proportion of transcobalamin II conjugated to vitamin B_{12}). If tested after oral administration of cobalamin, it can be used to assess intestinal uptake and diagnose vitamin B_{12} malabsorption.[62]

Use of the Schilling test (which measures cyanocobalamin absorption by increasing urine radioactivity after an oral dose of radioactive cyanocobalamin) for detection of pernicious anemia has been supplanted for the most part by serologic testing for parietal cell and intrinsic factor antibodies.[65]

Treatment

Treatment strategies for folate or B_{12} deficiency are dictated by the underlying cause and B_{12} repletion. Protocols entail parenteral B_{12} administration of 1000 μg cyano-B_{12} or hydroxy-B_{12} intramuscular injections daily or every other day, followed by weekly injections for up to 8 weeks, then every 3–4 weeks. Oral administration (high-dose cyano-B_{12} 2000 μg oral tablets daily until remission, then 1000–2000 μg daily) is an effective alternative to injections to manage deficiency. Even when intrinsic factor is not present to aid in the absorption of vitamin B_{12}, as in pernicious anemia or in other diseases that affect the usual absorption sites in the terminal ileum, oral therapy is still effective. However, prescribed folate supplementation may still be necessary in scenarios of alcoholism and malnutrition.

Accelerated Destruction, Consumption, or Loss

The normal RBC lifespan is 110–120 days in the circulation. Hemolytic diseases result in anemia, if the bone marrow is not able to replenish adequately, the prematurely destroyed RBCs. The hemolytic anemias are classified as either inherited or acquired. Inherited forms include sickle cell disease (SCD), thalassemias (described above), hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phasphate dehydrogenase (G6PD) deficiency, and pyruvate kinase deficiency. Acquired forms of hemolytic anemias are immune hemolytic anemia, mechanical hemolytic anemias, paroxysmal nocturnal hemoglobinuria (PNH), and exposure to certain infections, toxins, or snake venom.

With acute hemolytic disease, the signs and symptoms depend on the mechanism that leads to red cell destruction. The release of free hemoglobin occurring in intravascular hemolysis may present as acute flank pain, free hemoglobin in the plasma and urine, and renal failure. In patients with chronic or progressive anemias, symptoms depend on the patient's age and adequacy of blood supply to critical organs. With moderate anemia, symptoms may include fatigue, loss of stamina, breathlessness, tachycardia, and, less commonly, jaundice and hemoglobinuria. Physical findings include jaundice of skin and mucosae, splenomegaly, and other findings associated with specific hemolytic anemias.

A careful history and physical examination provide important clues to the diagnosis of hemolytic anemias. Once a patient presents with clinical signs and symptoms of anemia, laboratory testing should be supported by a complete drug and toxin exposure history and family history. Laboratory tests in the anemic patient may be used initially to demonstrate the presence of hemolysis and define its cause. An elevated reticulocyte count is the most useful indicator of hemolysis, reflecting erythroid hyperplasia of the bone marrow. Assessment of RBC morphology, findings on the peripheral blood smear, and, rarely, bone marrow biopsy may provide additional clues to support the specific diagnosis.

Sickle Cell Disease

SCD, formerly known as sickle cell anemia (SCA), is an umbrella term that defines a group of inherited diseases (including SCA, HbSC- and HbS-beta-thalassemia) characterized by mutations in the gene encoding hemoglobin subunit beta, resulting in a glutamic acid-to-valine substitution in the sixth position on the beta-hemoglobin chain. The resulting mutant protein generated from the sickle beta-globin subunit is sickle Hb (HbS). When the Hb is not bound to oxygen, HbS can polymerize and cause the erythrocytes to assume a crescent or sickled shape.[66] The sickled erythrocytes form distorted rigid sickle cells, which lose their ability to effectively transport oxygen to the microcirculation and are prone to hemolysis. The sickled cells also cause recurrent vaso-occlusive episodes, leading to end-organ ischemia and necrosis affecting nearly every organ in the body.

SCD is an inherited autosomal codominant trait. It affects an estimated 100,000 people in the United States and the global annual incidence of SCD exceeds 300,000.[67] About 100,000 individuals in the United States have the disease and most are African American. Globally, there are over 300 million carriers of SCD. The life expectancy of adults with SCD in high-income and middle-income countries yields a median survival of 67 years. In lower-income regions, life expectancy is reduced by about 30 years and patients have a poor quality of life. Treatments remain costly, limiting access to care to those of higher socioeconomic standing.

While vaso-occlusive events clinically characterize SCD, the etiopathogenesis of SCD is far more complex and involves ongoing hemolysis; increased RBC dehydration and adherence to endothelium; vascular instability due to nitric oxide deficiency; inflammation, hypercoagulability, increased neutrophil adhesiveness, and platelet activation. Patients with SCD may have other hemoglobin genotypes including compound heterozygosity for the HbS gene and other Hb variants such as HbC, HbE, and HbD or variants of HbS-beta-thalassemia.[67] Fetal hemoglobin (HbF) is excluded from the HbS polymer. It usually peaks by mid-gestation and drops to about 1% by the age of 6 months. In SCD, it is maintained in adults at higher levels.

Endothelial activation, induced directly or indirectly by the proinflammatory behavior of sickle erythrocytes, is the most likely initiating step toward vaso-occlusion. Stressors that can lead to vaso-occlusion typically include viral and bacterial infection, hypoxia, dehydration, iron overload, and cell and fluid phase–related causes. Microvascular occlusion arises predominantly in localized areas of marrow, leading to necrosis. Inflammatory mediators activate nociceptive afferent nerve fibers, evoking the pain response. Commonly affected areas are the long bones, ribs, sternum, spine, and pelvis, often with multiple-site involvement.

Clinical and Oral Manifestations

Nearly every organ is affected in SCD.[67] Damaged erythrocytes cause vaso-occlusion, which lead to acute complications including vascular–endothelial dysfunction, functional nitric oxide deficiency, inflammation, oxidative stress and reperfusion injury, hypercoagulability, increased neutrophil adhesiveness, and platelet activation, ultimately leading to ischemic damage to tissues.[68] This damage results in severe pain and/or organ failure.

Pain is characteristic of SCD and the most common reason for hospitalization. Pain management is personalized and guided by pain severity. Home management with analgesics and hydration is first-line therapy. If that is insufficient, rapid administration of opioids is recommended. The most frequently affect sites are the lower back, knee/shin area, and hips. One study describes four phases of the pain event: prodromal, consisting of mild localized pain without hematologic aberrations; initial/infarctive, consisting of acute pain lasting 2–3 days; a postinfarctive phase; and a recovery phase. Laboratory findings include elevated reticulocytes, lactate dehydrogenase, and C-reactive protein (CRP). The resolving phase occurs when the pain intensity is decreased, usually as a result of appropriate care.[69]

Acute chest syndrome is the second most frequent cause of hospitalization and the leading cause of death in patients with SCD. It is associated with >10% fatality or association with neurologic events. It can be defined as a *new* infiltrate in at least one segment of the lung, along with fever and respiratory symptoms. Splenic dysfunction plays a key role in increased susceptibility to bacterial infections. The impaired immune function associated with SCD places children at risk of developing life-threatening infections, especially from *Streptococcus pneumonia* and *Haemophilus influenzae*.[70,71] Long-term penicillin prophylaxis and vaccinations are recommended; however, concerns of penicillin resistance may lead to changes.[66] Children with vascular velocity >200 cm/s are at risk for central nervous system (CNS) injury (stroke). Prevention consists of chronic transfusion therapy and/or hydroxycarbamide. Pulmonary and renal complications as well as depression are other comorbidities.

Numerous nonpathognomonic oral findings have been described in SCD and include mucosal pallor (70%), delayed eruption (23%), mandibular pain (20%), osteomyelitis (5%), and discolored and depapillated tongue.[72] Radiographic changes have been noted in 70%–100% of patients.[73] In radiographic assessment of SCD patients, higher prevalence of external resorption; number of teeth with pulp

calcification; partial and total loss of lamina dura; changes in trabecular structure of maxilla and mandible; and hypercementosis was found when compared to controls.[74]

Diagnosis

Premarital, antenatal, and neonatal screening programs have been established in some high-income countries, including parts of the Middle East and the United States, and areas with a high prevalence of the disease.[67] Screening consists of DNA-based testing for prenatal diagnosis, and after-birth diagnosis by hemoglobin electrophoresis, thin layer isoelectric focusing, solubility testing, and examination of peripheral blood smear.

Treatment

Advances in medical therapies have dramatically improved the lifespan of SCD patients due to supportive care and hydroxyurea. General measures to provide palliation and reduce the myriad of SCD complications require a multidisciplinary approach and comprehensive patient education. Hydroxyurea has been used to prevent acute pain and acute chest syndrome. Preventive measures include penicillin prophylaxis in children, Doppler screening for stroke prevention, and regular blood transfusions. Clinical trials using small-molecule therapies are underway. A New Drug Application has been submitted to the FDA for L-glutamine to reduce the frequency of acute pain. Hematopoietic stem cell transplantation (HSCT) is curative, but the costs associated with it are prohibitive, particularly in lower-income populations.[67] There are currently several ongoing trials with emerging treatment approaches including L-glutamine powder, rivipansel, hydroxycarbamine, prasugrel, vepoloxamer, L-arginine, N-acetylcysteine, and magnesium sulfate.

Penicillin prophylaxis for children with SCD under the age of 5 years reduces infection-related morbidity and mortality, as does appropriate vaccination against pneumonia and influenza. Vaccination with both the 13-valent pneumococcal-conjugated vaccine (PCV13) and pneumococcal polysaccharide vaccine PPSV23 can prevent infections by most serotypes. Acute chest syndrome is the leading cause of death. Therapy is intensive and expansive, and possible interventions include transfusion, supplemental oxygen, continued respiratory therapy, antibiotics, bronchodilators, pain management, fluid management, corticosteroids, and mechanical ventilation.

Oral Health Considerations

Measures to reduce oral disease burden and infection in the SCD patient are clearly indicated. Long-term penicillin prophylaxis in SCD children under age 6 years inhibits the acquisition of *Streptococci mutans*, resulting in significantly lower caries rates in these children.[75] However, within 4 years of cessation of prophylaxis, the levels of mutans streptococci reached that of matched controls. While SCD is not associated with increased periodontal disease per se,[76] cases of periodontal infections[77] and mandibular osteomyelitis[78] precipitating a sickle cell crisis have been reported.

Given the wide variability in disease severity, it is essential that a comprehensive history and medical consultation be obtained to determine the patient's status. During non-crisis periods, there are no contraindications concerning the delivery of routine dental care under local anesthesia with inhalational sedation.[79,80] The avoidance of using a local anesthetic agent without a vasoconstrictor is unwarranted. The need for providing antibiotic prophylaxis before rendering dental care is controversial and no clear consensus or guidance exists.[80,81] Most patients can be treated safely in an outpatient setting.[82] For patients deemed high risk, dental therapy may be considered in a hospital setting where appropriate medical support is readily available.

Cell Membrane Defects

Another mechanism for an absolute decrease in the number of circulating RBCs is through increased hemolysis due to membrane defects. This results in morphologic changes of the RBC, leading to cell weakness, fragility, and/or rigidity. These conditions include hereditary spherocytosis (HS), hereditary elliptocytosis (HE), pyropoikilosis (a subtype of HE resulting in severe hemolytic anemia), stomatocytosis, and paroxysmal nocturnal hemoglobinuria (PNH).[83,84]

HS is the most common inherited red cell membrane disorder. It occurs in 1 of every 2000–3000 individuals and is most frequently seen in Europe and North America. There is a loss of surface area on reticulocytes and RBCs due to disruption of the vertical linkages between the phospholipid bilayer and the membrane skeleton as a consequence of mutations in genes encoding for various red cell membrane proteins, including ankyrin, band 3, protein 4.2, spectrin, and RhAg 0C. HE is a red cell membrane disorder characterized by mutations in genes coding for skeletal proteins involved with horizontal protein connections, including SPTA1 and SPTB and protein 4.1R, causing the morphologic changes. It affects 3–5 per 10,000 individuals.

Stomatocytosis is a rare red cell disorder divided into two entities, xerocytosis and dehydrated hereditary stomatocytosis (DHSt) and overhydrated hereditary stomatocytosis (OHS), in which there are alterations in intracellular cation content and cell volume alterations resulting in osmotic deformities of the RBCs.[84]

For all of the red cell membrane diseases, the clinical manifestations are variable and the diagnosis is made based on clinical signs (pallor, jaundice, splenomegaly) and examination of the blood smear. Treatments include splenectomy, transfusions, and clinical trials of senicapoc and PIEZO1 channel inhibitors for hydration disorders.

Paroxysmal Nocturnal Hemoglobinuria

PNH is a rare acquired condition characterized by episodes of hemolysis, bone marrow failure, thrombosis, and smooth muscle dystonia. It affects 1–1.5 cases per million worldwide.[85] Patients with PNH are deficient in proteins that bind to the cell surface through a glycosylphosphatidylinositol (GPI) anchor due to mutations in the phosphatidylinositol glycan anchor biosynthesis class A gene (*PIGA*) gene. Several of these proteins (CD55, CD59) are complement-regulatory proteins, and treatment with a humanized monoclonal antibody that inhibits terminal complement activation such as eculizumab can ameliorate hemolysis and symptoms. Many cells contain GPI anchors, but since erythrocytes lack a nucleus, they are more susceptible to lysis. Clonal expansion of HSCs harboring somatic mutations in the X-linked gene renders lineage cells vulnerable to complement-mediated intravascular and extravascular hemolysis. Intravascular hemolysis leads to release of free hemoglobin, a potent scavenger of nitric oxide. The subsequent lack of tissue nitric oxide is believed to underlie many of the clinical manifestations of PNH, including fatigue, pain, esophageal spasm, erectile dysfunction, and possibly platelet activation. Patients with classic PNH are at increased risk for thrombosis and other complications of intravascular hemolysis. Without therapy, the median survival rate is 10–20 years.[86] Allogeneic bone marrow transplantation is the only curative therapy available for PNH, with reported success rates of 50%–70%. The human monoclonal antibody eculizumab blocks terminal complement activation at C5 and markedly reduces the risk of intravascular thrombosis, decreases or eliminates the need for transfusions, improves quality of life, and offers a more favorable prognosis.[85,86]

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is inherited as an X-linked hemolytic anemia caused by mutations in the *G6PD* gene and more than 400 mutational variants have been defined.[87] Affected individuals are at risk for developing hemolytic anemia. The World Health Organization classifies the different variants according to the magnitude of enzyme deficiency and severity of hemolysis: class I is <1% of enzyme activity, class II is <10%, class III is 10%–60%, class IV is 60%–90%, and class V is >110%.[88] G6PD deficiency is the most common enzyme deficiency in the world and is estimated to affect 330–400 million people worldwide. The two most commonly observed variants are classes II and III. The geographic areas of highest prevalence correlate well with areas where malaria is endemic, such as Africa, Mediterranean Europe, Southeast Asia, and Latin America. It is widely believed that G6PD deficiency confers some level of protection against *Plasmodium falciparum* malaria.

The *G6PD* enzyme acts via the hexose monophosphate shunt to catalyze the oxidation of glucose-6-phosphate to 6-phosphogluconate, while concomitantly reducing the oxidized form of nicotinamide adenine dinucleotide phosphate ($NADP^+$) to nicotinamide adenine dinucleotide phosphate (NADPH). NADPH, a required cofactor in many biosynthetic reactions, maintains glutathione in its reduced form. Reduced glutathione acts as a scavenger for dangerous oxidative metabolites in the cell. While other cells may produce NADPH via alternate pathways, the RBC relies exclusively on G6PD activity. Hemolysis typically occurs when the RBCs undergo excessive oxidative stress, usually due to an external trigger such as drug exposure, fava bean ingestion, or infection. Other potential triggering factors include diabetes mellitus, myocardial infarction, and strenuous exercise.[89,90]

Clinical Manifestations

The vast majority of individuals with G6PD deficiency remain clinically asymptomatic throughout their lives. If hemolysis occurs in an affected patient, characteristic signs and symptoms include fatigue, flank pain, anemia, and jaundice. Patients with the most severe class I variant of the disease (also known as congenital nonspherocytic hemolytic anemia) typically experience chronic anemia, more severe hemolytic episodes requiring transfusion, reticulocytosis, gallstones, and splenomegaly.

About one-third of male newborns who manifest neonatal jaundice within the first 1–4 days of life are G6PD deficient.[91] The icterus of neonatal jaundice is not due to hemolysis, but to the inability of the liver to adequately conjugate bilirubin. If not treated appropriately, it can lead to serious neurologic consequences.[90]

Infection is a common trigger of hemolysis in at-risk patients as well as medications used to treat infections. While the mechanism of triggering hemolysis is unknown, it is postulated that leukocytes release oxidative stressors during phagocytosis. Drug-induced hemolysis typically occurs within 24–72 hours of exposure and dark urine due to hemoglobinuria is common as anemia progresses for about a week, followed by recovery over the next 8–10 days.

Ingestion of fava beans is a recognized trigger. Fava beans contain high concentrations of vicine and convicine, which are transferred to the intestinal epithelium and into the blood to produce reactive oxygen species (ROSs). The reduction of NADPH in G6PD-deficient red cells is unable to reverse glutathione depletion and RBCs sustain severe oxidative damage when exposed to ROSs and promote hemolysis.[89] Patients with class II variant G6PD deficiency are at greatest risk. Fava bean–related hemolysis occurs within the first 24 hours of ingestion, is usually severe, and often leads to acute renal failure.

Diagnosis

Two point-of-care tests have been developed for G6PD activity.[92,93] A definitive diagnosis of G6PD deficiency entails assessment of enzyme activity, by quantitative spectrophotometric analysis of the rate of NADPH production from NADP. Quantifying the specific percentage of activity is necessary to determine the severity.

Treatment

Most cases of acute hemolysis are short-lived and resolve without complication. Severe cases of hemolysis may require transfusion, the provision of fluids to prevent hemodynamic shock, and possibly hemodialysis due to acute renal failure. Neonatal jaundice is usually treated with phototherapy and, when severe, exchange blood transfusion. Once the diagnosis of G6PD deficiency is established, measures to reduce exposure to oxidative stressors are warranted. Infections should be promptly treated and immunizations kept up to date. Patients susceptible to fava bean–induced hemolysis should avoid their ingestion. Patients with G6PD deficiency can tolerate the delivery of all necessary dental care.

Aplastic Anemia

Aplastic anemia (AA) represents bone marrow failure with loss of HSCs (empty marrow) and pancytopenia. AA may be secondary to direct bone marrow damage, inherited syndromes, or an immune-mediated process. AA is a rare disorder with the majority of cases occurring in Asia, manifesting mostly during the first three decades of life. Marrow failure can be secondary to direct injury from radiotherapy, chemotherapy, intermediate metabolites of some common drugs, and benzene (a workplace toxin mainly used in developing countries).[94] Other cases are associated with viral infections, transfusion-associated graft-versus-host disease, hepatitis, pregnancy, and genetic and clonal diseases. Marrow damage results from loss-of-function germline mutations, usually inherited. The most frequently mutated genes include *ASXL1*, *BCOR*, *BCORL1*, *DMNT3A*, and *PIGA*; common karyotypic abnormalities include 6pUPD (acquired uniparental disomy with loss of heterozygosity in the short arm of chromosome 6) and abnormalities of chromosomes 7 and/or 13.

In inherited bone marrow failure syndromes, mutations have been identified in more than 30 genes that encode for subunits of three multiprotein complexes, providing powerful genetic evidence for the role of these complexes in bone marrow failure. Examples include Fanconi anemia (replication-dependent removal of interstrand DNA cross-links), dyskeratosis congenita (telomere maintenance and repair), or stem and progenitor cell differentiation and self-renewal pathways, as in GATA27. Marrow failure has been also observed in syndromes affecting immune regulation, such as in DADA and CTLA48.[95]

Clinically, patients may present with fatigue, pallor, petechiae, ecchymoses (due to thrombocytopenia), and infections (due to neutropenia). Some patients may develop hemolytic anemia or thrombosis as well. A diagnosis of AA is made with a bone marrow aspiration and biopsy that shows hypocellular/aplastic bone marrow, with normal residual hematopoietic cells, and no infiltration with malignant cells or fibrosis. Lab work shows pancytopenia with relatively normal lymphocyte count, decreased reticulocytes of the bone marrow replaced by fat from chemical or physical damage, and increased erythrocyte mean cell volume. The peripheral blood smear reveals macrocytic or normocytic red cells with reticulocytopenia, decreased neutrophils and platelets, and the absence of abnormal circulating white blood cell forms.[96]

AA is classified in different forms depending on the severity. Severe AA patients present with bone marrow cellularity <25% (or 25%–50% if <30% of residual hematopoietic cells) and at least two of the following: (1) peripheral blood absolute neutrophil count (ANC) <500/μL (<0.5×10^9/L); (2) peripheral blood platelet count <20,000/μL; or (3) peripheral blood reticulocyte count <20,000/μL. Very severe AA cases follow the same criteria for SAA and present with an ANC <200/μL.

Nonsevere AA patients manifest with hypocellular bone marrow (as for severe AA) and a peripheral blood cytopenia not fulfilling criteria for severe AA or very severe AA.[96]

Management of AA depends on the severity of the disease and the underlying cause. Approximately 75% of patients initially respond well to immunosuppression, but relapse occurs in about 30%–40% of cases. Cytopenia is managed with sequential transfusion and antibiotics. In some rare cases patients may require therapy with growth factors. Individuals with severe AA who are younger than 20 years of age, and those aged 20–50 with no significant past medical history, are recommended to undergo allogeneic stem cell transplant. For patients over the age of 50, the decision to use immunosuppressive therapy versus supportive care alone depends on the patient's past medical history and comorbidities. If the patient can tolerate immunosuppressive therapy, eltrombopag

for 6 months plus horse antithymocyte globulin and cyclosporin A is the treatment of choice. These patients are monitored on a regular basis for hematologic response.[97–99] The most serious fatal complication of AA is infection and patients with severe AA are at increased risk for fungal, viral, and bacterial infections. While no standard guidelines are available to manage these patients, prophylactic antibiotic therapy (when deemed clinically appropriate), use of antivirals, and antifungals in this patient population is imperative.

Oral Health Considerations

The goal of dental therapy is to establish and maintain optimal oral hygiene, thus reducing the risk of infections. Patients with AA can generally tolerate routine care and the need for prophylactic antibiotic prophylaxis in this AA cohort remains controversial. Patients with severe AA are at high risk for hemorrhage and infection, both oral sourced and nosocomial. These patients should be managed in a hospital setting to ensure appropriate perioperative management and follow-up. Severely neutropenic patients (neutrophil count <500/μL) may require prophylactic antibiotics. Invasive dental procedures should be done in conjunction with the patient's hematologist.

WHITE BLOOD CELL DISORDERS

White blood cells (WBCs) are composed of granulocytes (neutrophils, eosinophils, and basophils) and agranulocytes (T and B lymphocytes, monocytes, and macrophages). Granulocytes are distinguished by their appearance under Wright's stain. The most abundant granulocyte is the neutrophil, which has neutrally staining cytoplasmic granules. The granules in granulocytes contain hydrolases, elastase, myeloperoxidase, cathepsin G, cationic proteins, bactericidal/permeability-increasing protein, and defensins, with broad antimicrobial activity against bacteria, fungi, and certain enveloped viruses. WBC disorders can be either quantitative or qualitative in nature. Table 17-4 outlines alterations in the WBC and differential cell counts that occur in various disorders. This section provides an overview of the most common WBC disorders encountered in a hospital-based oral medicine practice.

Granulocytosis/Neutrophilia

Neutrophilia is a term that refers to an increase of peripheral blood neutrophils, usually >7700 neutrophils/μL (in adults). Neutrophilia is frequently used interchangeably with granulocytosis, although the latter also includes an increased basophil or eosinophil count. Elevated WBC counts typically reflect a normal response to infection or inflammation and usually represent an increase in the number of neutrophils. In acute infections, leukocyte counts typically are 15,000–25,000/μL. Less often, leukocytosis is the sign of a primary bone marrow abnormality related to leukemia or a myeloproliferative disorder. Causes of neutrophilia change depending on the individual and the clinical setting. For example, young patients are more likely to have inherited diseases compared to adults. In addition, 2.5% of the population present with physiologic fluctuating neutrophil counts.[100,101] Cigarette smoking is a common cause of modest neutrophilia and the underlying mechanism remains unknown.[102,103] Mild neutrophilia has also been associated with stressful events such as surgical procedures, seizures, and exercise.[104] In general, neutrophil production may be reactive (e.g., following an infection), autonomous (e.g., secondary to a malignancy), or idiopathic.[105,106]

Reactive Neutrophilia

Inflammation

Acute and chronic inflammation may result in neutrophilia. Examples include Kawasaki disease, rheumatoid arthritis in adult patients, inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis), and Sweet syndrome. The diagnosis is made based on the clinical findings and by exclusion. CRP and erythrocyte sedimentation rate (ESR) are usually elevated, but unspecific.

Infection

Infection is a common cause of neutrophilia.[107] A total WBC count greater than 25,000/μL is usually indicative of an acute infectious process. Bacterial infections are associated with a left shift and the blood smear may exhibit Döhle bodies, cytoplasmic vacuoles in neutrophils, and toxic granulations. In younger patients, neutrophilia may be involved also in several viral infections (e.g., Varicella zoster virus [VZV], herpes simplex virus [HSV]), mononucleosis, and advanced tuberculosis.

Medication

Medications may lead to an increased neutrophil count by (1) stimulating bone marrow myelopoiesis; (2) releasing granulocytes from the bone marrow (e.g., glucocorticoids); (3) an allergic reaction to a specific drug; and (4) demarginating neutrophils within the vasculature.

Autonomous Neutrophilia

Asplenia

Neutrophilia is also observed in patients with asplenia secondary to splenectomy, auto infarction in SCD, or other conditions.[108,109]

Myeloproliferative Neoplasms

Myeloproliferative neoplasms may be associated with an increased neutrophil count in both patients with a malignant disorder (such as chronic myeloid leukemia) or a benign condition (such as PV, or essential thrombocythemia). Neutrophilia secondary to a malignancy often presents with

Table 17-4 Key laboratory tests for white cell disorders.

Test Name	Normal Range (SI Units)	Increased	Decreased	Oral Findings
White blood cell (WBC)	4400–11,000/μL	Infections Inflammation Cancer Leukemia	Hematologic neoplasia Early leukemia Drug-induced cyclic neutropenia Viral infection Severe bacterial infections Bone marrow failure Congenital marrow aplasia	Enlarged gingiva, oral ulcerations, infection due to immune suppression from disease or therapy
Differential WBC				
Polymorphonuclear neutrophils	41%–78%	See Table 17-5	See Table 17-5	
Band neutrophils	0%–6%	Immature neutrophils; indicates rapid production of cell line often seen in infection		
Lymphocytes	23%–44%	Viral infections, mononucleosis, infectious lymphocytosis, hypoadrenalism, hypothyroidism	Immunodeficiencies, adrenal-corticosteroid exposure, severe debilitating illness, defects in lymphatic circulation	
Monocytes	0%–7%	Chronic infections (tuberculosis), bacterial endocarditis, granulomatous disease		
Eosinophils	0%–4%	Parasitic diseases, certain allergic diseases, chronic skin diseases, various miscellaneous diseases (sarcoidosis, Hodgkin disease, metastatic cancer)		
Basophils	0%–2%	Chronic hypersensitivity states, no specific allergen, myeloproliferative disorders		

anemia of chronic disease/inflammation. Leukocytosis to values in excess of 50,000 cells/μL, which is not associated with leukemia, is termed a leukemoid reaction.

Genetic and Inherited Conditions

Neutrophilia secondary to an inherited or genetic cause (e.g., leukocyte adhesion deficiency, hereditary chronic neutrophilia, Down syndrome) is usually more common during childhood and in neonates. Inheritance should be suspected when other family members present hematologic or somatic abnormalities. A bone marrow examination may be necessary to confirm the diagnosis.[110,111]

Evaluation and Diagnosis

The evaluation of a patient with neutrophilia starts with the clinical history and physical examination, including a CBC and differential. In patients with a suspicious hematologic disease, a peripheral blood smear examination is necessary. Nonspecific markers of inflammation (e.g., CRP, ESR), serum chemistries, and coagulation studies may be helpful to assess possible secondary complications.

Neutropenia

Neutropenia refers to an ANC <1500/μL. Exceptions are made for newborns who have a slightly elevated ANC during the first few days post partum and certain ethnic groups (such as Yemenite Jews, West Indians, Arab Jordanians, and black people of South African extraction) who have a physiologically lower WBC and ANC. The ANC is defined as the number of WBCs that are neutrophils {(WBC [cells/μL] x percent [PMNs + bands]) ÷ 100}.

Neutropenia can be categorized into mild, moderate, or severe. In mild neutropenia the ANC ranges between 1000 and 1500/μL, moderate between 500 and 1000/μL, and severe <500/μL. The risk of infection typically increases

Table 17-5 Neutrophil disorders.

Quantitative Disorders	
Neutrophilia	**Neutropenia**
Primary	*Primary*
Hereditary	Cyclic neutropenia
Idiopathic inflammation	Familial benign myeloka thexis
Cancer	Severe chronic glycogen storage disease
Leukemia	Failure to release
Colchicine sulfonamides	*Secondary (Immunodeficiencies)*
Down syndrome	X-linked hyperimmunoglobulin M
Chronic myelogenous	X-linked agammaglobunemia
Polycythemia vera	*Acquired Anemia of Inflammation*
Leukocyte adhesion deficiency	Drug-induced
Secondary	Clozapine
Infections	Antithyroid
Smoking	Sulfasalazines
Chronic inflammation	Others
Stress	*Destruction*
Exercise	Hypersplenism
Steroids	Felty's syndrome
Lithium	Systemic lupus erythematosus
Marrow stimulation	*Nutritional*
Solid tumor	B_{12} and folate deficiencies
Heat stroke	Copper deficiency
Asplenia	
Sweet syndrome	
Qualitative Disorders	
Adhesion	Granule Disorders
Leukocyte adhesion deficiency (types 1, 2 and 3)	Myeloperoxidase deficiency
	Chediak–Higashi syndrome
Phagocyte Activation	Chronic granulomatous disease
Hyper-immunoglobulin E (Job syndrome)	Neutrophil-specific granule deficiency
Chronic granulomatous disease	Impaired chemotaxis
Chediak–Higashi syndrome	Shwachman–Diamond syndrome

when the ANC is <1000/μL. Agranulocytosis is a condition in which the ANC is <100/μL. Neutropenia can be either acquired or congenital, transient or chronic.

Transient Neutropenia

Transient neutropenia is usually associated with a viral infection. Epstein–Barr virus (EBV)-associated infectious mononucleosis is a common cause of transient neutropenia. Other causes include bacterial infections, autoimmune conditions, and medications, as outlined in detail in Table 17-6.[112] Medications cause neutropenia and/or agranulocytosis by direct toxicity on marrow granulocytic precursors or by an immune-mediated destruction of circulating neutrophils by drug-related antibodies. Specifically, medications (or their metabolites) bind to the membrane of the neutrophils, which causes production of T cells or antibodies against the neutrophil membrane. Monitoring the WBC count and differential periodically may be helpful to detect early signs of neutropenia and agranulocytosis secondary to certain drugs such as clozapine. If a patient is diagnosed with drug-induced neutropenia, the offending agent should be discontinued if possible and in the presence of fever and/or positive blood, urine, or sputum, broad-spectrum intravenous antibiotics should be initiated. Bone marrow aspiration and biopsy may be considered as well.

In the presence of an active infection, administration of granulocyte colony-stimulating factor (G-CSF) subcutaneously is recommended (dose of 5 μg/kg per day) in individuals

Table 17-6 Causes of transient neutropenia.

Infection	
Viral	Cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, influenza, parvovirus B19, hepatitis
Bacterial	*Brucella*, paratyphoid, tuberculosis, tularemia, typhoid; *Anaplasma phagocytophilum* and other rickettsia
Protozoan	*Plasmodium vivax, P. falciparum*
Medications	
Anticonvulsant	Carbamazepine, valproate
Antimicrobial	Sulfonamides, penicillin, trimethoprim/sulfamethoxazole
Antipsychotic	Clozapine, olanzapine, phenothiazines
Antirheumatic	Gold, levamisole, penicillamine
Antithyroid	Methimazole, propylthiouracil
Other	Aminopyrine, azathioprine, cyclophosphamide, colchicine, deferiprone, ganciclovir, methotrexate, levamisole-adulterated cocaine, rituximab, quinine
Immune	
Neonatal isoimmune	
Autoimmune	Felty's syndrome, rheumatoid arthritis, lupus erythematosus, Wegener's granulomatosis

Source: Modified from Newburger PE, Dale DC. Evaluation and management of patients with isolated neutropenia. *Semin Hematol.* 2013;50(3):198–206. doi:10.1053/j.seminhematol.2013.06.010.

with severe medication-induced neutropenia and suspected reduced marrow reserve.

Congenital Neutropenia

Congenital neutropenia typically presents at birth and is caused by a primary bone marrow failure syndrome. There are three main types of congenital neutropenia: severe, cyclic, and Shwachman–Diamond syndrome (SDS). In addition to these conditions, there are now other known primary genetic defects that may cause important chronic neutropenia (e.g., WHIM syndrome, GATA2 deficiency/MonoMAC syndrome, glycogen storage disease type 1b, Chediak–Higashi syndrome, and congenital cobalamin deficiencies). Congenital neutropenia manifests with otitis media, oropharyngeal symptoms, cellulitis, respiratory infections, and dermatologic infections, usually due to staphylococci and streptococci. Oral ulcers with pain are common. When the GI tract is affected, patients may present with symptoms similar to those seen in Crohn's disease. Bone marrow aspiration may be helpful to differentiate the various forms of congenital neutropenia.[113]

Severe Congenital Neutropenia

Severe congenital neutropenia (SCN) is a rare, genetically transmitted disorder with dominant, recessive, or X-linked inheritance. Newborns usually present with an ANC <200/μL and high monocytes. The neutropenia in SCN is thought to be caused by an increased myeloid cell apoptosis. G-CSF administration is the treatment of choice and hematopoietic cell transplantation is theoretically curative.[114]

Cyclic Neutropenia

Cyclic neutropenia is a rare, autosomal dominantly inherited condition due to mutations in the gene for neutrophil elastase (*ELANE*) on chromosome 19p13.3 (positive in 90%–100% of cases).[115] These patients usually present with a circulating neutrophil count that fluctuates with severe neutropenia, occurring every 21 days and lasting for 3–5 days. During these periods, patients report malaise, fever, gingivitis or periodontitis, aphthous-like ulcers, and pharyngitis, and are susceptible to bacterial infections. Symptoms usually improve when the ANC recovers to >500/μL. Blood tests during these episodes reveal low neutrophil counts. All children with confirmed cyclic neutropenia should be treated with G-CSF. Patients require monitoring for osteoporosis, regular dental care, and genetic counseling. Antibacterials may be needed in patients who are febrile during periods of neutropenia.

Shwachman–Diamond Syndrome

SDS is an autosomal recessive disorder that generally presents in newborns with bone marrow failure (including isolated neutropenia) and exocrine pancreatic dysfunction. As a result of the bone marrow dysfunction, patients with SDS are at a higher risk of developing myelodysplastic syndrome,

AA, and acute myeloid leukemia. SDS is also characterized by growth thrive, dental (enamel hypomaturation, hypocalcification, and hypoplasia), and skeletal abnormalities, and/or recurrent infections. The majority of patients present with mutations of the Shwachman–Bodian–Diamond syndrome (*SBDS*) gene. The diagnosis of SDS is made using clinical criteria (bone marrow failure and exocrine pancreatic insufficiency) or molecular findings (biallelic homozygous or compound heterozygous *SBDS* mutation). Laboratory testing includes CBC with differential, platelet count and tests of exocrine pancreatic function. No cure is available for SDS. Treatment is directed to the control of symptoms, with a multidisciplinary team including hematologists, gastroenterologists, geneticists, orthopedics, endocrinologists, immunologists, dentists, and others. G-CSF may be needed in cases of severe neutropenia and HSCT may be considered for those patients with severe pancytopenia.[116,117]

Chronic Idiopathic Neutropenia

Chronic idiopathic neutropenia is characterized by long episodes of neutropenia without a known cause. The ANC usually ranges from 500 to 1000/μL and is associated with monocytosis. Clinically, patients may be asymptomatic or develop gingivitis, periodontitis, early tooth loss, aphthous-like ulcers, and infections. Treatment to increase the neutrophil count is only for patients with severe recurrent infection-related complications.[118–120]

Agranulocytosis

Agranulocytosis is a rare disorder caused by medication use in 70% of cases. The majority of cases develop in the first 3–6 months after beginning the causing agent. Clinically, patients may present with oral ulceration and fever. Sepsis may occur in those cases with a sudden presentation. Agranulocytosis is not predictable and any patient on a medication known to cause agranulocytosis should be educated about this possible complication, and the drug discontinued as soon as the symptoms arise.[121,122]

Oral Health Considerations

In patients with significant neutropenia (ANC <1,000/μL) requiring urgent dental treatment, pre- and/or postoperative antibiotics may be initiated. A consult with the patient's managing physician concerning the risk of infection is indicated. In cases of severe neutropenia (ANC <500/μL), elective dental treatment should be postponed.

Leukemia

Leukemia is a clonal malignancy of any of the blood-forming cellular elements, consisting largely of immature precursors (blasts), preferentially involving the blood, bone marrow, or both. The disease course progresses over weeks to months, ultimately culminating in bone marrow failure. In 2019, the American Cancer Society estimated 61,780 new cases and 22,840 deaths attributable to leukemia, with a 62.7% 5-year survival rate. Leukemia was the 10th most common cancer to affect men of all races and represented 3.5% of all new cancer cases in the United States.[123] According to the most recent World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues, leukemia is classified based on clinical behavior (acute or chronic) and the primary hematopoietic cell line affected (myeloid or lymphoid) (Table 17-7). The four principal diagnostic categories are (1) acute myelogenous leukemia (AML); (2) acute lymphocytic leukemia (ALL); (3) chronic myelogenous leukemia (CML); and (4) chronic lymphocytic leukemia (CLL).[124]

Leukemic cells multiply at the expense of normal hematopoietic cell lines, resulting in marrow failure, altered blood cell counts, and, when untreated, death from infection, bleeding, or both. Leukemia is more common in adults than in children, with most chronic leukemia occurring in adults. Of acute leukemias, ALL is more common in children, whereas AML is more common in adults.

Leukemia is typically diagnosed via abnormal results on a full blood count. The peripheral granulocyte count is markedly elevated in chronic leukemia, but may be increased (with numerous blast forms), decreased, or normal in acute leukemia. Confirmation is determined with identification of abnormal hematopoietic cells in bone marrow. Additional techniques that may be used to further classify the type of leukemia include flow cytochemical staining (myeloperoxidase, Sudan black B), cytometric immunophenotyping, and genetic analysis.

Patients affected by leukemia may experience oral bleeding and are at a higher risk of infection. All patients should be instructed to maintain optimal oral hygiene by their oral healthcare professional. Precautions to be followed by dental providers are provided for each hematologic malignancy in the sections below.

Acute Lymphoblastic Leukemia

ALL, also known as acute lymphocytic leukemia or acute lymphoid leukemia, is the most common malignant disorder in children. ALL and lymphoblastic lymphoma (LBL) fall under the same classification and diagnosis. In the US, ALL/LBL is more frequent among Hispanic and Whites, compared to Blacks and Asians, with a peak incidence at 2–5 years of age and a male-to-female ratio of 55% to 45%.[123]

ALL/LBL is associated with genetic factors (such as Down syndrome), although the majority of patients have no known inherited cause. Radiation and exposure to specific chemicals have been linked with ALL in a small subset of children.[125] Large genome-wide association studies have shown

Table 17-7 World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia.

Myeloproliferative Neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1+*
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/Lymphoid Neoplasms with Eosinophilia and Rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), BCR-ABL1–
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic Syndromes (MDS)
MDS with single-lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single-lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Myeloid Neoplasms with Germ Line Predisposition
Acute Myeloid Leukemia (AML) and Related Neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
Acute promyelocytic leukemia (APL) with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
AML (megakaryoblastic) with t(1;22) (p13.3;q13.3);*RBM15-MKL1*
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS

(*Continued*)

Table 17-7 (Continued)

AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome
Blastic Plasmacytoid Dendritic Cell Neoplasm
Acute Leukemias of Ambiguous Lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2);*BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic Leukemia/Lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1);*ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like*
B-lymphoblastic leukemia/lymphoma with iAMP21*
T-lymphoblastic Leukemia/Lymphoma

Source: Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. *Blood*. 2016;128(3):462–463. doi:10.1182/blood-2016-06-721662. © 2016, American Society of Hematology.

polymorphic variants of the *ARID5B*, *CEBPE*, *GATA3*, and *IKZF1* genes being associated with an increased risk of ALL. Rare germline mutations in *ETV6* and *PAX5* are related to familial ALL.

The clinical presentation of ALL/LBL is nonspecific. Patients may present with hepatomegaly (64%) and/or splenomegaly (61%). Lymphadenopathy is present in 50% of patients; fever, fatigue, and musculoskeletal pain are frequent at the time of diagnosis. Oral manifestations of ALL/LBL include gingival bleeding, ulcers, and gingival enlargement. ALL/LBL manifests with bleeding, bruising, and petechiae in the setting of thrombocytopenia (<100,000/μL). The WBC count may be low, normal, or high, although it is typically <10,000/μL in 50% and >50,000/μL in 20% of children. Children with persistent fever, pallor, bleeding/bruising, bone pain, hepatosplenomegaly, and/or lymphadenopathy should be evaluated for possible ALL/LBL.[125]

Laboratory tests include a CBC with differential, a review of the peripheral smear, and bone marrow biopsy. Morphology is variable, with small blasts, chunky chromatin, small nucleoli, and scant cytoplasm. T-lineage

lymphoblasts are positive for cytoplasmic or surface CD3, and negative for myeloperoxidase and B-cell antigens. B-lineage lymphoblasts are often positive for B-cell markers such as CD19, cytoplasmic CD22 and cytoplasmic CD79a; negative for CD3 and myeloperoxidase.

Treatment consists of induction, consolidation, and maintenance therapy. The goal of induction to eradicate all the leukemic cells (complete remission) from the blood and bone marrow. Induction therapy lasts 4–6 weeks and includes a therapy regimen with vincristine, corticosteroids, and asparaginase. Anthracycline may be added in high-risk patients. Response is measured with sequential bone marrow aspirates. The majority of t(9;22)/BCR-ABL1-negative ALL patients enter complete remission after completion of induction therapy. t(9;22)/BCR-ABL1-positive ALL children benefit from the administration of tyrosine kinase inhibitors (TKI; e.g., dasatinib or imatinib).[126,127]

Consolidation therapy is started after complete remission is achieved. Consolidation therapy is needed because a few leukemic lymphoblasts may still be present in the bone marrow despite evidence of complete remission. Consolidation therapy lasts 6–8 weeks and includes several different drug combinations (such as cytarabine, methotrexate, alkylating agents, or anthracyclines).

After completion of the consolidation therapy, children receive maintenance chemotherapy with daily oral 6-mercaptopurine and weekly methotrexate, with periodic vincristine, prednisone, and intrathecal therapy. Allogeneic hematopoietic cell transplantation remains an option for high-risk ALL/LBL patients such as t(9;22)/BCR-ABL1-positive ones (even when treated with a TKI), those with a poor initial response to treatment, and adults with MLL gene rearrangements (e.g., t[4;11]). Survivors are then monitored on a regular basis for long-term complications.[128] More recently, tisagenlecleucel, a CAR T cell immunotherapy, was FDA approved as standard of care for relapsed or refractory ALL up to age 25.[129]

Acute Myeloid Leukemia

AML is a hematopoietic neoplasm characterized by a clonal proliferation of precursor of the myeloid lineage that cannot differentiate into mature hematopoietic cells.[130,131] AML blasts have morphologic, cytochemical, and/or immunophenotypic characteristics of granulocytes, monocytes, megakaryocytes, erythrocytes, or their precursors.

AML represent the most common acute leukemia in adult patients, with a median age at diagnosis of 65 years and an incidence of 2–20 per 100,000 population. Acute promyelocytic leukemia (APL) is a specific subset of AML that has a much more favorable cure rate and an overall survival rate of 90%–95%, especially in those <60 years.[132] Risk factors for AML include genetic changes (such as familial mutations of *CEBPA*, *DDX41*, *RUNX1*; Fanconi anemia; Bloom's syndrome; and trisomy 21) and exposure to environmental factors, including ionizing radiation, chemotherapy, tobacco, and certain chemicals. Some cases of AML arise from myelodysplastic syndrome and other myeloproliferative neoplasms.[131]

Patients with AML usually present with signs and symptoms secondary to pancytopenia, fatigue, and generalized weakness. Infections, ecchymosis, and bleeding are common findings. The dentist should be familiar with the oral signs and symptoms associated with AML: patients may present with gingival enlargement, oral mucosal nodules, and ulcerations. APL is associated with an increased risk of bleeding with bruising, including gingival bleeding. Approximately 50% of patients with a diagnosis of AML demonstrate cytogenetic abnormalities. Most peripheral smears show large blasts, big nucleoli, a moderate amount of cytoplasm, and Auer rods. Flow cytometry of the marrow aspirate or peripheral blood express CD34, HLA- DR, CD117, CD13, and CD33. According to the World Health Organization classification system, blast forms must account for at least 20% of the total cellularity of the bone marrow.[130]

Treatment of AML varies depending on the risk profile associated with age (Table 17-8).[133] For medically fit older adults (>60 years), induction therapy is with cytarabine and daunorubicin ("7+3" therapy). Patients with adverse prognosis AML require CPX-351 or a hypomethylating agent. Subsequent treatment is guided by pretreatment determinants and response to initial therapy. In poorer-risk groups, when age, comorbidities, and donor availability permit, an

Table 17-8 Risk profile of the acute myeloid leukemia patient.

Risk Profile	Type	Defect
Favorable	APL CBFL Normal karyotype	t (15;17) (q22; q22) t (8;21) (q22; q22) inv (16) (p13.1; q22) t (16;16) (p13.1; q22) Mutated NPM1 w/o FLT3 ITD mutation Biallelic mutated CEBPA
Intermediate	Trisomy 8	t (9;11) (p22; Q23)
Poor	Normal karyotype Complex karyotype (>3 abnormalities) Monosomal karyotype abnormalities 17p 11q23 Abnormalities other than t(9;11), inv(3)(q21;q26.2) T(3;3)(q21;q26.2), T(6;9)(q23;34)	FLT3 ITD mutation−5 or del(5q) −7

APL, acute promyelocytic leukemia; CBFL, core binding factor leukemias.

Source: Brown CMS, Larsen SR, Iland HJ, et al. Leukaemias into the 21st century: part 1: the acute leukaemias. *Intern Med J*. 2012;42(11):1179–1186. doi:10.1111/j.1445-5994.2012.02938.x. © 2012, John Wiley & Sons.

allogeneic stem cell transplant (SCT) is also a consideration. A proportion of these patients will be cured by chemotherapy alone; however, determining which patient is likely to relapse and hence benefit from allogeneic SCT in first remission is not easily defined. For medically frail patients, therapy is focused primarily on relief of symptoms, and improving quality of life.[134] For the APL patient, treatment is aimed at reversing coagulopathy, with aggressive plasma and platelet support, and a distinct treatment regimen of all-trans retinoic acid (ATRA), in combination with anthracycline-based chemotherapy and intensification during consolidation with intermediate- or high-dose cytarabine and addition of arsenic trioxide during both induction and consolidation.[131]

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is a lymphoproliferative disorder characterized by an accumulation of monoclonal B lymphocytes due to a defect in apoptosis. It is associated primarily with cellular accumulation rather than proliferation and rarely transforms to an acute leukemia. CLL is considered to be identical to SLL (an indolent non-Hodgkin lymphoma); the term SLL is used when the disease is present mainly in the nodes, and CLL when the disease is in the blood.[135,136]

CLL is a disease of the elderly (median age at diagnosis 70 years) and patients often die of other causes before succumbing to CLL. CLL is associated with inexorable progression and concomitant immune deficiency. CLL is the most frequent adult leukemia in Western countries and represents 25%–30% of all leukemias in the United States. In 2019, there are likely to have been 20,720 new cases of CLL/SLL in the United States (7840 females), with 191,000 cases worldwide.[123] Staging is based on the extent of lymph node, liver, or spleen involvement and anemia, thrombocytopenia, or both. The Rai and Binet clinical staging systems are commonly used in the United States and Europe, respectively (Table 17-9).[137,138]

The majority of patients present with no symptoms and the CBC reveals absolute lymphocytosis. Some cases may have painful lymph nodes. A small subset of patients (5%–10%) present "B" symptoms of lymphoma, which include (1) weight loss ≥10% of body weight within the previous six months; (2) fevers for ≥2 weeks with no evidence of infection; (3) severe night sweats; and (4) fatigue.

A diagnosis of CLL is made when patients present with an absolute B lymphocyte count in the peripheral blood ≥5000/μL for at least 3 months. The peripheral blood smear shows lymphocytosis with small leukemic cells, mature-appearing lymphocytes with a darkly stained nucleus, partially condensed (clumped) chromatin, and indiscernible nucleoli. Flow cytometry demonstrates expression of the B cell–associated

Table 17-9 Rai and binet clinical staging.

Rai Staging System		
Risk Group	**Clinical Features**	**Median Life Expectancy (Years)**
Low risk (Rai stage 0/I)	Lymphocytosis without cytopenia, lymphadenopathy, or splenomegaly	13
Intermediate risk (Rai stage II)	Lymphocytosis, lymphadenopathy, and/or splenomegaly, but without cytopenia	8
High risk (Rai stage III/IV)	Lymphocytosis and cytopenia (a hemoglobinvlevel of ≤11 g per dL and/or a platelet count of ≤100,000 cells per μL)	2
Binet Staging System		
Low risk (Binet stage A)	<3 palpably enlarged sites without cytopenia	13
Intermediate risk (Binet stage B)	3+ palpably enlarged sites without cytopenia	8
High risk (Binet stage C)	Cytopenia (a hemoglobin level of ≤10 g per dL and/or a platelet count of ≤100,000 cells per μL)	2

Source: Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. *Nat Rev Dis Prim*. 2017;3:16096. doi:10.1038/nrdp.2016.96. © 2016, Springer Nature.

antigens CD19, CD20, and CD23. The staining intensity of CD20 is usually low/dim. There is expression of CD5, an antigen expressed on T cells and subsets of mature B cells, as well as low levels of surface membrane immunoglobulin (i.e., SmIg weak). The immunoglobulin is most often IgM or both IgM and IgD, and typically only a single immunoglobulin light chain is expressed (i.e., either kappa or lambda but not both), confirming the clonal nature of these cells.[136,139]

Treatment for CLL is not necessary in all patients, since the survival rates for CLL are similar to those observed in the general population. Observation is usually indicated for patients with early-stage asymptomatic CLL. Treatment is recommended for "active disease" in patients with advanced-stage, high tumor burden, disease-related anemia or thrombocytopenia, or severe disease-related "B" symptoms.[139] Various combination regimens may be used, although fludarabine, a nucleoside analog, is the most frequently used first-line agent in CLL along with ibrutinib. Alemtuzumab is an FDA-approved monoclonal antibody directed at CD52 approved for CLL patients as first-line therapy and for patients with fludarabine-refractory CLL. Patients refractory to both fludarabine and alemtuzumab may be receiving ofatumumab, an anti-CD20 monoclonal antibody. Other FDA-approved agents include venetoclax (a selective inhibitor of the B-cell lymphoma 2 [Bcl-2] regulator protein) for patients with CLL with 17p deletion; and the combination of venetoclax and obinutuzumab for patients with previously untreated CLL.[140]

Patients with CLL are at a greater risk of developing infections, autoimmune disorders, or secondary malignancies. One of the most severe complications of CLL is the transformation to diffuse large B-cell lymphoma or Hodgkin lymphoma, which occurs in 2%–10% of CLL cases (Richter's transformation).

Oral Health Considerations

Oral manifestations at presentation of CLL are infrequent and generally involve bleeding or infection. CLL is a relatively indolent chronic hematologic malignant disease that often has a prognosis compatible with relatively normal dental treatment planning. Patients in late-stage disease, with severe thrombocytopenia (<50,000/μL), should be considered for platelet supplementation prior to dental surgery.

Chronic Myelogenous Leukemia

CML represents a hyperproliferation of the bone marrow due to a "partial" transformation of the HSCs. CML displays the t(9;22) chromosome translocation. This translocation results in the *Bcr-Abl1* fusion gene that produces Bcr-Abl tyrosine kinase, an abnormal protein that causes the excess WBCs typical of CML.[141] The prevalence of CML has been increasing in Western countries, with 1–2 new cases per 100,000 each year and a slight male predominance.[142]

CML has a chronic indolent phase (present in 85% of patients), an accelerated phase, and a blast crisis. During the chronic indolent phase, there is proliferation of a partially transformed hematopoietic stem cell, resulting in increased numbers of cells. In the accelerated phase neutrophil differentiation becomes increasingly impaired and leukocyte counts are more challenging to control with therapy. The constant proliferative drive promotes secondary genetic events that contribute to the development of the acute phase (blast crisis). Bone marrow aspiration and biopsy show granulocytic hyperplasia with a maturation pattern that reflects what is seen in the peripheral smear.[143]

The treatment of CML depends on the specific disease phase. TKIs are the first-line treatment for CML. Imatinib was the first agent approved for patients in the chronic phase. Imatinib competitively occupies the adenosine triphosphate-binding site required for BCR-ABL to phosphorylate its substrates; consequently, signal transduction is inhibited, and the leukemic cells die.[144,145] Second-generation TKIs (nilotinib, dasatinib, bosutinib) have demonstrated faster responses, but no improvement in overall survival. However, neither can inhibit BCR-ABL T315I. Several other TKIs are also in development, including bosutinib and ponatinib; the latter is the first TKI with activity against the T315I mutation. Other drugs that are active against T315I include omacetaxine mepesuccinate (homoharringtonine), a protein synthesis inhibitor that induces apoptosis through its effect on MCL1, a member of the BCL2 family of antiapoptotic proteins. The prognosis in the accelerated or blast phase is poor and allogeneic HCT is the treatment of choice. CML patients are monitored on a regular basis by quantitative polymerase chain reaction (Q-PCR) measurement in the peripheral blood of BCR-ABL1 transcripts.[146–148]

Lymphomas

Non-Hodgkin Lymphoma

Lymphomas are malignancies of normal lymphoid cells that originate in lymphoid tissues. Non-Hodgkin lymphoma (NHL) includes a group of malignant neoplasms variously derived from T-cell progenitors, B-cell progenitors, mature T cells, mature B cells, or natural killer cells (in sporadic cases). In the United States, NHL is one of the most prevalent cancers. In 2019, the American Cancer Society estimated 74,200 new cases (41,090 men).[123]

Clinically, NHL presents with various signs and symptoms depending on the type of lymphoma and region involved. Lymphomas are classified into aggressive and indolent[149] based on a combination of morphology, immunophenotype, genetic, molecular, and an expanded concept of clinical features such as age and tumor location, as defining criteria in several newly recognized categories (Table 17-10).

Table 17-10 World health organization classification of non-hodgkin lymphoma.

The Indolent Lymphomas
B-Cell Neoplasms
Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia
Lymphoplasmacytic lymphoma (± Waldenstrom's macroglobulinemia)
Plasma cell myeloma/plasmacytoma
Hairy cell leukemia
Follicular lymphoma (grade I and II)
Marginal zone B-cell lymphoma
Mantle cell lymphoma
T-Cell Neoplasms
T-cell large granular lymphocyte leukemia
Mycosis fungoides
T-cell prolymphocytic leukemia
Natural Killer Cell Neoplasms
Natural killer cell large granular lymphocyte leukemia
The Aggressive Lymphomas
B-Cell Neoplasms
Follicular lymphoma (grade III)
Diffuse large B-cell lymphoma
Mantle cell lymphoma
T-Cell Neoplasms
Peripheral T-cell lymphoma
Anaplastic large-cell lymphoma, T/null cell
The Highly Aggressive Lymphomas
B-Cell Neoplasms
Burkitt lymphoma
Precursor B-lymphoblastic leukemia/lymphoma
T-Cell Neoplasms
Adult T-cell lymphoma/leukemia
Precursor T-lymphoblastic leukemia/lymphoma

Source: Modified from UpToDate, December 2019.

Examples of aggressive lymphomas include diffuse large B-cell lymphoma, Burkitt lymphoma, adult T-cell leukemia-lymphoma, precursor B- and T-lymphoblastic leukemia/lymphoma, and other peripheral T-cell lymphomas. Indolent lymphomas include chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, and splenic marginal zone lymphoma. The aggressive types manifest with a rapid growing mass, "B" symptoms (such as profound night sweats, unexplained weight loss, and fever >100.4 °F), and/or elevated lactic acid dehydrogenase (LDH) and uric acid serum levels. Lymphomas that have indolent presentations present with slow-growing lymphadenopathy, splenomegaly, hepatomegaly, or cytopenias. Extranodal sites include the GI tract, skin, and bone. Rarely, kidney, bladder, adrenal glands, heart, lungs, breast, testes, and thyroid may be affected too.

NHL is known to be associated with autoimmune diseases including Sjögren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus. Both viral and bacterial infections are also associated with several lymphomas. *Helicobacter pylori* infection has been associated with most gastric mucosa–associated lymphoid tissue (MALT) lymphoma, human T-cell leukemia/lymphoma virus with adult T-cell lymphoma, EBV with Burkitt lymphoma (see below) and nasal NK-T-cell lymphoma, *Chlamydia psittaci* and ocular adenexal lymphomas, *Borrelia burgdorferi* and *Chlamydia psittacosis* with marginal zone lymphomas, and hepatitis C with splenic or large-cell lymphomas.

Diagnosis is made with an excisional biopsy of an involved lymph node or tumor in another organ, although cutting-needle biopsy may be acceptable. Following the diagnosis, patients are staged through a careful history and clinical examination, and imaging with a combined positron emission tomography–computed tomography (PET-CT). A bone marrow biopsy is usually performed to identify bone marrow involvement in indolent lymphomas (e.g., follicular lymphoma). Currently, there are a variety of systems for predicting prognosis and making a treatment recommendation. The first of these systems was the International Prognostic Index (IPI; panel 2) which was developed for aggressive B-cell and T-cell lymphomas, but is predictive in fundamentally all other types of NHL.[150]

NHL is a radiosensitive tumor; thus, radiotherapy is used for all subtypes and stages. Patients with indolent lymphoma may be cured with radiotherapy; for those with aggressive disease, radiotherapy is used after or to consolidate chemotherapy and for palliative treatment. The optimal radiation dose in indolent and aggressive lymphoma remains unclear. Adults with NHL who were treated either with standard high-dose (HD) radiation (40–45 Gy in both indolent and aggressive NHL) or low-dose (LD) radiation (24 Gy in indolent NHL or 30 Gy in aggressive NHL) experienced the same efficacy with both radiation schemes. While safety was not statistically significantly reduced with the lower radiation dose, the lower dose might influence long-term outcomes positively. Chemotherapy of NHL differs between indolent or aggressive lymphoma. Additionally, the IPI influences the therapy option (such as watch and wait, chemotherapy, radiotherapy, or combined modality treatment). Treatment with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) improves overall survival, is associated with reduced toxicity, and is the mainstay of the treatment of aggressive and indolent NHL.

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 40% of all NHL cases. Trials have demonstrated that the addition of a monoclonal antibody such as rituximab to CHOP (CHOP-R; typically administered every 3 weeks) is associated with increased overall survival. Recent studies have shown that doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone, and rituximab (ACVBP-R) are superior to CHOP-R in young patients with DLBCL (3-year progression-free survival of 87% compared to 73%). In addition, infusional chemotherapy regimens including etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R) might be superior to CHOP-R. The FDA approved the use of CAR T-cell therapy for patients with relapsed or refractory DLBCL, high-grade B-cell lymphoma, and DLBCL that arises from follicular lymphoma.[151,152]

Double-hit lymphomas are at the interface between DLBCL and Burkitt lymphoma, although some diffuse large B-cell lymphomas fit into this category. They show mutations of both *MYC* and either *BCL6* or *BCL2*. These are typically seen in lymphoma patients that respond poorly to standard chemotherapy regimens, present with a lower incidence of complete remission, and frequently progress despite treatment. Patients often undergo autologous hemopoietic stem cell transplants when they are in complete remission, with controversial results. In general, patients who do not respond to an autologous transplant may occasionally benefit from an allogeneic hemopoietic stem cell transplant.

Follicular lymphoma (FL) accounts for 25% of all NHL and follows an indolent course, so patients are usually in advanced stages at diagnosis. For such patients, CHOP-R is standard therapy. Patients with indolent B-cell NHL also receive chemotherapy. In patients with advanced-stage indolent B-cell NHL and FL grade 3B, there is currently no standard therapy, but CHOP-R shows promising results as well. There is no evidence that HD radiation therapy improves overall survival in newly diagnosed or relapsed FL patients, but its prolongation of progression-free survival favors its use. For patients with relapsed FL, autologous and allogeneic haemopoietic stem cell transplantation may be curative. Several new treatment approaches are available for patients with relapsed FL, such as idelisilib and ibrutinib, lenalidomide, venetoclax, PD-1 or PDL-1 inhibitors.[153]

Cutaneous T-cell lymphomas (CTCL) are a clinically and histologically distinct group of T-lymphocyte malignancies that manifest primarily in the skin. They represent about 13% of all NHL. Mycosis fungoides and Sézary syndrome are the most prevalent subtypes of CTCL, which remains incurable by conventional therapies. Although initial response rates on mono- or poly-chemotherapeutic regimens are high, remissions are often short-lived and the prolongation of lifespan is questionable. Furthermore, there are considerable toxicities associated with these regimens. Therefore, therapies focus on the effect of allogeneic stem cell transplantation as the only potential cure and alternative to conventional therapy for advanced primary cutaneous T-cell lymphoma.[154]

Oral Considerations

Primary NHL of the oral region is rare and may present as a gingival or mucosal tissue swelling or mass. NHL may also manifest intrabony involvement characterized by osseous rarefaction around the roots of symptomatic teeth, mimicking toothache. In such a case, extraction of the associated tooth is followed by rapid growth of the tumor from the nonhealing extraction site. Nerve invasion can lead to paresthesia or anesthesia of related oral mucosal tissue. NHL may also present as a nonhealing mucosal ulceration with ill-defined borders, a benign-appearing gingival lesion, and a mucosal lesion resembling a vesiculobullous disease. Involvement of the oral mucosa in cutaneous T-cell lymphoma (mycosis fungoides) is uncommon and is usually associated with a poor prognosis.

Hodgkin Lymphoma

Hodgkin lymphoma (HL) is rare (0.5% of all cancers) and typically occurs in adolescents and young adults. In 2019, 8110 new cases of HL were expected. HL has a bimodal age distribution, between 15 and 30 years and in patients older than 55 years.[123] The incidence has been on the rise in industrialized countries. Two types of HL exist: classic HL and the rare nodular lymphocyte predominant HL (NLPHL). The classic type is then subdivided into nodular sclerosis (the most common), mixed-cellularity, lymphocyte-depleted, and lymphocyte-rich HL.[155]

The lymphocyte-depleted HL and mixed cellularity are more common in patients of lower socioeconomic status and are often associated with EBV, while the nodular sclerosis HL has been associated with a high standard of living. Risk factors for HL include immunodeficiency, solid organ or stem cell transplantation, and use of immunosuppressive drugs. Histologically, HL has Reed–Sternberg cells (multinucleated cells surrounded by inflammatory cells). Immunophenotyping helps with differentiating between classic HL and NLPHL. In the classic form the Reed–Sternberg cells typically express CD15 and CD30 and lack expression of B-cell markers, CD19, CD20, and CD79b, although infrequently B-cell antigens can be seen on a subset of cells.[155]

Children with HL may present with lymphadenopathy (cervical, supraclavicular, axillary, or, rarely, inguinal), fatigue, anorexia, weight loss, and mediastinal mass (observed in 75% of cases on a chest radiograph).[156] Pediatric patients usually receive chemotherapy with or without radiotherapy. Regimens include ABVE-PC (doxorubicin, bleomycin, vinblastine, etoposide-prednisone cyclophosphamide) or OEPA

(vincristine, etoposide, prednisone, doxorubicin) with COPDAC (cyclophosphamide, vincristine, prednisone, and dacarbazine) in intermediate/high-risk HL patients. When used, radiotherapy is administered at 15-25 Gy.[157]

HL patients are staged using the Ann Arbor staging system with Cotswold modification. More recently, the Lugano classification incorporated the use of fluorodeoxyglucose (FDG) PET-CT for staging (Table 17-11). HL is highly curable, and treatment depends on age and the severity of the disease. Patients with early-stage disease (stages I–II) are treated with combined modality strategies utilizing abbreviated courses of combination chemotherapy followed by involved-field radiation therapy (IFRT). For advanced stages (stages III–IV), ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) is the most widely used regimen in the United States, and escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) is used commonly in Europe, with improved progression-free survival when compared to ABVD, but with increased toxicity, including infection and infertility. Radiation therapy may be used for specific patients as consolidation. Stanford V (doxorubicin [Adriamycin], mechlorethamine [nitrogen mustard], vincristine, vinblastine, bleomycin, etoposide, prednisone) is another regimen available for advanced stages. Patients with a second relapse or progressive disease are candidates for high-dose chemotherapy and autologous hematopoietic cell transplantation. For patients who fail high doses of chemotherapy with autologous hematopoietic cell transplantation, brentuximab vedotin, an anti-CD-30 antibody conjugated to an antimicrotubule drug, is recommended. In 2016, the FDA approved nivolumab for the treatment of classical HL in patients who have relapsed or progressed after an auto transplant and brentuximab vedotin and pembrolizumab for refractory classic HL, or HL patients who have failed at least three prior treatments.[158,159]

Table 17-11 Lugano classification for staging of lymphomas.

Stage I—Involvement of a single lymph node region (e.g., cervical, axillary, inguinal, mediastinal) or lymphoid structure such as the spleen, thymus, or Waldeyer's ring.
Stage II—Involvement of two or more lymph node regions or lymph node structures on the same side of the diaphragm. Hilar nodes should be considered to be "lateralized" and, when involved on both sides, constitute stage II disease. For the purpose of defining the number of anatomic regions, all nodal disease within the mediastinum is considered to be a single lymph node region, and hilar involvement constitutes an additional site of involvement. The number of anatomic regions should be indicated by a subscript (e.g., II-3).
Stage III—Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. This may be subdivided stage III-1 or III-2: stage III-1 is used for patients with involvement of the spleen or splenic hilar, celiac, or portal nodes; and stage III-2 is used for patients with involvement of the paraaortic, iliac, inguinal, or mesenteric nodes.
Stage IV—Diffuse or disseminated involvement of one or more extranodal organs or tissue beyond that designated E, with or without associated lymph node involvement.
All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms of significant unexplained fever, night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.
The designation "E" refers to extranodal contiguous extension (i.e., proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. More extensive extranodal disease is designated stage IV.
Bulky disease—a single nodal mass, in contrast to multiple smaller nodes, of 10 cm or ≥⅓ of the transthoracic diameter at any level of thoracic vertebrae as determined by CT; record the longest measurement by CT scan. The term "X" (used in the Ann Arbor staging system) is no longer necessary.
The subscript "RS" is used to designate the stage at the time of relapse.
Patients can be clinically or pathologically staged. Splenectomy, liver biopsy, lymph node biopsy, and/or bone marrow biopsy are mandatory for the establishment of pathologic stage. The pathologic stage at a given site is denoted by a subscript (e.g., M = bone marrow, H = liver, L = lung, O = bone, P = pleura, and D = skin).

Source: Adapted from UpToDate, December 2019.

Oral Health Considerations

The radiation fields for HL that involve bilateral cervical nodes have the potential to result in damage to the salivary glands. These include (1) involved-field RT when lymphoma involves the oral structures or Waldeyer's ring; (2) mantle; and (3) mini or modified mantle. Of these, the mantle field is the largest and involves radiation therapy to all supradiaphragmatic lymph node regions, including the following groups: bilateral cervical, supraclavicular, bilateral axillae, mediastinal, and bilateral lung hilar, treated contiguously. Mini or modified mantle typically refers to radiation therapy covering bilateral cervical, supraclavicular, and axillary lymph nodes. Because the parotid glands are usually not in the field of radiation, the risk of radiation-induced caries is minimal; however, topical fluoride varnish, gel, or 5000 ppm fluoride toothpaste can be used for caries prevention if the patient's mouth appears to be dry or the caries rate appears elevated. The risk of osteoradionecrosis is very low due to low radiation doses delivered and is limited to the inferior border and angle of the mandible. HL survivors who received mediastinal radiation 10–20 years earlier may develop late-onset heart disease characterized by heart valve pathology and accelerated atherosclerosis.

Burkitt Lymphoma

Early in the twentieth century, Sir Albert Cook, a missionary physician in Uganda, and other medical staff working in west, east, and central Africa noted the high frequency of

jaw tumors and childhood lymphomas. Years later, Denis Burkitt, a surgeon working in Africa, further described these jaw swellings, which have come to be known as Burkitt lymphoma (BL). Burkitt lymphoma is an aggressive B-cell NHL that manifests with fast-growing masses and/or a leukemia that can have substantial clinical and morphologic overlap with ALL/LBL.[160] A large majority of BL is characterized by the translocation involving chromosome 8 and/or MYC rearrangement, but in the 2016 World Health Organization revision, a Burkitt-like lymphoma with an alternative 11q aberration was included as a provisional entity. Three variants exist: endemic (African), sporadic (nonendemic), and immunodeficiency associated.[161]

Endemic BL is present in New Guinea and equatorial Africa with an incidence 50 times higher than in the United States, with 3–6 cases per 100,000 children each year. The sporadic form is observed in Western European countries and in the United States, representing 30% of all pediatric lymphomas and less than 1% of adult NHL in the United States. Most patients are males and Caucasian. The immunodeficiency-associated variant is linked with patients affected by HIV (usually those with a CD4 count >200 cells/μL). Chronic EBV infection is associated with virtually all cases of endemic BL and a few sporadic and immunodeficiency-associated BLs. The expression of the proto-oncogene MYC (located on chromosome 8q24) that encodes the MYC protein transcription factor plays a role in the development of BL. This transcription factor is responsible for modulation of the expression of target genes that regulate many cellular processes (such as cell growth and division, immortalization, Warburg metabolism, and apoptosis).

Patients present with fast-growing masses and demonstrate tumor lysis with different clinical manifestations depending on the BL form. Patient with endemic (African) BL usually have a facial bone or jaw tumor, which can spread to other sites such as breast, kidney, mesentery, ovary, testis, and meninges. The bone marrow is involved in 10% of cases at initial diagnosis, but becomes a frequent complication of refractory BL cases or recurrent BL. Other oral manifestations include tooth mobility and pain, intraoral swelling of the mandible and maxilla, and anterior open bite. Mobile teeth may be present even in the absence of clinically detectable jaw tumors. Radiographic features on panoramic images include resorption of alveolar bone; loss of lamina dura; enlargement of tooth follicles; destruction of the cortex around tooth crypts; displacement of teeth and tooth buds by the enlarging tumor, resulting in the impression of "teeth floating in air"; and sun-ray spicules as bone forms perpendicular to the mandible from subperiosteal growth.

The sporadic variant affects the abdomen with ascites and involvement of the stomach, cecum and/or mesentery, distal ileum, kidney, breast, testis, ovary, bone marrow, or CNS (15% of cases). Patients may report symptoms similar to those in acute appendicitis or intussusception. The bone marrow is involved in 30% of cases, while the jaw or facial bones are involved in 25% of patients with localized lymphadenopathy. Patients affected by immunodeficiency-related BL usually present with signs or symptoms associated with the immunodeficiency (e.g., immunodeficiency secondary to hematopoietic or solid organ transplantation, AIDS). The bone marrow, CNS, and lymph nodes are often involved.

A diagnosis of BL is made with a biopsy of the tissue involved (e.g., abdominal mass or other extranodal site), along with flow cytometry, chromosome analysis using Giemsa banding or FISH, and immunostains. The disease is staged according to a blood smear, CSF, bone marrow biopsy, and presence/absence of HIV infection. Histopathology consists of intermediate-sized B cells (12 μ) with high nuclear-to-cytoplasmic ratio. Nuclear contours are round to oval without cleaves or folds, a key feature in the distinction from diffuse large-cell lymphoma. Nucleoli are typically multiple, small to intermediate in size, and the nuclear chromatin is relatively immature, being finely granular. The characteristic starry sky is due to scattered tingible body–laden macrophages that contain apoptotic tumor cells. BL cells express surface IgM and B cell-lineage antigens (CD19, CD20, CD22, CD79a), as well as CD10, HLA-DR, and CD43, but the cells are generally negative for Bcl-2, CD5, and TdT.[162]

BL is aggressive, and once a diagnosis is made there is some urgency for an intensive chemotherapy regimen. Treatment can be divided into three broad group of patients. Patients with a localized tumor that was completely removed with a surgical procedure may be started on a short course of chemotherapy (<2 months). Commonly used drugs are cyclophosphamide, vincristine, prednisone, and doxorubicin. A regimen with dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and regular- or double-dose rituximab (DA-EPOCH-R or -RR) is less toxic than standard BL drugs. Patients with a mass that cannot be surgically removed and does not involve the CNS, or more than 25% of the bone marrow, received chemotherapy for 4 months with the same agents used for the first group, with the addition of high-dose methotrexate and low-dose cytarabine. Rituximab is often included in the treatment and has been shown to improve the outcome for patients with a high LDH serum level. Several doses of chemotherapy into the spinal fluid are also administered as part of the treatment. Patients with CNS involvement, or at least 25% of bone marrow involvement, receive 6 months of chemotherapy with the addition of high-dose cytarabine and rituximab. Children with refractory or relapsed BL are difficult to treat successfully and should be encouraged to participate in clinical trials. Alternative agents are available for these patients and include ifosfamide, carboplatin, and etoposide

and rituximab followed by high-dose chemotherapy and either auto or all HSCT. New monoclonal antibodies (ofatumumab, blinatumomab, inotuzumab ozogamicin) and targeted agents against c-MYC may be effective for treatment of BL and are under investigation.[163–165]

Myelodysplastic Syndrome

The myelodysplastic syndromes (MDS) are a group of malignant hematopoietic stem cell disorders characterized by dysplastic and ineffective blood cell production and a variable risk of transformation to AML. Patients typically present with chronic cytopenia and are at risk of bleeding, infection, and symptomatic anemia.[166]

The incidence rate of MDS is approximately 4.9 per 100,000 people each year.[123] Most patients found to have MDS are older than 60 years with a male predominance; however, some children and young adults may develop MDS in the context of congenital mutations that lead to bone marrow failure syndromes or inherited predisposition to myeloid tumors. The pathogenesis of MDS remains unclear and involves the stepwise process of oncogenic mutations that may arise de novo or after exposure to environmental toxins (e.g., benzene), radiation, or certain chemotherapeutic agents (e.g., alkylating agents). Some cases have been linked to inherited genetic conditions (e.g., ataxia telangiectasia, Bloom syndrome, Fanconi anemia, trisomy 21) and other benign hematologic disorders (e.g., congenital neutropenia, paroxysmal and nocturnal hemoglobinuria). The most frequently mutated genes are *ASXL1*, *TP53*, *DNMT3A*, *TET2*, *RUNX1*, and genes that are components of the 3' RNA splicing machinery (e.g., *SF3B1*, *U2AF1*, *SRSF2*, and *ZRSR2*).[167] Some studies showed that a few cases of MDS respond to immunosuppressive therapy, suggesting that defects in the immune system may trigger myelosuppression and/or marrow hypocellularity, especially in younger patients.

Clinically, patients present with nonspecific signs and symptoms. Most patients are asymptomatic, and a diagnosis is made after incidental findings during a routine blood count. Others may report fatigue, weakness, dizziness, angina, or infections (secondary to neutropenia and granulocyte dysfunction).

Diagnosis is made through an evaluation of the bone marrow and peripheral blood smear, after careful clinical assessment, to document the requisite morphologic dysplastic cytologic changes of all hematopoietic cells. Blast forms account for <20% of the total nucleated cells of the bone marrow aspirate and peripheral smear. Minimal diagnostic criteria for MDS include (1) stable cytopenia; and (2) the exclusion of other potential diseases as a primary reason for dysplasia or cytopenia or both. In addition, the diagnosis requires ≥1 of 3 MDS-related decisive criteria: (1) dysplasia (≥10% in ≥1 of the three major bone marrow lineages); (2) a blast cell count of 5-%–9%; and (3) a specific MDS-associated karyotype, such as del(5q), del(20q), +8, or -7/del(7q).[168,169]

Management of MDS ranges from supportive care with transfusions or hematopoietic growth factors and administration of low-intensity cytarabine, to intensive chemotherapy. Three FDA agents approved for treatment of specific subtypes of MDS include azacytidine and decitabine for higher-risk patients or those with nonresponsive disease, and lenalidomide for patients with del(5q) cytogenetic abnormalities.[170] Although allogeneic HSCT is the only potentially curative therapy for MDS, mortality post transplantation is high, due to disease relapse and to transplant-related complications. Several prognostic models have been proposed to identify those patients at risk for relapse. Current prognostic models include patient-related factors, the disease, and molecular characteristics. *TP53* mutations were found to be the best predictor of survival after HSCT in patients with MDS, independent of age, Karnofsky performance-status score, and hematologic variables.

Multiple Myeloma

Plasma cell myeloma is a clonal plasma cell neoplasm that may present as a single lesion (solitary plasmacytoma) or multiple lesions (multiple myeloma or MM). This clone of plasma cells proliferates in the bone marrow and often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or fractures.[171] MM represents 1.8% of all cancers in the United States, with a median age at diagnosis of 69 years. There were 32,110 estimated new cases in 2019, with a higher incidence in African Americans.[123]

Almost all MM cases are preceded by a premalignant plasma cell proliferative disorder known as monoclonal gammopathy of undetermined significance (MGUS). In MGUS, clonal cells are usually not detectable in bone marrow biopsies. Patients present with low levels of monoclonal protein present in serum (IgG <3 g/dL; IgA <1 g/dL) and serum monoclonal protein remain stable over long periods of time. These patients have no clinical manifestations of the disease and require careful observation. Long-term follow-up studies of patients with MGUS showed malignant transformation to MM at an annual rate of 1%–1.5%. In some patients, an intermediate asymptomatic but more advanced premalignant stage (smoldering multiple myeloma or SMM) can be recognized clinically. SMM is defined by the presence of a serum monoclonal protein (IgG or IgA) ≥3 g/dL and/or 10%–60% clonal bone marrow plasma cells, with no evidence of end-organ damage.[172]

MM is characterized by a plasma cell dyscrasia producing monoclonal immunoglobulins. This proliferation often results in extensive skeletal destruction (e.g., osteolytic lesions, hypercalcemia, anemia) and the excess production of monoclonal protein can result in renal failure, hyperviscosity syndrome, recurrent bacterial infections, and hematopoietic and immune dysfunction.[171] Risk factors for MM include chronic exposure to low-dose ionizing radiation, occupational exposure (e.g., chemical), genetic factors, and chronic antigenic stimulation (e.g., recurrent infections and drug allergies). Chromosome translocations involving the IgH locus and hyperdiploidy, with multiple trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21, are considered primary events in MM patients, while del(17p) and amp(1q21) develop during disease progression. Hyperdiploidy is seen in approximately half of patients with MM and is associated with better progression-free survival and overall survival. Primary early chromosomal translocations occur at the immunoglobulin switch region on chromosome 14 (q32.33), which is most commonly juxtaposed to MAF (t[14;16] [q32.33;23]) and MMSET on chromosome 4p16.3. This process results in the deregulation of two adjacent genes, *MMSET* in all cases and *FGFR3* in 30% of cases. Secondary late-onset translocations and gene mutations that are implicated in disease progression include complex karyotypic abnormalities in *MYC*, the activation of *NRAS* and *KRAS*, mutations in *FGFR3* and *TP53*, and the inactivation of cyclin-dependent kinase inhibitors CDKN2A and CDKN2C. Other genetic abnormalities involve epigenetic dysregulation, such as alteration in microRNA expression and gene methylation modifications. Gene expression profiling allows for classification and risk classification of multiple myeloma.[173]

Most patients with MM present with signs and symptoms secondary to plasma cell infiltration into the bone or other organs, or to renal damage from excess light chains.[173] Two-thirds of patients develop anemia, 60% bone pain, 50% elevated creatinine, fatigue/generalized weakness in 30%, hypercalcemia in 28%, and weight loss in 24% of patients. Extramedullary plasmacytomas (EMP) are seen in approximately 7% of patients with MM at the time of diagnosis and are best diagnosed by PET/CT scan. EMP accounts for <1% of all head and neck malignancies, with the oral cavity being the rarest site affected. Oral EMPs may resemble other gingival nodules, with various signs and symptoms including spontaneous bleeding, pain, and paresthesia. Radiographic changes in patients with MM include typical "punched-out" lesions in the skull from the focal proliferation of plasma cells inside the bone marrow and jaw bone (mandible > maxilla) involvement, ranging from asymptomatic osteolytic lesions to pathologic fracture.

The initial diagnostic workup of patients with suspected MM includes whole-body low-dose CT or FDG-PET/CT skeletal survey, serum protein electrophoresis along with immunofixation, and a serum-free light chain assay. A 24-hour urine collection for electrophoresis and immunofixation is recommended if a diagnosis of MM is made. Further evaluation includes a bone marrow aspiration and biopsy, imaging, a CBC with differential, and a chemistry screen. The International Myeloma Working Group (IMWG) Updated Criteria for the Diagnosis of Multiple Myeloma require the presence of ≥10% clonal bone marrow plasma cells or biopsy-proven bony or EMP, plus one or more myeloma-defining events: (1) ≥ CRAB feature (CRAB: **C**alcium [hypercalcemia], **R**enal failure, **A**nemia, and **B**one lesions) or ≥ SLiM feature (SLiM: ≥**S**ixty percent [≥60%] clonal bone marrow plasma cells; serum-free **Li**ght chain ratio involved:uninvolved ≥100; >1 focal lesion (≥5 mm each) detected by **M**RI studies).[174,175]

Following diagnosis and risk stratification, patients undergo an evaluation to assess eligibility for autologous hematopoietic cell transplantation. Transplant patients receive induction therapy with a triplet regimen for 3–4 months prior to stem cell collection. Patients ineligible for HCT receive 8–12 cycles of novel agent-based three-drug regimens followed by maintenance therapy until progression unless there are significant adverse events. Though allo-HSCT showed good long-term disease control for certain MM patients, there were only some benefits from this approach because of significant transplant mortality rate and high relapse rates. Lenalidomide remains the preferred maintenance agent for both transplant-eligible and transplant-ineligible individuals. Management of focal bone lytic lesions may require radiation therapy, surgery, and use of analgesics. In cases of hypercalcemia, bisphosphonates, denosumab, and/or calcitonin are recommended to reduce calcium levels.[172]

Newer therapeutic agents including second-generation proteasome inhibitors (e.g., carfilzomib), third-generation immunomodulators (e.g., pomalidomide), monoclonal antibodies, and checkpoint inhibitors are emerging as promising and are currently under investigation.

Oral Health Considerations

Medication-related osteonecrosis of the jaw (MRONJ) is a serious complication of long-term intravenous antiresorptive therapy (e.g., bisphosphonate, denosumab). Another consideration for MM patients requiring invasive dental procedures is the risk of hemorrhage. Patients with MM and other disorders associated with high-titer serum paraproteins can manifest unique hemostatic disorders, predisposing the patient to hemorrhage, especially following surgical procedures. Predental surgical assessments should include radiographic

assessment for plasma cell tumors of the jaw and CBC and coagulation studies. Prevention of hemorrhage should be managed by consultation with the patient's hematologist regarding the status of treatment of the underlying disease and, depending on clinical circumstances, the need for additional therapies that might include plasmapheresis with appropriate factor replacement, desmopressin acetate (Stimate), fibrinolysis inhibitors ε-aminocaproic acid (Amicar) and tranexamic acid (Cyclokapron), and splenectomy.

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18

Bleeding and Clotting Disorders

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Oral healthcare professionals are increasingly called upon to provide care to individuals whose bleeding and clotting mechanisms have been altered by acquired or inherited mechanisms. This engagement in care of the coagulopathy patient provides an opportunity for the dentist trained in the recognition of oral and systemic signs of altered hemostasis to assist in the screening and monitoring of the underlying condition.

Inherited coagulopathies, such as the hemophilias and von Willebrand disease (VWD), may be mild to severe in clinical presentation, are present life-long, are often diagnosed in infancy, and are predictable based on the hereditary pedigree. If it is not diagnosed in childhood, exposure to the first surgical procedure, which is often the removal of third molars, may reveal the underlying inherited bleeding disorder. Acquired coagulation disorders can result from drug actions or side effects of underlying systemic disease or their treatment. Over the past few decades, there have been expanding options for therapeutic anticoagulation for the prevention and management of thromboembolic disease. In addition to heparins and vitamin K antagonists (VKAs; e.g., warfarin), anticoagulants targeting enzymatic activity of

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

thrombin and factor Xa (F Xa), often referred to as novel oral anticoagulants (NOACs) or direct oral anticoagulants (DOACs), have been developed and have become widely used. In addition to anticoagulants, antiplatelet therapy has become ubiquitous for the prevention of stroke or thromboembolic cardiac events (e.g., post coronary artery stenting, post myocardial infarction).

Moreover, systemic disease involving the liver and kidney, inherited or acquired platelet disorders, and myelosuppressive chemotherapy or treatment of hematologic malignancy add to the burden of altered hemostasis. Patients with liver disease may have impaired hemostasis due to thrombocytopenia and/or lack of coagulation factors, whereas renal failure may result in qualitative disorders in platelet function. Patients with hematologic malignancies may have thrombocytopenia as a result of overgrowth of malignant cells in the bone marrow that leaves no room for platelet precursors (megakaryocytes). In addition, cancer patients may have thrombocytopenia as a result of the cytotoxic effects of chemotherapeutic agents to treat their disease.

Invasive dental procedures resulting in bleeding can have serious consequences for the patient with a bleeding disorder, including severe hemorrhage or even death. Safe dental care may require consultation with the patient's medical provider, institution of systemic management, and dental treatment modifications.

EPIDEMIOLOGY

The World Health Organization's Global Burden of Disease (WHO-GBD) study indicates that diseases requiring medication to manage premature clotting are on the rise. By 2017, among all diseases, ischemic heart disease and stroke had risen to number 1 and 3 for leading causes of early death and number of years lived with disability at all ages.[1] In many countries, today the use of DOACs has surpassed the use of traditional VKAs.[2]

VWD is reported as the most common inherited coagulopathy, with a prevalence, including the multiple types and subtypes, of up to 1% of the population.[3] Hemophilia A (F VIII deficiency) is the most common congenitally missing coagulation factor deficiency, with a prevalence in the United States of 1:6500 live male births.[4] Hemophilia B or Christmas disease (F IX deficiency) occurs about a fifth as frequently as hemophilia A at 1:30,000 live male births.[5]

Systemic diseases that alter hemostasis are also increasing in prevalence. The American Cancer Society estimates that 1,806,590 individuals will be newly diagnosed with cancer in 2020, many being placed on myelosuppressive chemotherapy that creates thrombocytopenia; of these new cancer cases, 60,530 will be patients with leukemia who in addition may have malignancy-related thrombocytopenia.[6] Using WHO-GBD data, epidemiologists note that the rise of hepatitis C infection and other causes have increased cases of liver cirrhosis and increased years living with this disease. This places patients at risk for thrombocytopenia and coagulopathies from the inability of the liver to properly form clotting factors; liver cirrhosis accounted for 1.45 million deaths globally in 2013, a 63% increase from 0.89 million in 1990.[7] Systemic diseases with alteration of both coagulation and platelet number and/or function increase the complexity of hemostasis management during dental surgical procedures.

MECHANISMS OF HEMOSTASIS

Hemostasis is the process of blood clot formation at the site of vessel injury. Multiple processes occur in a rapid sequence that is localized and regulated. There is a careful balance between thrombin-stimulated clot formation and plasmin-induced clot lysis. Abnormal bleeding occurs when there is insufficient clot formation due to decreased thrombin (e.g., from F VIII deficiency) or increased clot lysis. Thrombosis that is nonphysiologic or functional clotting occurs when there is an excessive production of thrombin.

Hemostasis can be divided into four general phases:

- Endothelial injury and platelet plug formation—underway within 10–20 seconds of injury.
- Coagulation cascade and propagation of clotting—an initial hemostatic plug is formed in 1–3 minutes, and fibrin has been generated and added to stabilize the clot by 5–10 minutes.
- Termination of clotting by antithrombotic control mechanisms.
- Fibrinolysis and removal of the clot.

Endothelial Injury and Platelet Plug Formation

When vessel integrity is disrupted, reactants such as serotonin, histamine, prostaglandins (PGs), and other products that are vasoactive cause vasoconstriction of the microvascular bed in the area of the injury and the vessels contract. The immediate reflex vasoconstriction may alone be hemostatic in small vessels. Platelets are activated as well and adhere to the site of injury, forming a platelet plug that reduces or temporarily arrests blood loss.[8]

Endothelial injury activates endothelial cells to promote the recruitment of platelets, other cells, and procoagulant factors. This occurs in four steps (Figure 18-1).

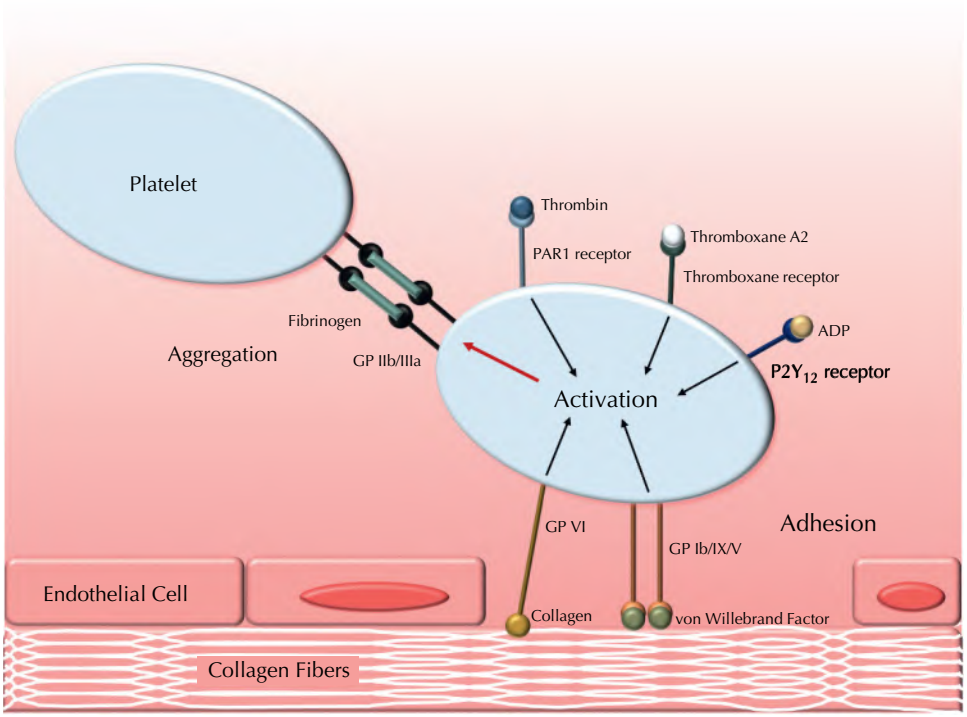

Figure 18-1 Platelet phase. Platelet adhesion occurs immediately (within 1–2 seconds) via the binding of platelet surface receptor glycoprotein (GP) Ib/IX/V complex to von Willebrand factor. Adenosine diphosphate (ADP) is a potent nucleotide that binds to receptors P2Y1 and P2Y12, activating and recruiting other platelets in the area and adding to the size of the plug. Once platelets are stimulated by thrombin, collagen, or ADP the integrin GPIIb/IIIa on platelet surfaces are activated and bind to fibrinogen, in which aggregation occurs (within 10–20 seconds). Platelets then secrete a number of other factors, including thromboxane A2, which promotes vasoconstriction and further platelet aggregation.

Step One: Adhesion

Once the endothelium is injured, subendothelial collagen, laminin, and microfibrils are exposed. Platelet stimuli include adenosine diphosphate (ADP), epinephrine, thrombin, and collagen. Platelet adhesion occurs via the binding of platelet surface receptor GPIb/IX/V complex to von Willebrand factor (VWF) in the subendothelial matrix.[9] GPIa/IIa and GPVI are important collagen receptors on the surface of platelets, involved in adhesion and activation, respectively.[10] ADP is a potent nucleotide that binds to receptors P2Y1 (which leads to calcium mobilization, platelet shape change, and aggregation) and P2Y12 (responsible for platelet secretion and stable aggregation), in effect activating and recruiting other platelets in the area and adding to the size of the plug. Platelets have two receptors for thrombin, protease-activated-receptors 1 and 4 (PAR-1 and PAR-4).[11] Platelet factor 3 is the intracellular phospholipid that activates F X and subsequently results in the conversion of prothrombin to thrombin.

Step Two: Aggregation

Once platelets are stimulated (e.g., by thrombin, collagen, or ADP), the integrin GPIIb/IIIa on platelet surfaces is activated and becomes a high-affinity fibrinogen receptor. The GPIIb/IIIa complex also binds to immobilized VWF, resulting in platelet spreading and clot retraction.

Step Three: Activation and Secretion

Platelets secrete a number of substances upon cell stimulation, including:

- ADP and serotonin—activates and recruits additional platelets.
- Fibronectin and thrombospondin—adhesive proteins that stabilize platelet aggregates.
- Fibrinogen.
- Thromboxane A2 (TXA A2)—promotes vasoconstriction and further platelet aggregation.
- Growth factors—mediate tissue repair at the site of vascular injury.

Step Four: Procoagulant Activity

This involves the exposure of procoagulant phospholipids (e.g., phosphatidylserine) and the assembly of the enzyme complexes in the coagulation cascade on the platelet surface.[12] This leads to fibrin formation and the generation of an insoluble fibrin clot that strengthens the platelet plug.[8]

The Coagulation Cascade and Propagation of Clotting

The generation of thrombin and fibrin is the end product of the coagulation phase. This process involves multiple proteins, many of which are synthesized by the liver (fibrinogen; prothrombin; F V, F VII, F IX, F X, F XI, F XII, and F XIII) and are vitamin K dependent (F II, F VII, F IX, and F X); see Table 18-1. Vitamin K is an essential cofactor for a carboxylase that catalyzes the carboxylation of glutamic acid residues on vitamin K–dependent proteins, thereby making them biologically active.

A sequence of interactions between the various clotting factors occurs following tissue injury. The scheme of reaction is a bioamplification, in which a precursor is altered to an active form, which, in turn, activates the next precursor in the sequence. The coagulation of blood requires the presence of both calcium ions and exposed phospholipid on platelet surfaces. Beginning with an undetectable biochemical reaction, the coagulation mechanism results in a final explosive change of a liquid to a gel.

Classical Coagulation Cascade Model

The traditional model of the cascade (Figure 18-2) is useful for interpreting in vitro tests of coagulation (e.g., prothrombin time [PT], international normalized ratio [INR]); however, it does not fully represent what occurs in vivo (i.e., in the body). It involves two separate pathways (intrinsic and extrinsic) that converge by activating a third (common) pathway:

- The intrinsic pathway is initiated by the exposure of blood to a negatively charged surface. F XII is activated by surface contact (e.g., with collagen or subendothelium), and it involves the interaction of F XII and F XI to an active form (F Xia). The next step, the activation of F IX to F IXa, requires a divalent cation such as calcium.[13] Once activated, F IXa forms a complex with F VIII, in a reaction that requires the presence of both calcium ions and phospholipid, which, in turn, converts F X to an activated form—F Xa.
- The extrinsic pathway is initiated by the release of tissue factor (TF), also called tissue thromboplastin, and does not require contact activation. TF binds to F VII in the presence of calcium, and this complex is capable of activating F IX and X, linking the intrinsic and extrinsic pathways.
- The common pathway begins through the activation of F X. Once activated, F Xa converts prothrombin to thrombin in a reaction similar to the activation of F X by F IXa. The activation of prothrombin by F Xa requires the presence of calcium ions and phospholipid as well as F V, a plasma protein cofactor.[14] Once formed, thrombin converts fibrinogen, a soluble plasma protein, to insoluble fibrin. Fibrin polymerizes to form a gel, stabilizing the platelet plug. Finally, F XIII, which has been converted to an activated form by thrombin,[15] produces covalent cross-links between the fibrin molecules that strengthen the clot and make it more resistant to lysis by plasmin.

In Vivo Coagulation Cascade

The current established in vivo physiologic model of clotting has three overlapping phases: initiation, amplification, and

Table 18-1 Coagulation factors.

	Coagulation Factor Affected		
Factor (Name)	**Intrinsic**	**Extrinsic**	***t*1/2 (h)**
XIII (fibrin-stabilizing factor)	*	*	336
XII (Hageman factor)	*		60
XI (plasma thromboplastin antecedent)	*		60
X (Stuart factor)	*	*	48
IX (Christmas factor)	*		18–24
VIII (antihemophilic factor)	*		8–12
VII (proconvertin)		*	4–6
V (proaccelerin)	*	*	32
IV (calcium)	*	*	—
III (tissue thromboplastin)		*	—
II (prothrombin)	*	*	72
I (fibrinogen)	*	*	96

*t*1/2, half-life.

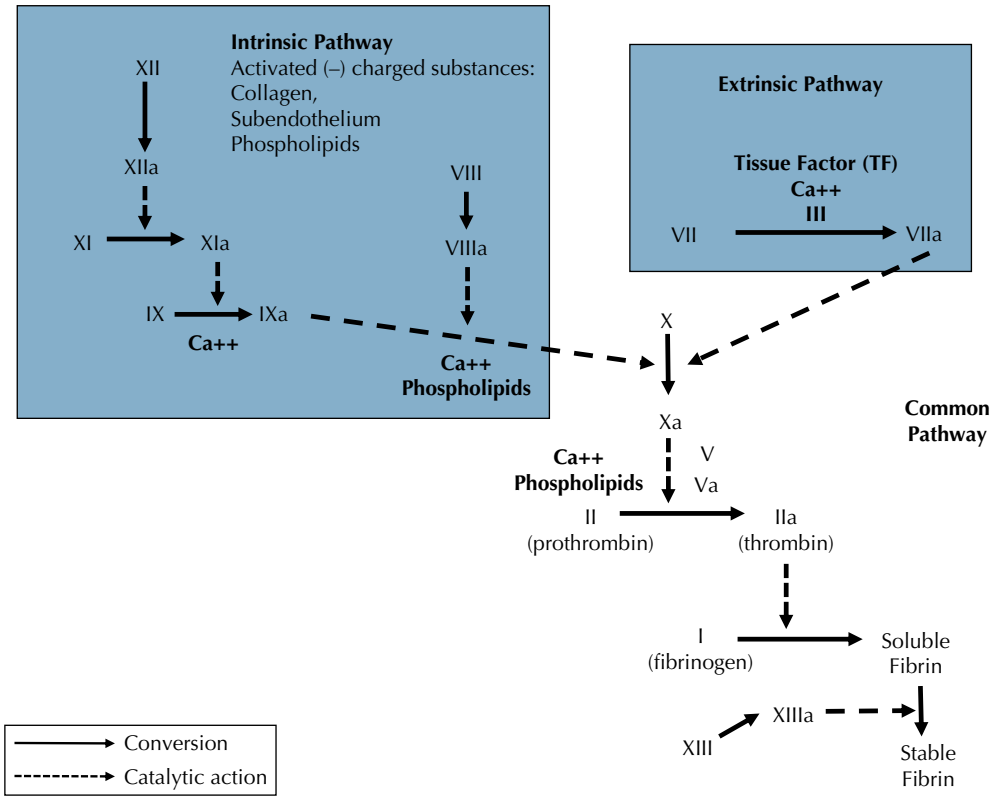

Figure 18-2 Classical in vitro coagulation cascade.

propagation (Figure 18-3). The activations and reactions of clotting factors occur on cell surfaces (e.g., activated platelets, endothelial cells) and a number of different cells (e.g., monocytes, fibroblasts). Standard laboratory clotting tests, which detect initial fibrin clot formation, primarily measure the initiation and not the propagation phase of clotting.

- The primary initiation event in clotting is the generation or exposure of TF at the wound site, on TF-bearing cells, and its interaction with and activation of F VII with the aid of F IXa.[16,17] This TF–F VIIa complex activates F X, which gives rise to a small amount of thrombin (minor).
- The amplification phase occurs on the surface of platelets. In addition to activating platelets, the small amount of thrombin also activates F V, F VIII, and F XI, which participate in generating large amounts of thrombin (major).[18]
- In the propagation phase, procoagulant complexes are assembled on platelet membrane surfaces in the presence of calcium. An extrinsic tenase (X-ase) complex consists of F Va and TF, and activates F X and F IX. An intrinsic X-ase complex consists of F IXa and F VIIIa, and activates F X. The F Xa generated from either X-ases binds with F Va to form the prothrombase on the surface of the platelet, which then generates a large amount of thrombin through the conversion from prothrombin (F II) to thrombin (F IIa). This ultimately leads to the conversion of fibrinogen to fibrin.[18] In addition, thrombin activates F XIII (fibrin-stabilizing factor), which cross-links the monomeric fibrin to stabilize the clot.

Termination

Coagulation is modulated by several mechanisms: dilution of procoagulants in flowing blood, removal of activated factors through the reticuloendothelial system by the liver, and control of the activated procoagulants and platelets by natural antithrombotic pathways, mostly on vascular endothelial cells.

The inhibitors of the coagulation pathways are:

- Tissue factor pathway—tissue factor pathway inhibitor (TFPI) inhibits factor X activation in two ways: by directly inhibiting F Xa and by inhibiting the extrinsic X-ase complex by complexing with factor Xa.
- Contact activation pathway—C1 esterase inhibitor (C1-inh).

The regulation of the terminating phase of coagulation involves:

- Antithrombin (AT)—a circulating plasma protease inhibitor, which neutralizes most of the enzymes (i.e., thrombin, F Xa, F IXa, F XIIa).
- Protein C pathway (Figure 18-4)—protein C is activated by thrombin after it binds to thrombomodulin during the

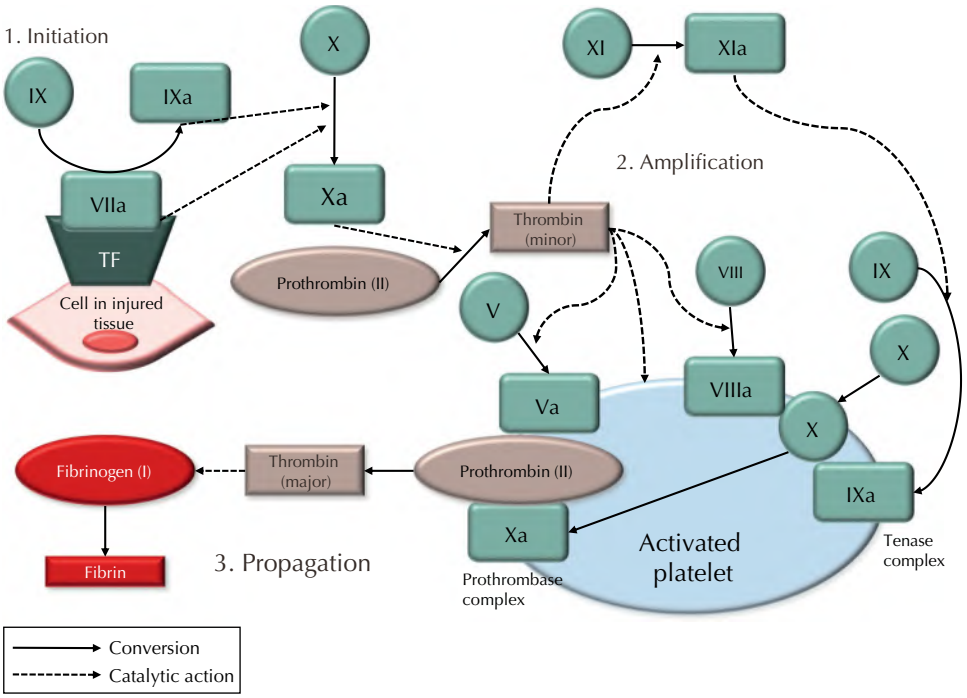

Figure 18-3 In vivo coagulation cascade. TF complexes with factor VIIa (F VIIa) at the site of tissue injury. Activation of F X produces small amounts of thrombin, which in turn activate platelets and F V and VII (F VIII), which assemble on the surface of platelets to form prothrombinase and tenase complexes, respectively. The tenase complex activates F X, which forms on the prothrombinase complex that converts prothrombin to thrombin, which then converts fibrinogen to fibrin for the stable clot.

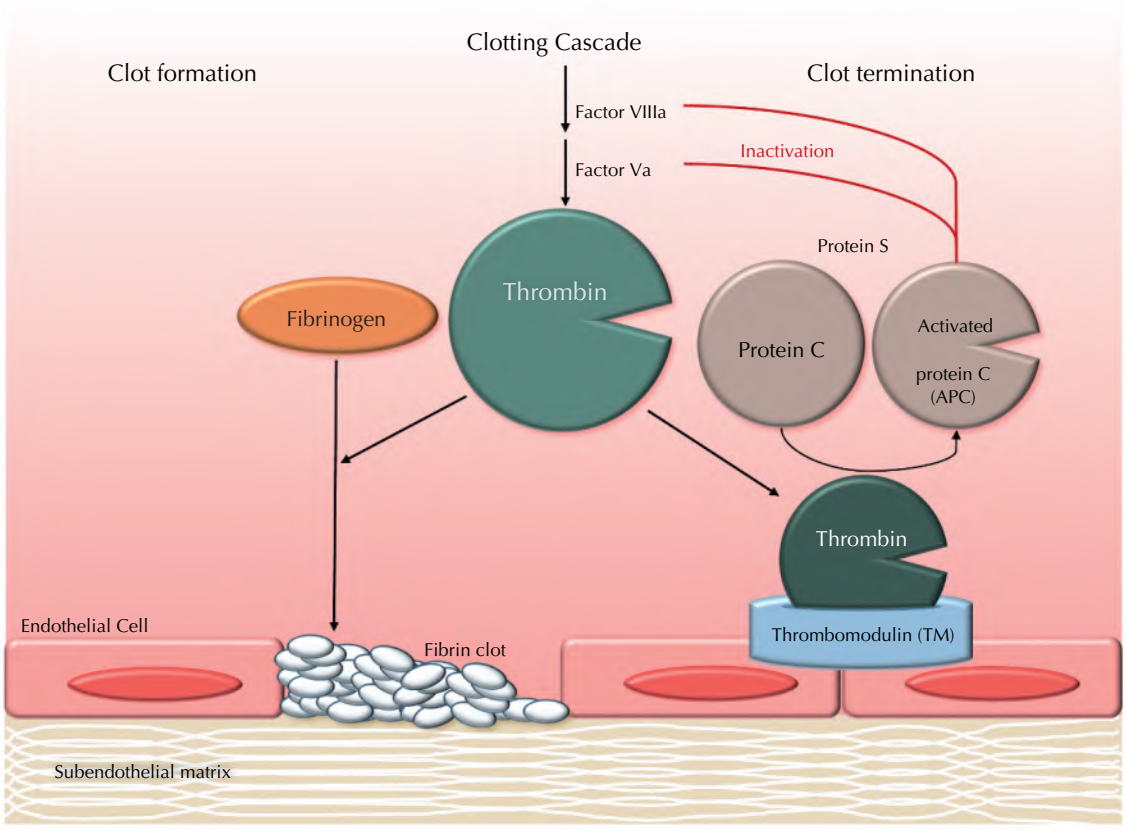

Figure 18-4 Termination of clotting.

process of clot formation, to form the protein C anticoagulant complex. Activated protein C, in association with protein S on phospholipid surfaces, inactivates F Va and F VIIIa, effectively inactivating the prothrombinase and intrinsic X-ase complex, respectively.[19]

Fibrinolysis

Fibrinolysis is considered the major means of disposing of fibrin after its hemostatic function has been fulfilled (Figure 18-5). This is critical to the process of wound healing, in order to restore vessel patency, and for tissue remodeling. Tissue plasminogen activator (tPA) is released from the endothelial cells and converts plasminogen to plasmin, which degrades fibrinogen and fibrin into fibrin degradation products (FDPs). tPA is a proteolytic enzyme that is nonspecific and also degrades F VIII and F V. Urokinase is also a plasminogen activator that is responsible for extravascular fibrinolysis. Kallikrein, which is an intrinsic activator of plasminogen, is generated when prekallikrein is bound to kininogen, thereby becoming a substrate for F XIIa. Activation of the fibrinolytic system can be turned off by inhibition of plasmin activity by α_2-antiplasmin, or inhibition of plasminogen activators by plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2).[20,21]

GENERAL WORKUP OF PATIENTS WITH SUSPECTED BLEEDING OR CLOTTING DISORDER

Patient History and Clinical Features

Patient evaluation starts with a routine medical history, via a thorough questionnaire and interview. As part of the overall query, patients should be asked about any history of previous unusual bleeding episodes after surgery or injury, easy or frequent bruising, or spontaneous bleeding (Figure 18-6). Specifically, patients should be asked about prolonged bleeding after invasive dental procedures, spontaneous bleeding from the gingivae, and history of nasal bleeding. They should also be asked about a family history of bleeding disorders. For the purpose of history-taking, a clinically significant bleeding episode has been defined as follows:[22]

- Continues beyond 12 hours.
- Requires patient to call or return to treating dentist, or seek emergency care with a medical provider.
- Results in development of hematoma or ecchymosis in soft tissues.
- Requires blood product support.

A complete list of medications is essential, to include over-the-counter products, prescription drugs, and supplements, as they can have implications for hemostasis. A social history that determines alcohol consumption and illicit drug use is also essential.

A number of clinical features can be seen in patients with bleeding disorders:

- *Petechiae*. Petechiae are small, flat, red, discrete areas of skin bleeding that are typically <2 mm in diameter, nonblanching, and nonpalpable. Although typically occurring in lower extremities, sacral area, and areas of skin fragility, they can also occur in the oral cavity, especially with severe thrombocytopenia.
- *Bruise/ecchymosis*. A bruise (also called ecchymosis) is caused by subcutaneous/submucosal accumulation of

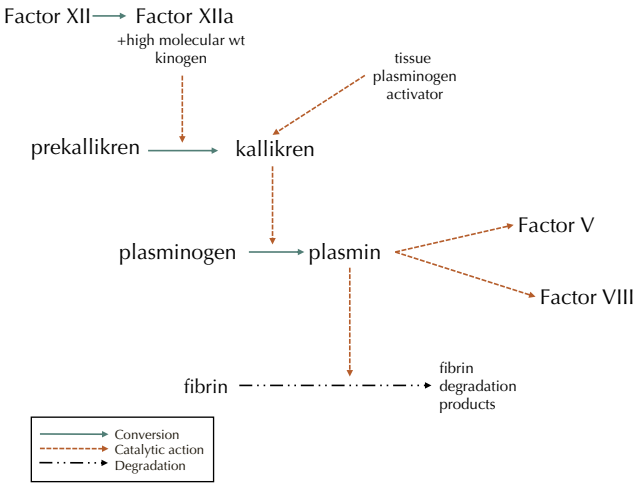

Figure 18-5 The fibrinolytic system.

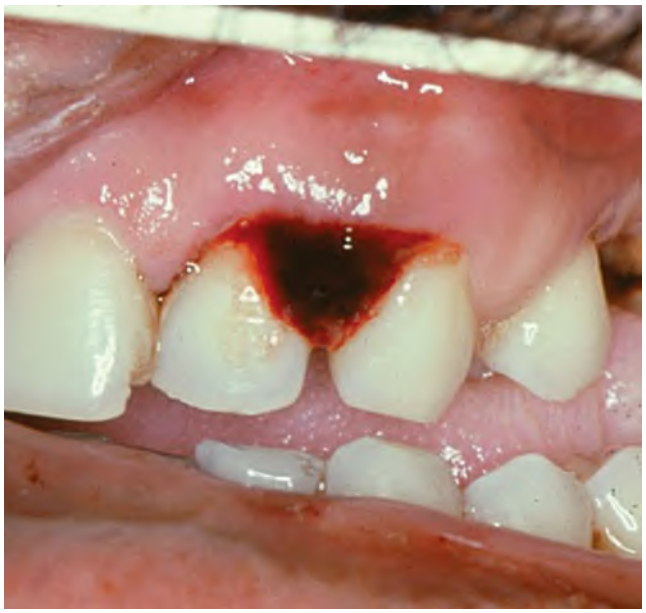

Figure 18-6 Spontaneous gingival bleeding between the upper left lateral incisor and canine and labial petechiae in a 38-year-old white male with idiopathic thrombocytopenic purpura.

extravasated blood (Figure 18-7). The color can range from purplish blue to reddish brown to greenish yellow, indicative of breakdown of hemoglobin to biliverdin and bilirubin.

- *Hematoma*. A hematoma is a collection of blood in the extravascular space. A subcutaneous hematoma may raise the skin profile. Hematomas in deep tissues (e.g., muscle, retroperitoneal) may be suspected due to pain, a drop in hemoglobin level, or a fluid collection on imaging studies. Hematomas and hemarthroses are typical of coagulation factor deficiencies.

Features to look for in the general examination of a patient include multiple ecchymoses of the skin, bleeding wounds, hematomas, and swollen joints. Clinical manifestations of bleeding disorders can involve various systems, depending on the extent and type of disorder (Table 18-2). Individuals with mild disease may present with no clinical signs, whereas individuals with severe coagulopathies may have definite stigmata. When skin and mucosa are involved, individuals may present with petechiae, ecchymoses, spider angiomas, hematomas, or jaundice. Deep dissecting hematomas and hemarthroses of major joints may affect severe hemophiliacs and result in disability or death. Disorders of platelet quantity may result in hepatosplenomegaly, spontaneous gingival bleeding, and risk of hemorrhagic stroke. Specific clinical manifestations will be discussed in detail for the various conditions. Intraorally, petechiae, ecchymoses, hematomas, or excessive gingival bleeding should be of concern to the dentist.

Laboratory Studies

When a bleeding disorder is suspected, laboratory studies should be initiated prior to an invasive procedure. There are a variety of laboratory tests that help identify a deficiency of required elements or dysfunction of the phases of coagulation (Tables 18-3 and 18-4). To evaluate primary hemostasis involving platelets, there are platelet count and

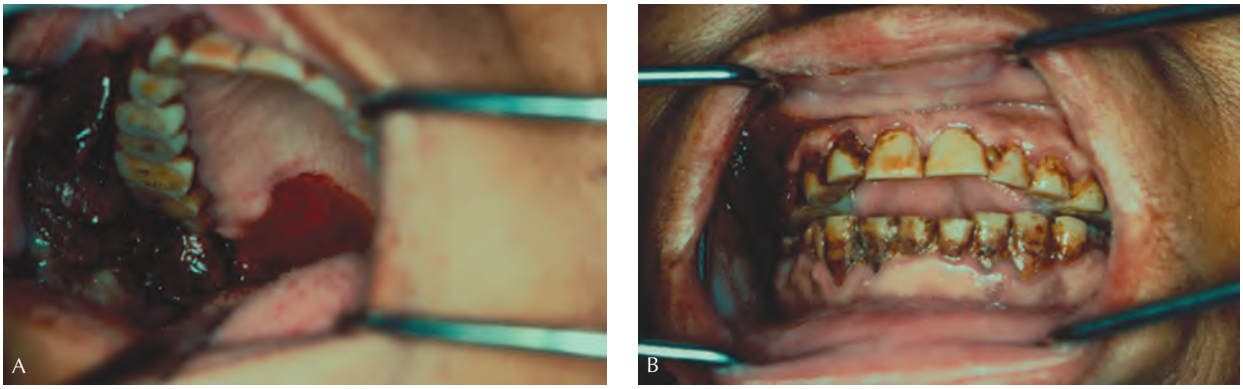

Figure 18-7 A 68-year-old woman with acute myelogenous leukemia and a platelet count of 9000/mm^3. Platelet transfusions and e-aminocaproic acid oral rinses were used to control bleeding. (A) Buccal mucosa and palatal ecchymoses. (B) Extrinsic stains on teeth from erythrocyte degradation following continual gingival bleeding.

Table 18-2 Clinical features of bleeding disorders.

Feature	Vascular or Platelet Disorders	Coagulation Disorders
Bleeding from superficial cuts and scratches	Persistent, often perfuse	Minimal
Delayed bleeding	Rare	Common
Spontaneous gingival bleeding	Characteristic	Rare
Petechiae	Characteristic	Rare
Ecchymoses	Characteristic, usually small and multiple	Characteristic, usually large and solitary
Epistaxis	Common	Common
Deep dissecting hematomas	Rare	Characteristic
Hematoma and hemarthrosis	Rare	Characteristic

Table 18-3 Laboratory tests for assessing hemostasis.

Test	Normal Range
Platelet count	150,000–450,000/mm^3
Bleeding time	<7 min (by simplate); 1–6 min (modified Ivy's test)
PFA-100 closure time	CT-EPI < 164 s; CT-ADP < 116 s
PT/INR	Control ± 1 s (e.g., PT: 11–13 s / INR 1.0)
Activated partial thromboplastin time (aPTT)	Comparable to control (e.g., 15–35 s)
Thrombin time (TT)	Control ± 3 s (e.g., 9–13 s)
Fibrin degradation products (FDPs)	<10 μg/dL
Fibrinogen assay	200–400 mg/dL
von Willebrand antigen	60–150% vWF activity
Coagulation factor assays (e.g., F VIII assay)	60–100% F VIII activity
Coagulation factor inhibitor assays (e.g., Bethesda inhibitor assay for F VIII)	0.0 Bethesda inhibitor units

CT-ADP, closure time with collagen and adenosine diphosphate membrane; CT-EPI, closure time with collagen and epinephrine membrane; F, factor; INR, international normalized ratio; PT, prothrombin time; vWF, von Willebrand factor

Table 18-4 Laboratory test results for select disorders.

	Screening Laboratory Tests			
Bleeding Disorder	Platelet Count	PT/INR	aPTT	BT
Thrombocytopenia Leukemia Liver disease	↓	N	N	↑
F VIII, IX, XI deficiency Heparin anticoagulation Thrombin inhibitor anticoagulation	N	N	↑	N
F II, V, X deficiency Vitamin K deficiency Intestinal malabsorption	N	↑	↑	N
F VII deficiency Coumarin anticoagulation F Xa inhibitor anticoagulation Liver disease	N	↑	N	N
von Willebrand disease	N, ↓	N	N, ↑	↑
DIC Severe liver disease	↓	↑	↑	↑
F XIII deficiency	N	N	N	N
Vascular wall defect	N	N	N	↑

aPTT, activated partial thromboplastin time; BT, bleeding time; DIC, disseminated intravascular coagulation; INR, international normalized ratio; N, normal; PT, prothrombin time; ↑ = increased; ↓ = decreased.

platelet function tests (e.g., bleeding time [BT]) and other assays (e.g., platelet function analyzer [PFA-100]). Tests to evaluate the status of coagulation function include PT/INR, activated partial thromboplastin time (aPTT), thrombin time (TT), FDPs, specific coagulation factor assays (e.g., F VII, F VIII, F IX, fibrinogen), and coagulation factor inhibitor screening tests (blocking antibodies).

Initial tests for patients with a suspected bleeding disorder include a complete blood count (CBC) with platelet count, PT/INR, and aPTT. Subsequent testing can be performed based on initial clinical and laboratory findings or the suspected underlying condition.

Platelet Count

Platelet counts are obtained as part of a standard CBC. Normal values are 150,000–450,000/mm^3. Spontaneous hemorrhage is usually not observed with platelet counts above 10,000–20,000/mm^3. Many hospitals have established a critical value of 10,000/mm^3 platelets, below which platelets are transfused to prevent serious bleeding sequelae, such as hemorrhagic stroke; however, such thresholds are dependent upon the anticipated risk of bleeding based on the procedure. Surgical or traumatic hemorrhage may be more likely with severely reduced platelet counts.

Tests of Platelet Function

The Platelet Function Analyzer (PFA-100) measures the time it takes for blood flow to stop under shear stress in a capillary tube that has a membrane lined with collagen and epinephrine, or collagen and ADP, and then exposed to shear stress, which is deemed the closure time (CT).[23] This test was found to be more sensitive to aspirin-induced platelet dysfunction and VWD, and was more rapid and less expensive than the BT.[24] However, because it is a global test system and also sensitive to low hematocrit, low platelet counts, and platelet dysfunction (both congenital and acquired), it is neither specific for, nor predictive of, any particular disorder (inclusive of VWD), therefore it is recommended that a CBC be performed along with this test.[25] It is also insensitive to other therapeutic antiplatelet agents such as clopidogrel, ticlopidine, and cyclooxygenase-2 (COX-2) inhibitors.[26,27] Though one clinical trial reported the use of the PFA-100 CT as a screening tool for oral surgery patients on antiplatelet therapy,[28] the role of the PFA-100 CT in routine therapeutic monitoring of platelet function for dental procedures remains to be established.

For assessing the response to clopidogrel, a US Food and Drug Administration (FDA)-approved test for assessing P2Y-12-mediated platelet function is called the "Plavix Response" or the "VerifyNow P2Y-12 assay." This uses anticoagulated whole blood for turbidometric detection of platelet aggregation in which activated platelets bind to nearby platelets via fibrinogen-coated beads in the assay.

Bleeding Time

The BT test was previously used as a screening test for platelet function. It is thought to identify qualitative or functional platelet defects. The modified Ivy test involves a standardized incision on a forearm distal to a blood pressure cuff inflated to 30 mm Hg. The wound is blotted with filter paper and monitored until absorption of blood on the paper ceases. Normal range is between 1 and 6 minutes and is considered significantly prolonged when greater than 15 minutes. However, because of the technique's sensitivity, it lacks specificity. The skin BT test has been shown to be a poor indicator of clinically significant bleeding at other sites, including oral postoperative bleeding after oral surgical procedures, and its use as a predictive screening test has been discouraged.[29,30]

Prothrombin Time and International Normalized Ratio

The PT and INR tests measure the time it takes for blood to clot by forming thrombin. They evaluate the extrinsic and common coagulation pathways, screening for the presence or absence of fibrinogen (F I), prothrombin (F II), and F V, F VII, and F X. The normal range of PT is approximately 11–13 seconds. Because of individual laboratory reagent variability and the desire to be able to reliably compare the PT from one laboratory with that from another, the PT test is commonly reported with the INR.[31,32] The INR, introduced by the World Health Organization in 1983, is the ratio of PT that adjusts for the sensitivity of the thromboplastin reagents, such that a normal coagulation profile is reported as an INR of 1.0, and higher values indicate abnormal coagulation.[33] Its most common use is to measure the effects of VKAs and reduction of the vitamin K–dependent F II, F VII, F IX, and F X. It is not effective for hemophilias A and B, since it does not measure F VIII or F IX. Although most patients on VKAs are monitored by monthly venous blood draws and laboratory analysis, the CoaguChek system allows Clinical Laboratory Improvements Amendments (CLIA)-waived point-of-care PT/INR testing of fingerstick blood in physicians' and dentists' offices.[34]

Activated Partial Thromboplastin Time

Also among the standard initial tests that measure clotting via thrombin formation, aPTT is used to evaluate the intrinsic coagulation pathway, and screen for deficiencies in F VIII, F IX, F XI, and F XII, in addition to prekallikrein and high molecular weight kiningen. It is performed by calcifying plasma in the presence of a thromboplastic material (i.e., phospholipid tablet) and a contact activator that is a negatively charged substance (e.g., kaolin) in the absence of TF. It is considered normal if the control aPTT and the test aPTT are within 10 seconds of each other. Control aPTT times are usually 15–35 seconds. Normal ranges depend on the manufacturer's limits, as each supplier varies slightly. As a screening test, the aPTT is prolonged only when the factor levels in the intrinsic and common pathways are less than approximately 30%. It is altered in hemophilias A and B and with the use of the anticoagulant heparin, which may result in clinical bleeding problems. However, elevated aPTT due to deficiencies in F X II, prekallikrein, and high molecular weight kiningen do not correlate with clinical bleeding.

Thrombin Time

TT measures the final step in the clotting cascade, the cleavage of fibrinogen to fibrin. It specifically tests the ability to form the initial fibrin clot from fibrinogen, by adding thrombin to plasma. Its normal range is 9–13 seconds, with values in excess of 16–18 seconds considered to be prolonged. It is used to measure the activity of thrombin inhibitor anticoagulants (e.g., heparin, dabigatran), FDPs, or other paraproteins that inhibit the conversion of fibrinogen to fibrin. Fibrinogen can also be specifically assayed and should be present at a level of 200–400 mg/dL.

Fibrin Degradation Products

Disorders of fibrinolysis (clot breakdown) often show delayed bleeding. FDPs are measured using a specific latex agglutination system to evaluate the presence of the D-dimer of fibrinogen and/or fibrin above normal levels. Such presence indicates that intravascular lysis has taken place or is occurring. This state can result from primary fibrinolytic disorders or disseminated intravascular coagulation (DIC).

Specific Clotting Factor Assays

Specific activity levels of factors are measured if one or more of the screening tests are abnormal, in order to further identify factor deficiencies and their level of severity. Normal factor activity is usually in the 60%–150% range. Coagulation factor inhibitor tests, often referred to as the Bethesda titer assay, measured in units, are essential when sufficient factor concentrate to correct the factor deficiency under normal conditions fails to control bleeding. To identify the specific type of VWD (types I–III and platelet type), additional studies, such as ristocetin cofactor, ristocetin-induced platelet aggregation studies, and monomer studies, are helpful. These are discussed in more detail later in this chapter.

Tests of Capillary Fragility

The tourniquet test for capillary fragility is useful for identifying platelet disorders and is the only test to demonstrate abnormal results in vessel wall disorders. A moderate degree of stasis is produced by a tourniquet or by inflating a blood pressure cuff around the arm in the usual manner to a pressure halfway between systolic and diastolic levels, and maintained for 5–10 minutes. At 2 minutes following tourniquet or cuff deflation and removal, a 2.5 cm diameter region (size of a quarter) of skin on the volar surface of the arm at 4 cm distal to the antecubital fossa is observed for petechial hemorrhages. This petechial display is called the Rumpel–Leede phenomenon; normally the petechiae count does not exceed 5 in men and 10 in women and children, and is considered abnormal at more than 10–20.

BLOOD VESSEL DISORDERS

Vessel wall disorders can be due to structural malformation of vessels and inherited or acquired disorders of connective tissue. They can result in hemorrhagic features, though bleeding is usually mild and confined to the skin, mucosa, and gingiva. Vascular purpura can result from damage to capillary endothelium, from abnormalities in the vascular subendothelial matrix or extravascular connective tissue bed, or from abnormal vessel formation.

Scurvy

Scurvy results from a dietary deficiency of water-soluble vitamin C, when dietary vitamin C falls below 10 mg/d. Vitamin C is necessary for the synthesis of hydroxyproline, an essential constituent of collagen. The US Recommended Daily Allowance of vitamin C is 90 mg daily for men and 75 mg daily for women. Scurvy is found primarily in regions of urban poverty, among either infants on nonsupplemented processed milk formulas, the elderly who cook for themselves, adults with alcohol or drug dependencies, children with special needs and underlying medical conditions such as sickle cell anemia or thalassemia with iron overload from multiple transfusions, neurologic conditions, and a history of chemotherapy or aversion to vitamin C–rich foods, or the intellectually disabled.[35,36,37,38] Many of the hemorrhagic features of scurvy result from defects in collagen synthesis. Among the first clinical signs are petechial hemorrhages, corkscrew hair at the hair follicles, and purpura on the back of the lower extremities that coalesce to form ecchymoses. Hemorrhage can occur in the muscles, joints, nail beds, and gingival tissues. Severe vitamin C deficiency is considered a systemic risk factor for periodontitis, as it compromises antioxidant micronutrient defenses to oxidative stress and adversely influences collagen synthesis, resulting in weakened capillary blood vessel walls and enhanced gingival bleeding.[39] Gingival involvement may include swelling, friability, bleeding, secondary infection, and loosening of teeth. Implementation of a diet rich in vitamin C and administration of 1 g/d of vitamin C supplements provides rapid resolution.

Cushing's Syndrome

Cushing's syndrome, resulting from excessive exogenous or endogenous corticosteroid intake or production, leads to general protein wasting and atrophy of supporting connective tissue around blood vessels. Patients may show skin bleeding or easy bruising. Aging causes similar perivascular connective tissue atrophy and lack of skin mobility. Tears in small blood vessels can result in irregularly shaped purpuric areas on arms and hands, called purpura senilis. Other metabolic or inflammatory disorders resulting in purpura include Schönlein–Henoch or anaphylactoid purpura, hyperglobulinemic purpura, Waldenström's macroglobulinemia, multiple myeloma, amyloidosis, and cryoglobulinemia.

Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome (EDS) is an autosomal dominant or autosomal recessive inherited disorder of connective tissue matrix, generally resulting in fragile skin blood vessels and easy bruising. It is characterized by hyperelasticity of the skin and hypermobile joints. Thirteen types have been identified with unique biochemical defects and varying clinical features, and were sorted using a pathogenetic scheme into the 2017 International Classification:[40,41]

- Classic EDS (former type I) presents with soft, velvety, hyperextensible skin; easy bruising and scarring; hypermobile joints; varicose veins; and prematurity.[42]
- Periodontal EDS (former Type VIII), which was mapped to chromosome 12q13,[43] has skin findings similar to those in classic EDS, with easy bruising following minor trauma due mainly to the resulting fragility of the oral mucosa and blood vessels, and is characterized by early-onset periodontal disease with severe loss of alveolar bone and permanent dentition.[44]
- Children with arthrochalasia EDS (former type VII) may present with microdontia and collagen-related dentinal structural defects in primary teeth, in addition to bleeding after tooth brushing.[45]
- Patients with vascular EDS (former type IV) may have a characteristic facial appearance, gingival recession, and gingival fragility.
- Those with spondylodysplastic EDS (former progeroid type) may have characteristic facial features and tooth discoloration or dysplastic teeth.

Other oral findings include fragility of the oral mucosa, gingiva, and teeth, as well as hypermobility of the temporomandibular joint (TMJ) and stunted teeth and pulp stones on dental radiographs.[46] Oral health may be severely compromised as a result of specific alterations of collagen in orofacial structures. A number of tissue responses (mucosa, periodontium, pulp) and precautions (e.g., prevention of TMJ dislocation) should be considered when planning dental treatment.[47]

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), also called Rendu–Osler–Weber syndrome, is a group of autosomal dominant disorders with abnormal telangiectatic capillaries, frequent episodes of nasal and gastrointestinal (GI) bleeding, and associated brain and pulmonary lesions.[48,49,50] The Scientific Advisory Board of the HHT Foundation International's consensus clinical diagnostic criteria, known as the Curaçao criteria, requires the presence of at least three of the four following criteria:[51]

- Spontaneous and recurrent epistaxis.
- Multiple telangiectasia at characteristic sites (lips, oral cavity, nose, fingers).
- Visceral arteriovenous malformations.
- First-degree relative with HHT history.

Perioral and intraoral angiomatous nodules or telangiectases are common with progressive disease, involving areas of the lips, tongue, and palate that may bleed upon manipulation during dental procedures.[52] Small nonpulsating visceral arteriovenous malformations may blanch in response to applied pressure, unlike petechiae or ecchymoses. Mucocutaneous lesions may bleed profusely with minor trauma, or on occasion spontaneously.[53] Persistently bleeding oral lesions may be treated with cryotherapy, laser ablation, electrocoagulation, or antifibrinolytics.[54] Submucosal and intravenous (IV) bevacizumab, a humanized recombinant monoclonal antibody to the angiogenic vascular endothelial growth factor that is elevated in HHT, has recently shown promise in treatment of epistaxis in HHT.[55] It has also been suggested that antibiotic prophylaxis should be considered before dental care to reduce the occurrence of cerebral abscesses for patients with HHT and concomitant pulmonary arteriovenous malformation.[56]

PLATELET DISORDERS

Congenital Platelet Disorders

Congenital abnormalities of platelet function or production are rare and the causes are quite diverse. Causes range from defects in receptors critical to platelet adhesion and aggregation, to defects in signaling molecules, or in transcription factors important for the production of functional platelets. Conditions may present with large, small, or normal-sized platelets and be associated with other diseases or clinical features (Table 18-5).[57]

Bernard–Soulier Syndrome

Bernard–Soulier syndrome, a hemorrhagioparous thrombocytic dystrophy, is a rare autosomal recessive disorder that results from an identified absence of the platelet membrane GPIb-IX-V complex from the platelet membranes, rendering the platelets unable to interact with VWF.[58,59] Features include epistaxis as the most common clinical sign, giant platelets, decreased platelet count, and increased bleeding time. The main treatment modality for Bernard–Soulier syndrome is supportive measures combined with specific treatment of bleeding episodes, typically with human leukocyte antigen (HLA)-matched platelet transfusions.[58]

Glanzmann's Thrombasthenia

Glanzmann's thrombasthenia is a qualitative disorder characterized by mucocutaneous bleeding due to mutations in the *ITGA2B* and *ITGB3* genes encoding the integrin αIIbβ3.[60] As a result, platelet membrane GPIIb/IIIa cannot bind to fibrinogen and cannot aggregate with other platelets, although platelet count is not altered. Clinical signs include bruising, epistaxis, gingival hemorrhage, and menorrhagia. Rarely, Glanzmann's thrombasthenia may be acquired in association with pregnancy, autoimmune conditions (e.g., systemic lupus erythematosus [SLE], immune thrombocytopenia), and therapeutic GPIIb/III antagonists (e.g., abciximab, eptifibatide). Treatment of oral surgical bleeding involves platelet transfusion, antifibrinolytics, recombinant factor (rF) VIIa, and local hemostatic agents, alone or in combination.[61] Treatment of bleeding episodes in the patient with Glanzmann's thrombasthenia is usually not warranted unless hemorrhage is life-threatening.

Wiskott–Aldrich Syndrome

Wiskott–Aldrich syndrome is a rare X-linked recessive disease, with ill-defined pathophysiology, characterized by mild to severe presentation of cutaneous eczema (usually beginning on the face), bleeding from thrombocytopenic purpura, and propensity to infection due to an immunologic defect.[62] It is a quantitative and qualitative platelet disorder. Oral manifestations include gingival bleeding and palatal petechiae. Thrombocytopenia of Wiskott–Aldrich syndrome may be managed with platelet transfusions, antifibrinolytic drugs, splenectomy (with risk of increased infections), or allogeneic hematopoietic stem cell transplantation, with hope of gene therapeutic approaches available in the future.[62]

Table 18-5 Classification of platelet disorders. *Source:* Based on Sharma R, Perez Botero J, Jobe SM. Congenital disorders of platelet function and number. *Pediatr Clin North Am*. 2018;65(3):561–578.

	Thrombocytopenic—quantitative platelet deficiency	Nonthrombocytopenic—qualitative or functional platelet defect	
		Decreased platelet activity	Increased platelet activity
Congenital			
May–Hegglin anomaly	X		
Wiskott–Aldrich syndrome	X	X	
Gray platelet syndrome	X		
Neonatal alloimmune thrombocytopenia	X		
Glanzmann's thrombasthenia		X	
Platelet-type von Willebrand disease		X	
Bernard–Soulier syndrome		X	
Sticky platelet syndrome			X
Acquired			
Primary immune thrombocytopenia	X		
Thrombotic thrombocytopenic purpura	X		
Leukemia	X		
Aplastic anemia	X		
Myelodysplasia	X		
Systemic lupus erythematosus	X		
Disseminated intravascular coagulation	X		
Drug induced—cancer chemotherapy	X	X	
Drug induced—therapeutic antiplatelet agents: ASA, NSAIDs, clopidogrel, ticlopidine, dipyridamole, cilostazol, abciximab, epitifibatide, tirofiban		X	
Penicillin, cephalosporins			
Cardiopulmonary bypass	X	X	
Renal disease		X	
Alcohol dependency	X	X	
Liver disease	X	X	
Diabetes			X
Dysproteinemia (i.e., myeloma, myeloproliferative disorders, macroglobulinemia)		X	
Acquired platelet-type von Willebrand disease		X	

NSAIDs, nonsteroidal anti-inflammatory drugs.

May–Hegglin Anomaly

May–Hegglin anomaly, one of the now four autosomal dominant MYH9-related inherited thombocytopenias (along with Sebastian, Fechtner, and Epstein syndromes), is a rare hereditary condition characterized by the triad of thrombocytopenia, giant platelets, and inclusion bodies in leukocytes.[63] Clinical symptoms include mild bleeding, and possible kidney dysfunction, deafness, and cataracts later in life.

Acquired Platelet Disorders—Systemic

An outline of acquired platelet disorders is found in Table 18-5.

Primary Immune Thrombocytopenia

Primary immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura [ITP] or immune

thrombocytopenic purpura) is caused by autoantibodies against platelet antigens.

In reviews from the United States, prevalence was approximately 9.5 per 100,000 persons, with 8 per 100,000 in children, 12 per 100,000 in adults, and an overall female to male ratio of 1.9:1.[64,65]

ITP is assumed to be caused by accelerated antibody-mediated platelet consumption. While genetic factors are considered for the onset of ITP, some cases have inciting events, either infections and/or systemic conditions that disrupt immune function.

Viral infections are the most common infectious cause. Human immunodeficiency virus (HIV), hepatitis C virus (HCV), cytomegalovirus (CMV), and varicella zoster virus have been implicated. It has been proposed that antibodies against viral antigens may cross-react with normal platelet antigens.[66,67,68] Bacterial infection is a less common trigger, with proposed mechanisms including lipopolysaccharide attachment to platelet surfaces and increased platelet phagocytosis, molecular mimicry via antibodies, immune alterations, and activities of bacterial products.[69,70] Immune-mediated thrombocytopenia may occur in conjunction with HIV disease in approximately 15% of adults, being more common with advanced clinical disease and immune suppression, although less than 0.5% of patients have severe thrombocytopenia with platelet counts below 50,000/mm^3.[71]

In autoimmune disorders, the development of autoantibodies occurs, as seen in antiphospholipid syndrome (APS), SLE, Evans syndrome, hematopoietic cell transplantation, chronic lymphocytic leukemia (CLL), and other low-grade lymphoproliferative disorders.[72,73] Antibody production in ITP is driven by CD4-positive helper T cells reacting to platelet surface glycoproteins, with splenic macrophages being the major antigen-presenting cells.[74,75] Autoimmune thrombocytopenia is found in patients with SLE, with mild thrombocytopenia (platelet counts between 100,000 and 150,000/mm^3) noted in 25%–50% of patients and severe thrombocytopenia (platelet counts <50,000/mm^3) in 10% of patients.[76] Severe bleeding from ITP due to SLE is only experienced by a minority of patients; however, when it occurs it requires aggressive treatment.[77]

Many patients with ITP are asymptomatic and overall risk of bleeding is low. Symptomatic patients can have fatigue and reduced quality of life. Bleeding may occur in up to two-thirds of patients. Clinical symptoms include petechiae and purpura over the chest, neck, and limbs, usually more severe on the lower extremities. Mucosal bleeding may occur in the oral cavity and GI and genitourinary tracts. In severe cases of ITP, oral hematomas and hemorrhagic bullae may be the presenting clinical sign (Figure 18-6).[78]

There is a lack of sensitive or specific diagnostic tests for ITP and other causes of thrombocytopenia, therefore posing a challenge, relying on a diagnosis of exclusion. Primary diagnostic investigations in patients with suspected ITP should include CBC with differential, peripheral blood smear, and HIV and HCV testing. Secondary tests may include PT, aPTT, *Helicobacter pylori* testing, antinuclear antibody, and vitamin B_{12} and folate levels. By consensus, the criteria for ITP is a platelet count of <100,000/mm^3, with greatest concern for bleeding with platelet counts <20,000/ mm^3.[79] Large platelets are often noted on the peripheral blood smear; however, their absence does not exclude the diagnosis. ITP is not accompanied by abnormal numbers or morphology of red and white blood cells, or abnormal coagulation parameters. If any of these are seen, then other conditions should be considered (e.g., infection, leukemia, thrombotic thrombocytopenic purpura [TTP], and DIC).

The goal of ITP therapy is to reduce the risk of clinically significant bleeding. Active interventions are guided by clinical symptoms and the platelet count. The objectives during treatment are to provide a safe, rather than normalized, platelet count.[80]

For ITP patients with severe bleeding, treatment is immediate platelet transfusion along with IV immunoglobulin (IVIg) and high-dose corticosteroids. For a new diagnosis of ITP and a platelet count <20,000/mm^3, IVIg and corticosteroids are also indicated to prevent thrombocytopenia from persisting and worsening. Target platelet counts are between 20,000 and 30,000/mm^3, except in the case of those with a history of bleeding at higher counts, other hemostatic defects, those requiring surgery, or at increased risk of bleeding in general (e.g., peptic ulcer, high activity, high risk of falls).

Splenectomy may be necessary in chronic ITP to prevent antiplatelet antibody production and sequestration and removal of antibody-labeled platelets.[81]

ITP may be acute and self-limiting (2–6 weeks) in children. In adults, ITP is typically more indolent in its onset, and the course is persistent, often lasting many years, and may be characterized by recurrent exacerbations of disease. The natural history and long-term prognosis of adults with chronic ITP remain incompletely defined.[82]

Platelet count thresholds for surgery are higher than those to prevent spontaneous bleeding. While there are no published guidelines for oral and maxillofacial surgery, 50,000/mm^3 has been the recommended threshold for most major surgery, and as high as 100,000/mm^3 for neurosurgery or ocular surgery[83] with lower values (i.e., 20,000/mm^3) acceptable for less invasive procedures such as central line placement. A recent systematic review failed to find evidence to support this 50,000/mm^3 threshold for the safety of invasive dental procedures in thrombocytopenic patients.[84]

Thrombotic Thrombocytopenic Purpura

TTP is a rare acute disease that, until recently, was uniformly fatal. It can be hereditary or acquired due to an autoantibody inhibitor. Incidence of acquired TTP is 3 cases per million adults per year, and 1 per 10 million per year in children.[85] It is a thrombotic microangiopathy caused by severely reduced activity of the VWF-cleaving protease ADAMTS13. Small-vessel platelet-rich thrombi form that cause thrombocytopenia, microangiopathic hemolytic anemia, and sometimes organ damage. Causes include metastatic malignancy, pregnancy, mitomycin C, and high-dose chemotherapy. If untreated, it carries a high mortality rate.

Initial presentation may include fatigue, dyspnea, petechiae, or other bleeding. In addition to thrombocytopenia, clinical presentation of TTP includes GI symptoms, weakness, and neurologic findings ranging from coma, stroke, and seizure to headache and confusion. Microangiopathic hemolytic anemia, fluctuating neurologic abnormalities, renal dysfunction, and occasional fever also can occur. Microvascular infarcts due to the thrombi occur in gingival and other mucosal tissues and are present in about 60% of cases. Serial studies of plasma samples from patients during episodes of TTP have often shown VWF multimer abnormalities.[86]

Although there are numerous therapeutic options, there is no consensus among experts or clear algorithms to treat TTP. Plasma exchange therapy combined with acetylsalicyclic acid (ASA)/dipyridamole or corticosteroids have recently lowered the mortality rate for patients with TTP over that previously obtained by treatment with fresh frozen plasma (FFP) infusions.[87,88] In addition, there is a role for newer therapies with diverse mechanisms of action, such as rituximab, anti-D, and thrombopoietin-like agents.[89]

Liver Disease

Patients with liver disease may have a wide spectrum of hemostatic defects, depending upon the extent of liver damage, which affect both the platelet and coagulation phases of hemostasis.[90] These changes increase the risks of both bleeding and thrombosis.

Liver disease, both chronic and acute, results in both quantitative and qualitative platelet defects. Chronic liver disease with cirrhosis leads to thrombocytopenia due to portal hypertension, and sequestration and breakdown of platelets by the spleen, in addition to decreased thrombopoietin production. Thrombocytopenia in acute hepatitis is hypothesized to be linked to systemic inflammatory response syndrome and resultant multiorgan system failure.[91] Liver failure may also be considered as a potential cause of unexplained thrombocytopenia.[92] For more on clinical manifestations, diagnosis, and management of patients with liver disease, see the section on liver disease–associated coagulation disorders.

Chronic Kidney Disease

The failure of the kidney to properly eliminate the breakdown products of proteins results in increased levels of urea and creatinine in the blood, creating a uremic bleeding risk, which, although multifactorial in pathogenesis, is largely related to platelets. Proposed mechanisms for platelet disorders in chronic kidney disease (CKD) include platelet metabolic defects, deficiencies in platelet-endothelial interactions, and the effect of anemia on normal platelet function.[93] With anemia, it is proposed that the decreased number of red blood cells allows platelets to be more dispersed within the lumen of blood vessels, making them less likely to adhere to the endothelium and form a platelet plug in the event of injury. In addition, anemia may also affect ADP and TXA release, circulating nitric oxide (an inhibitor of platelet aggregation), and cyclic guanosine monophosphate concentrations.[94] In addition to platelet disorders, bleeding tendencies in CKD patients are also increased due to coexisting coagulopathies and the heparin use during hemodialysis. Ecchymoses, epistaxis, and GI and genitourinary bleeding are commonly seen in renal failure patients. Spontaneous intraoral mucocutaneous bleeding can also occur.

The routine use of dialysis has decreased the incidence of spontaneous bleeding episodes.[95] While the severity of CKD does not directly correlate with abnormal platelet aggregation, the degree of anemia secondary to decreased renal erythropoietin production due to CKD does. Therefore, correction of anemia with blood transfusions, erythropoietin, or erythropoiesis-stimulating agents reduces the bleeding time in many patients; however, it does not decrease the incidence or risk of bleeding.[96] Desmopressin (DDAVP) is an analog of antidiuretic hormone with vasopressor activity. It appears to work by increasing the release of F VIII/VWF multimers from endothelial cells and increase platelet membrane glycoprotein expression.[97] DDAVP is administered at a dose of 0.3 μg/kg IV (in 50 mL of saline over 15–30 minutes), or 3 μg/kg intranasally, as in Stimate nasal spray (one spray per nostril, 150 μg each spray) 1–2 hours before procedure. Improvement in BT is seen in approximately 1 hour, and lasts 4–8 hours.[98] Conjugated estrogens, 0.6 mg/kg IV daily for 5 days, or 2.5–25 mg orally per day, or 50–100 μg of transdermal estradiol twice weekly, are most commonly indicated in patients on dialysis who have chronic GI tract bleeding when other treatment is contraindicated.[99] Cryoprecipitate is thought to enhance platelet aggregation by increasing F VIII/VWF multimers and fibrinogen. When administered IV (10 units every 12–24 hours), BT improves in uremic patients, beginning in 1 hour and lasting for 4–24 hours.[100]

Cardiopulmonary Bypass

Cardiopulmonary bypass (CPB), also known as a heart–lung machine or extracorporeal membrane oxygenation (ECMO),

causes significant platelet dysfunction due to platelet interaction with nonphysiologic surfaces of the bypass machine, complement activation, release of cytokines, thrombin generation, and hypothermia during bypass. Collectively, these lead to premature platelet activation, secretion of contents, and alteration in surface glycoprotein expression (decreased GPIb and IIb/IIIa), leading to compromised adhesion, activation, and aggregation. Due to the dysregulated activation and secretion of contents, platelet–neutrophil and platelet–monocyte conjugates are formed, thought to be central in a post-CPB inflammatory syndrome. Thrombocytopenia also occurs in CPB due to hemodilution, and adherence of platelets to nonphysiologic surfaces in the machine. Bleeding occurs in 30%–50% of patients on CPB and this can be life-threatening.[101]

Dysproteinemia

Patients with multiple myeloma or Waldenström macroglobulinemia may have platelet dysfunction due to the presence of abnormal paraproteins in these conditions, which can affect platelet adherence, activation, aggregation, and procoagulant activity. A paraprotein for platelet surface membrane glycoprotein GPIIIa has been described in a patient with multiple myeloma. In Waldenström macroglobulinemia, chronic epistaxis and gingival bleeding are common, along with perioperative and postoperative GI bleeding during surgery.[102] Laboratory studies include prolongation of the BT, impaired clot retraction, defective in vivo; platelet aggregation, and decreased in vitro; platelet adhesion. In the absence of clinical bleeding, or planned surgical procedures, routine studies to test bleeding and clotting function are not necessary. In such patients, evaluation for clotting should include PT, PTT, TT, and F X activity.

Myeloproliferative Disorders

Thrombocytopenia may also be a component of other hematologic diseases, such as myelodysplastic disorders,[103] aplastic anemia,[104] and leukemia.[105] Symptoms include gingival hemorrhage, epistaxis, GI bleeding, and bruising.[106]

Diabetes

Patients with diabetes mellitus (DM) are prone to increased platelet reactivity due to increased receptor expression and increased downstream signaling, with intensified adhesion, activation, and aggregation, and a higher percentage of circulating immature platelets.[107,108] These may account for a higher risk of acute coronary syndrome in DM patients, and a lesser response to antiplatelet agents in DM patients when compared to non-DM patients. As a result, it is suggested that patients with DM may require increased dosages of therapeutic antiplatelet agents (e.g., aspirin, clopidogrel) than normal to have an optimal therapeutic effect, or may require a more potent platelet inhibitor (e.g., prasugrel, ticagrelor).[109]

Acquired Platelet Disorders—Drug-Induced/Therapeutic

Medications can also reduce absolute numbers of platelets or interfere with their function, resulting in postsurgical hemorrhage.[110,111] Bone marrow suppression from cytotoxic cancer chemotherapy can result in severe thrombocytopenia, requiring platelet transfusions for prevention of spontaneous hemorrhage.

Antiplatelet agents are routinely used therapeutically for thromboembolic protection in patients with ischemic heart disease, prosthetic heart valves, coronary artery stents, and those at risk of ischemic cerebrovascular accidents. Antiplatelet therapy reduces the risk of death from cardiovascular causes by about one-sixth, and the risk of nonfatal myocardial infarction and stroke by about one-third for patients with unstable angina or a history of myocardial infarction, transient ischemia, or stroke.[112] A science advisory panel consisting of the American Heart Association and American Dental Association recommends that 12 months of dual antiplatelet therapy is required after the placement of drug-eluting coronary artery stents.[113]

Acetylsalicyclic Acid

ASA, also known as aspirin, is an inexpensive and effective drug that is widely used. ASA induces a functional defect in platelets detectable as altered PFA-100 CTs and prolongation of BT. It inactivates an enzyme called prostaglandin synthetase, resulting in inactivation of cyclooxygenase (COX) catalytic activity and decreasing biosynthesis of prostaglandin and thromboxanes (such as thromboxane A2), which are needed to regulate interactions between platelets and the endothelium.[112] A single 100 mg dose of ASA provides rapid complete and irreversible inhibition of platelet COX activity and thromboxane production. This type of drug-related platelet disorder is compensated for within 7–10 days. In addition, there is no increase in this antiplatelet effect at levels beyond the low daily dosages, therefore lower-dose formulations (e.g., 81 mg) are standard for this therapeutic indication.

Other COX Inhibitors

Most nonsteroidal anti-inflammatory drugs (NSAIDs) have a similar but less significant antiplatelet effect, thereby are of mild concern to patients who have other disorders of hemostasis. The COX-2 inhibitors, such as celecoxib (Celebrex), generally do not inhibit platelet aggregation at indicated doses.

Antiplatelet Medications

Other therapeutic antiplatelet medications work by different mechanisms affecting platelet adhesion, activation, and aggregation, which include the inhibition of ADP receptor (e.g., clopidogrel and ticolopidine); adenosine reuptake

(dipyridamole); phosphodiesterase (e.g., cilostazol); and GPIIb/IIIa (e.g., abciximab, eptifibatide, tirofiban). Clopidogrel bisulfate (Plavix) alone carries less risk of prolonged bleeding than ASA; however, it is commonly used in dual antiplatelet therapy.[114]

Medical Management of Platelet Disorders

The decision to actively manage is based on a patient history of clinically significant bleeding suggestive of platelet dysfunction, in combination with appropriate laboratory tests, keeping in mind that these do not necessarily predict whether there will be clinically significant bleeding or its extent. In the case of treatment, there are limited treatment options for the correction of platelet disorders, with little strong evidence from randomized trials to form the basis for recommendations.[115]

Platelet Transfusion

Platelet transfusions are indicated for an actively bleeding patient due to platelet disorder, preparation for an invasive procedure, and prevention of spontaneous bleeding. The thrombocytopenias are primarily managed acutely, with transfusions of platelets to maintain the minimum level of 10,000–20,000/mm^3 necessary to prevent spontaneous hemorrhage (Table 18-7). This has also been indicated for thrombocytopenias secondary to liver disease and for Glanzmann's thrombasthenia, and is the main therapy for Bernard–Soulier disease.[116] However, repeated platelet transfusions may carry the risk of development of antiplatelet isoantibodies, thereby losing its effectiveness. As a consequence, transfusions are usually reserved for cases in which there is concern over excessive surgical or traumatic bleeding, or in active cases of severe, uncontrolled bleeding, in which prior treatments (discussed below) are unsuccessful.

The standard dose of platelets for prevention in adults is approximately 4–6 units of pooled platelets, or 1 apheresis unit (or 1 random donor unit per 10 kg of body weight), which translates to approximately 3 or 4 x 10^{11} platelets, transfused for approximately 20–30 minutes.[117] A standard pediatric dose is 5–10 mL/kg. In general, this platelet dosing is expected to raise the platelet count by approximately 30,000/mm^3 within 10 minutes of the infusion, with peak being 10–60 minutes, and a gradual decline over 72 hours. For prevention of bleeding, transfusion platelet transfusions once a day should suffice. For those who are being transfused therapeutically, either for active bleeding or for preparation for an invasive procedure, higher dosages or more frequent platelet transfusions may be indicated.

There are several risks from platelet transfusion. Infection by bacteria is a serious complication that can be fatal, occurring in approximately 1 in 2000 platelet transfusions,[118] which is more than 10-fold the rate of those receiving red blood cells. Volume overload is of concern for certain patients (e.g., those with congestive heart failure, renal failure, respiratory failure), as platelet transfusion introduces approximately 200 mL of volume per transfusion. Incidence of transfusion-associated circulatory overload is 1–3 per 100,000 platelet transfusions.[119] As mentioned earlier, the risk of production of autoantibodies to class I HLA antigens expressed on platelets increases with repeated transfusions and can decrease the response. Allergic reactions to platelet transfusion occur due to IgE directed against proteins in the donor plasma, with common occurrences being urticaria and pruritis in mild cases, and wheezing, shortness of breath, and hypotension in more severe cases. Anaphylactic reactions due to platelet transfusion are very rare. Transfusion-associated graft-versus-host disease occurs with any transfusion that contains lymphocytes. Another complication is acute lung injury following transfusion, which can cause respiratory distress.

Patients with confirmed antibody development due to anti-HLA antibodies should receive HLA-matched platelets, platelets negative for the corresponding antigen(s), or cross-matched compatible platelets, to reduce the number of platelet transfusions needed for hemostasis. Apheresis involves running blood through a process of separating and removing constituents, to include plasma (plasmapheresis), platelets (plateletpheresis), and leukocytes (leukapheresis). Apheresis platelets remove circulating isoantibodies and limit the recipient's exposure to a single blood donor, which potentially reduces the possibility of infection and antibody development, as some centers use apheresis platelets exclusively. Use of apheresis platelets also permits transfusion of platelets from specific donors selected based on HLA matching or platelet cross-matching, cytomegalovirus (CMV) status, and ABO group. For patients without antibody development, either pooled and apheresis platelets can be used.[120]

In the absence of satisfactorily compatible platelets, blood volume and constituents can be maintained with low-antigenicity blood products. Leukoreduction passes platelets through a filter that blocks the passage of most white blood cells (WBCs). Irradiation prevents graft-versus-host disease, in which contaminating WBCs attack host tissues, by damaging the nuclei of WBCs.

Desmopressin

DDAVP is used in the management of VWD, in which it works by releasing endogenous VWF from the endothelium. In case reports and cohort studies, it has been shown to be effective in preventing postoperative bleeding in patients with milder platelet disorders after dental procedures and minor surgery.[121,122] In patients with acquired platelet dysfunction, DDAVP has been demonstrated to decrease bleeding time; however, it did not correlate with changes in

actual VWF levels, in vitro; platelet aggregation, or decreased bleeding risk.[123,124,125]

Estrogens

Conjugated estrogens have been used most commonly for patients with mild to moderate type 1 VWD, or for uremic bleeding. The effective dose is IV estrogen 0.6 mg/kg daily for 5 days, 2.5–25 mg orally per day, or 50–100 μg of transdermal bestradiol twice weekly.

Recombinant Factor VIIa

rFVIIa has been used successfully in patients with congenital platelet disorders[126] and is also useful for patients who cannot receive platelet transfusions due to autoantibody formation, and for Glanzmann thrombasthenia and Bernard–Soulier syndrome. Proposed mechanisms include a tissue factor–independent thrombin generation induced by binding of rFVIIa to the surface of activated platelets, and a local procoagulant effect at sites of vascular damage.[127]

COAGULATION DISORDERS

Congenital Coagulation Disorders

Inherited disorders of coagulation can result from deficiency of a number of factors (Table 18-1) that are essential in the coagulation cascade, or a deficiency of VWF. Clinical bleeding can vary from mild to severe, depending on the specific clotting factor affected and the level of factor deficiency.

Von Willebrand Disease

VWD is the most common inherited bleeding disorder, affecting between 0.1% and 1% of the population.[128,129] However, only a fraction of patients are symptomatic and seek medical attention due to bleeding symptoms. Described originally by Erik von Willebrand in 1926,[130] it can be due to quantitative or qualitative defects in VWF, a multimeric high molecular weight glycoprotein.[131] VWF has two functions that qualify it as both a platelet disorder and a disorder affecting coagulation: (1) it mediates the initial platelet adhesion to the injured blood vessel wall; and (2) binds and stabilizes F VIII in plasma.[132] The normal plasma VWF level is 10 mg/L, with a half-life of 6–15 hours.

There are three major types of inherited VWD based on clinical, laboratory, and genetic information, and each has distinct therapeutic requirements.[129]

Type 1

Type 1 VWD, an autosomal dominant disease, is the most common, accounting for approximately 75% of patients. It represents a partial quantitative deficiency of VWF. Laboratory findings include decreased VWF activity and antigen.

Type 2

Type 2 VWD, which is usually an autosomal dominant disease, is characterized by several qualitative abnormalities of VWF. Four subtypes have been identified: 2A, 2B, 2M, and 2N:

- Type 2A, which accounts for 10%–20% of individuals with VWD, includes variants with decreased platelet adhesion caused by selective deficiency of high molecular weight VWF multimers and reduced binding to platelet GPIb.
- Type 2B accounts for 5% of cases of VWD. The defect is an increase in the binding of VWF to platelet GPIb, which results in sequestration or loss of the bound platelets and VWF from the circulation due to the clearance of the platelet aggregates that are formed, which can cause thrombocytopenia.[133]
- Type 2M includes variants with markedly defective platelet adhesion, despite a relatively normal size distribution of VWF multimers, due to reduced binding of VWF to platelet GPIb.
- Type 2N includes variants with markedly decreased binding affinity of VWF to F VIII.

Type 3

Type 3, a total deficiency of VWF, is a rare autosomal recessive disorder that leads to severe disease with undetectable levels of VWF. Levels of F VIII may be reduced in types I and 2, while types 2N and 3 have a dramatic decrease in F VIII.[134]

A rare autosomal dominant fourth type is called pseudo- or platelet-type VWD with hyperresponsive platelets, and it is a primary platelet disorder that mimics VWD.[134] The increased platelet affinity for large multimers of VWF, with subsequent removal of VWF and platelets from circulation, results primarily in mild to moderate mucocutaneous bleeding, which increases during pregnancy or following use of antiplatelet medications such as ASA, making diagnosis difficult.[135] Unlike the other types of VWD, the platelet type is rare and presents with less severe clinical bleeding, and requires platelet transfusion for correction.

The clinical features of VWD are usually mild and include mucosal bleeding, soft tissue hemorrhage, and menorrhagia in women; however, there can be instances of moderate to severe bleeding, with type 1 having the lowest bleeding risk and type 3 having the highest bleeding risk.[129] VWD types 2N and 3 would have symptoms similar to hemophilia A, with hemarthrosis and soft tissue and urinary bleeding (Figure 18-8).

Patients are assessed for history of prior bleeding symptoms, such as bruising and/or bleeding with procedures (e.g., needles) and minor trauma, spontaneous bleeding episodes, or hemostatic challenges such as during menstrual cycles, trauma, dental extractions, or other surgical interventions. A physical examination notes any areas of ecchymoses

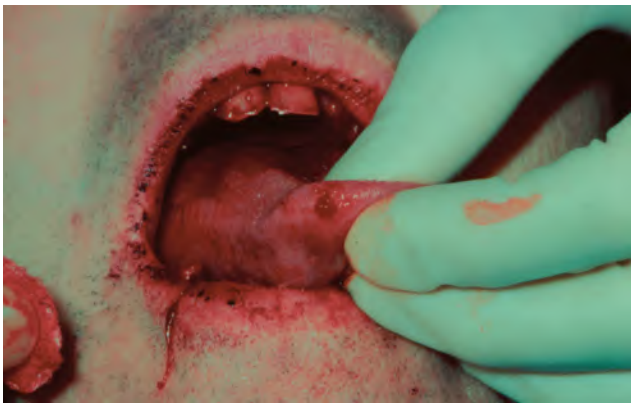

Figure 18-8 A 27-year-old man with Type 3 von Willebrand disease and a 2-week duration of bleeding from the tongue that reduced his hematocrit to 16%. Hemorrhage control was obtained with cryoprecipitate.

and hematomas, and evidence of mucosal bleeding. A family history is important and is also helpful in deciding between different inherited bleeding disorders. In terms of laboratory studies, individuals with VWD will have a normal CBC and platelet count (with the exception of mild thrombocytopenia in type 2B VWD), a normal or prolonged aPTT, and a normal PT. Tests that assess the quantity and function of VWF include VWF antigen (VWF:Ag), a quantitative measure of total VWF protein level and VWF activity via ristocetin cofactor (VWF:RCo), or the newer VWF:GPIbM assay.[129] Functional assays of VWF binding to platelets or collagen and F VIII activity are also assessed in some cases.

DDAVP in intranasal, IV, or subcutaneous injections may be used for bleeding episodes in VWD patients, with the exception of type 3 for which it is not effective. As DDAVP releases stored endothelial cell VWF, it should be tested initially in a trial dosing and with laboratory testing of response in order to assure effectiveness (defined as a threefold increase and assured hemostasis).[129] Stimate nasal spray is most commonly used, at 1 spray for patients under 50 kg weight and 2 sprays for those over 50 kg weight, due to convenience and effectiveness in 80% of type I VWD patients.[129] Plasma-derived intermediate and high-purity concentrates containing both VWF and F VIII, or recombinant VWF concentrates, are administered IV in moderate to severe patients in types 1, 2A, 2B, and 2M VWD. F VIII replacement is used in VWD types 2N and 3. Antifibrinolytics also have a hemostasis-supportive role in VWD, as does hormone therapy in women with heavy menstrual bleeding.[129]

Hemophilia

Hemophilia A

Hemophilia A is inherited as an X-linked recessive disorder that affects males (hemizygous), and the trait is carried in the female (heterozygous) without clinical evidence of the disease, although a few affected females do manifest mild bleeding symptoms. Males with hemophilia transmit the affected gene to all their female offspring, yet their sons are normal, and the effects skip a generation unless the mother was a carrier and their daughters received the maternal affected X chromosome as well. Only 60%–70% of families with newly diagnosed hemophiliacs report a family history of the disease, suggesting a high mutation rate. There is no racial predilection. Hemophilia A involves a deficiency of F VIII, the antihemophilic factor, and accounts for 79% of all hemophiliacs. There is a severe factor deficiency (<1% F VIII) in 43% of hemophiliacs, 26% have a moderate deficiency (1%–5% F VIII), and 31% present with a mild deficiency (6%–30% F VIII).[133]

Clinical symptoms and F VIII levels vary from pedigree to pedigree. Those with severe factor deficiency are more likely to have severe and spontaneous bleeding, and onset of bleeding episodes at an earlier age.[136] In contrast to the more superficial signs of bleeding observed in individuals with platelet-associated disorders, individuals with hemophilia exhibit bleeding into more deep-seated spaces, although bleeding from small cuts is uncommon. Immediate and delayed bleeding after trauma is common, ranging from very significant bleeds to continuous oozing for days or weeks. The more common signs include hematomas, hemarthroses, hematuria, GI bleeding, and bleeding from lacerations, or head trauma, or spontaneous intracranial bleeding that requires factor replacement therapy.[135] Retroperitoneal and central nervous system bleeds, occurring spontaneously or induced by minor trauma, can be life-threatening. Severe hemorrhage leads to joint synovitis and hemophilic arthropathies, intramuscular bleeds, and pseudo-tumors (encapsulated hemorrhagic cysts).

People with moderate deficiency often bleed in response to minor injury and invasive procedures, although with less frequent bleeding, typically 4–6 times yearly. Those with mild hemophilia only have bleeding in response to injury or trauma, such as prolonged bleeding following tooth extraction, other surgical procedures, or severe trauma.

Hemophilia B

Hemophilia B (Christmas factor; F IX) occurs in approximately 1 in 15,000–30,000 live male births. The genetic background, factor levels, and clinical symptoms are similar to those in hemophilia A. The distinction was made only in the late 1940s between these two X-linked diseases. Concentrates used to treat F VIII and F IX deficiencies are specific for each state; therefore, a correct diagnosis must be made to ensure effective replacement therapy.

Circulating blocking antibodies or inhibitors to F VIII and F IX may be seen in patients with these disorders. These inhibitors are specific for F VIII or F IX, more often develop in patients with severe hemophilia, and render the patient

refractory to the normal mode of treatment with concentrates. Significant morbidity in hemophiliacs with inhibitors relates to bleeding risk, allergic/anaphylactic reactions, and nephrotic syndrome.[137]

Diagnosis

Patients are assessed for prior bleeding history. A thorough family history is obtained. Genetic testing is also often performed to identify the presence of a specific gene mutation.

Hemophilia is characterized by a prolonged aPTT, with a normal platelet count and PT. However, aPTT may be normal in those with milder factor deficiencies. Diagnosis is made based on the measurement of factor activity levels when compared to normal controls (F VII in hemophilia A; F IX in hemophilia B). In patients with F VIII deficiency, it is important to rule out VWD. The diagnostic criteria are as follows:

- *Hemophilia A*. Confirmation of an F VIII activity level below 40% of normal (below 0.40 international units [IU]/mL) or, in some circumstances where the F VIII activity level is ≥40%, a pathogenic F VIII gene mutation. A normal VWF:Ag should also be documented to eliminate the possibility of some forms of VWD.
- *Hemophilia B*. Confirmation of an F IX activity level below 40% of normal or, in some circumstances where the F IX activity level is ≥40%, a pathogenic F IX gene mutation. Newborns have a lower normal range of F IX activity; the normal newborn range should be used as a reference when evaluating factor levels in newborns.
- *Hemophilia carrier*. Requires identification of a hemophilia gene mutation. Factor levels are important for managing carriers, but are not optimal for determining or eliminating the diagnosis of a hemophilia carrier.

Rare Coagulation Factor Deficiencies

Rare coagulation deficiency disorders include inherited qualitative or quantitative deficiencies of coagulation factors including F I (fibrinogen), F II (prothrombin), F V, F VII, F X, F XI, and F XIII, together accounting for 3%–5% of all congenital bleeding disorders.[138]

F II Deficiency

Prothrombin (F II) deficiency is the most rare congenital bleeding disorder. It is found to disproportionately affect Latinos in North America. Inheritance is autosomal recessive and both PT and aPTT are elevated.[137] Management is with prothrombin complex concentrates (PCCs).

F V Deficiency

Proaccelerin (F V) deficiency, like F XI and F X deficiencies, is a rare autosomal recessive trait that presents with moderate to severe clinical symptoms. When compared with hemophilia A and B, this hemorrhagic diathesis is moderate, only occasionally resulting in soft tissue hemorrhage and only rarely presenting with hemarthrosis. It does not involve the devastating degenerative joint disease seen in severe hemophilia A and B. FFP is the mainstay of treatment.

F VII Deficiency

Proconvertin (F VII) deficiency, with a prevalence of 1 in 500,000 population, makes it the most common of the rare coagulation factor deficiencies. Clinical bleeding is not as well correlated to level of deficiency as in hemophilia A or B, although PT is often prolonged with no effect on aPTT, and development of alloantibodies or inhibitors has been reported.[137] Treatment is with rFVIIa.

F X Deficiency

Stuart factor (F X) deficiency, also a rare bleeding diathesis, is inherited as an autosomal recessive trait. Clinical bleeding symptoms in the patient with levels less than 1% are similar to those seen in hemophilia A and B.

F XI Deficiency

Plasma thromboplastin antecedent (F XI) deficiency is clinically a mild disorder seen in pedigrees of Jewish descent; it is transmitted as an autosomal dominant trait. Bleeding symptoms do occur, but are usually mild. In the event of major surgery or trauma, hemorrhage can be controlled with infusions of FFP.

F XII Deficiency

Hageman factor (F XII) deficiency is another rare disease that presents in the laboratory with prolonged PT and aPTT. Clinical symptoms are nonexistent, therefore treatment is contraindicated.

F XIII and F I Deficiencies

Fibrin-stabilizing (F XIII) deficiency and fibrinogen (F I) deficiency are very rare, and these diagnoses can be made only with extensive laboratory tests, usually available only in tertiary-care medical centers. Both are autosomal recessive traits. Most dysfibrinogenemias result in no symptoms, others lead to moderate bleeding, and a few induce a hypercoagulable state. F XIII deficiency appears to have different forms of penetrance and in some families appears only in males. Treatment has historically been with cryoprecipitate; however, purified plasma-derived and recombinant products have been recently developed.[137]

Acquired Coagulation Disorders—Systemic

Vitamin K Deficiency

Vitamin K is a fat-soluble vitamin that is absorbed in the small intestine and stored in the liver. It plays an important role in hemostasis by activating various coagulation factors. Vitamin K deficiency is associated with having poorly

functioning vitamin K–dependent F II, F VII, F IX, and F X.[139] Deficiency is rare, but can result from inadequate dietary intake, intestinal malabsorption, or loss of storage sites due to hepatocellular disease. Biliary tract obstruction and long-term use of broad-spectrum antibiotics, particularly the cephalosporins, can also cause vitamin K deficiency.

Although there is a theoretic 30-day store of vitamin K in the liver, severe hemorrhage can result in acutely ill patients in 7–10 days. A rapid fall in F VII levels leads to an initial elevation in INR and subsequent prolongation of aPTT. When vitamin K deficiency results in coagulopathy, supplemental vitamin K by injection restores the integrity of the clotting mechanism within 12–24 hours.

Liver Disease

In addition to platelet defects, liver disease affects the coagulation cascade, and formation and removal of clots. Owing to impaired protein synthesis, important factors and inhibitors of the clotting and fibrinolytic systems are markedly reduced. Acute or chronic hepatocellular disease may display decreased vitamin K–dependent factor levels, with other factors still being normal. This is due to decreased bile salt synthesis, which leads to impaired vitamin K absorption and, as noted previously, decreased storage sites. Additionally, abnormal vitamin K–dependent factor and fibrinogen molecules have been encountered. In a cirrhotic patient, oral manifestations may include petechiae, hemorrhage, and gingival bleeding (Figure 18-9).

Liver disease that results in bleeding from deficient vitamin K–dependent clotting factors (F II, F VII, F IX, and F X) may be reversed with 3 days of vitamin K injections, either IV or subcutaneous. Infusion of FFP may be necessary when more immediate hemorrhage control is necessary, such as prior to dental extractions or other surgical procedures.[140] Cirrhotic patients with moderate thrombocytopenia and functional platelet defects may benefit from DDAVP therapy.[141] Antifibrinolytic drugs, if used cautiously, have markedly reduced bleeding and thus lowered the need for blood and blood product substitution.[90] Platelet transfusions may be required for liver disease patients who are thrombocytopenic.

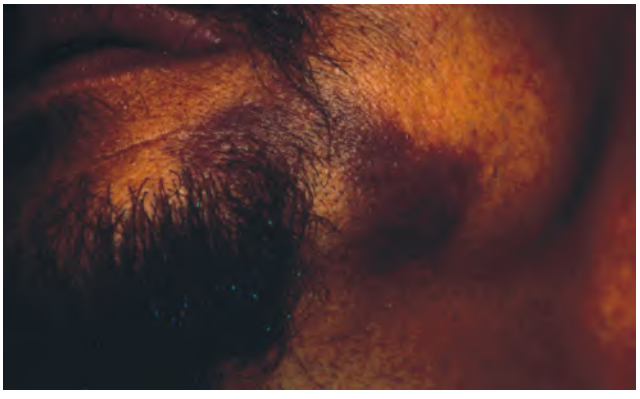

Figure 18-9 A 46-year-old man with severe liver cirrhosis due to hepatitis C infection. Shown is purpura of facial skin 1 week after full-mouth extractions.

Acquired von Willebrand Syndrome

Acquired von Willebrand Syndrome (aVWS) occurs as a result of an underlying cause, as opposed to the genetic disorder. Of all cases of VWD, only 1.2% were aVWS.[142] However, it is reported to be prevalent in significant numbers in certain conditions, such as myeloproliferative neoplasms (10%–20%), autoimmune disorders, congenital cardiac abnormalities or aortic stenosis (10%–70%), and left ventricular assist device (LVAD) or extracorporeal membrane oxygenation (ECMO; up to 100%).

Reduced VWF activity in aVWS can occur via immune and nonimmune mechanisms. For immune mechanisms, autoantibodies to the VWF protein may occur from lymphoproliferative neoplasms and autoimmune disease, in which they interfere with VWF function and lead to bleeding.[143] In terms of nonimmune mechanisms, VWF protein is damaged or cleaved secondary to changes in fluid flow and shear stress, which can occur whenever there is vessel stenosis, as is the case in ventricular septal defect, aortic stenosis, post mitral valve replacement, LVAD, and ECMO. In addition, VWF can be removed from circulation due to adsorption into cells, which may occur in multiple myeloma, Waldenström macroglobulinemia, and non-Hodgkin lymphoma.[144]

Lymphoproliferative disorders associated with aVWS include monoclonal gammopathy, multiple myeloma, Waldenström macroglobinemia, CLL, and non-Hodgkin lymphoma.[145,146] There have been case reports of aVWS occurring in SLE, though prevalence in SLE and other autoimmune disorders has not been established.[147]

Hypothyroidism can cause aVWS, though the prevalence is unknown and thought to be rare, with synthesis reduced in the setting of low thyroid hormone levels. In autoimmune thyroiditis, autoantibodies against VWF have been reported.[148] aVWS is also caused by medications, including valproic acid, ciprofloxacin, and griseofulvin. New-onset unexplained bleeding, usually involving mucosal surfaces, is found in patients with an underlying condition known to predispose them to having reduced VWF levels.

Initial tests include a CBC with platelet count, and coagulation testing to include PT, aPTT, and INR. Specific tests for VWF include VWF:Ag, VWF:RCo, and F VIII:C. Further tests include VWF collagen binding, VWF multimers, and VWF propeptide. aVWS may exhibit decreased collagen binding, decreased VWF multimers, and/or a high ratio of VWF propeptide to VWF:Ag.

Distinguishing aVWS from inherited VWD can be determined by onset of bleeding later in life, with a history of uneventful surgical procedures, negative family history of VWD, and remission of bleeding after treatment of underlying aVWS-associated disorder.

Treatment of the underlying aVWS-associated disorder will usually correct aVWS; however, treatment may take days to weeks to become effective. For immune-mediated causes of aVWS (e.g., SLE, CLL), immunosuppressive therapy (e.g., corticosteroids, cyclophosphamide, rituximab), or IVIg is appropriate. Plasmapheresis can be used to rapidly reduce VWF antibody levels, in cases of serious bleeding.[149]

For acute bleeding episodes, a number of interventions are available. VWF concentrate is administered IV. A dose of VWF concentrate of 40–60 IU per kg of body weight is initially given to reach a plasma level of VWF:RCo of 50–100 IU/dL, and subsequent doses of 20–40 IU per kg of body weight are given every 12 hours. DDAVP can be administered every 12–24 hours, either intranasally, subcutaneously, or IV. Topical antifibrinolytic agents are useful for bleeding from mucosal sites, including the mouth. Examples include tranexamic acid and aminocaproic acid, in addition to Gelfoam or Surgicel soaked in topical thrombin.

For patients requiring an invasive procedure, there are several specific prophylactic strategies. DDAVP is administered for minor procedures, with the first perioperative dose given 1 hour before the procedure, and subsequent dosages every 6–12 hours after surgery. VWF concentrates are used for major and high-bleeding-risk procedures. For dental procedures, topical antifibrinolytic agents are also used.

Disseminated Intravascular Coagulation

DIC is a process that causes both thrombosis and hemorrhage, occurring in approximately 1% of hospital admissions.[150] It is triggered by potent stimuli that activate both F XII and TF to initially form microthrombi and emboli throughout the microvasculature.[151] Thrombosis results in rapid consumption of both coagulation factors and platelets, while also creating FDPs that have antihemostatic effects. The most frequent triggers for DIC are obstetric complications, metastatic cancer, massive trauma, and infection with sepsis. Clinical symptoms vary with disease stage and severity. Most patients have bleeding at skin and mucosal sites. Although it can be chronic and mild, acute DIC can produce massive hemorrhage and be life-threatening.

In acute DIC, it is important to expeditiously identify the underlying triggering disease or condition and deliver specific and vigorous treatment of the underlying disorder to promote long-term survival. Diagnosis is made by laboratory studies that confirm increased thrombin generation (e.g., decreased fibrinogen, prolonged PT and aPTT) and increased fibrinolysis (e.g., increased FDPs and D-dimer). For chronic DIC, diagnosis is based on the evidence of microangiopathies on the peripheral blood smear, and increased FDPs such as D-dimer. The dentist may be called upon to provide a gingival or oral mucosal biopsy specimen for histopathologic examination to confirm the diagnosis of DIC by the presence of microthrombi in the vascular bed.

Although somewhat controversial, active DIC is usually treated initially with IV unfractionated heparin or subcutaneous low molecular weight heparin (LMWH), to prevent thrombin from acting on fibrinogen, thereby preventing further clot formation.[152] Infusion of activated protein C, ATIII, and agents directed against TF activity are being investigated as new therapeutic approaches.[153] Replacement of deficient coagulation factors with FFP and correction of the platelet deficiency with platelet transfusions may be necessary for improvement or prophylaxis of the hemorrhagic tendency of DIC prior to emergency surgical procedures. Elective surgery is deferred due to the volatility of the coagulation mechanism in these patients.

Fibrinolytic Disorders

Disorders of the fibrinolytic system can lead to either hemorrhage or excessive clotting and thrombosis, when clot breakdown is enhanced or when clot breakdown mechanisms are retarded, respectively.

Primary fibrinolysis typically results in bleeding and may be caused by a deficiency in α_2-antiplasmin or plasminogen activator inhibitors, natural proteins that turn off activation of the fibrinolytic system. Laboratory coagulation tests are normal, with the exception of decreased fibrinogen and increased FDP levels. In liver disease, impaired clearance of tPA may contribute to prolonged bleeding. As discussed above, deficiency of F XIII, a transglutaminase that stabilizes fibrin clots, is a rare inherited disorder that leads to hemorrhage. Patients with primary fibrinolysis are treated with FFP therapy and antifibrinolytics.

Differentiation must be made from the secondary fibrinolysis that accompanies DIC, a hypercoagulable state that predisposes individuals to thromboembolism. Dialysis patients with CKD show a fibrinolysis defect at the level of plasminogen activation.[154]

Reduced fibrinolysis may be responsible, along with other factors, for the development of thrombosis, atherosclerosis, and their thrombotic complications. Activators of the fibrinolytic system (tPA, streptokinase, and urokinase) are frequently used to accelerate clot lysis in patients with acute thromboembolism, for example to prevent continued tissue damage in myocardial infarction or treat thrombotic stroke.

Acquired Coagulation Disorders—Drug-Induced/Therapeutic

There are a variety of traditional and newer pharmaceutical agents that alter hemostasis (Table 18-6).

Heparin

Heparin is a potent anticoagulant that binds with AT to significantly inhibit activation of clotting enzymes, thereby reducing thrombin generation and fibrin formation. Indications for

Table 18-6 Drugs that therapeutically alter hemostasis.

Drug	Mechanism	Laboratory tests
Antiplatelet medications		
ASA	COX inhibition	BT, PFA-100
Clopidogrel	ADP receptor antagonist	BT, Platelet Function P2Y12
Ticlopidine		
Dipyridamole	ADP reuptake inhibitor	BT
Anticoagulant medications		
Heparin Low molecular weight heparins (enoxaparin, tinzaparin, dalteparin)	Binds to antithrombin, reducing thrombin generation	aPTT
Vitamin K antagonists Warfarin Dicumarol	Vitamin K antagonist	PT/INR
Direct oral anticoagulants Thrombin inhibitors (dabigatran)	Inhibition of thrombin (Factor IIa)	aPTT, TT
Factor Xa inhibitors (rivaroxaban, apixaban)	Inhibition of Factor Xa	Chromogenic anti-Xa assays

ADP, adenosine diphosphate; aPTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; BT, bleeding time; INR, international normalized ratio; P2Y12, platelet receptor; PFA-100, platelet function analyzer 100; PT, prothrombin time

heparin therapy include prophylaxis or treatment for venous thromboembolism, including prophylaxis in medical and surgical patients.[155] Heparin has a relatively short duration of action of 3–4 hours and so is typically used for acute anticoagulation, whereas chronic therapy is initiated with VKA drugs. For acute anticoagulation, IV infusion of 1000 units of unfractionated heparin per hour, sometimes following a 5000-unit bolus, is given to raise the aPTT to 1.5–2 times the preheparin aPTT. Alternatively, subcutaneous injections of 5000–10,000 units of heparin are given every 12 hours. The most common outpatient use of subcutaneous heparin is for the treatment of deep venous thrombophlebitis during pregnancy,[156] with the goal being regulation of the aPTT between 1.25 and 1.5 times control. Protamine sulfate can rapidly reverse the anticoagulant effects of heparin.

The major bleeding complications from heparin therapy are bleeding at surgical sites and bleeding into the retroperitoneum. Newer biologically active LMWHs (e.g., enoxaprin [Lovenox], tinzaparin [Innohep], dalteparin) are administered subcutaneously once or twice daily and are less likely to result in thrombocytopenia and bleeding complications.

Vitamin K Antagonists

VKAs such as the coumarin anticoagulants (which include warfarin and dicumarol [Coumadin]) slow thrombin production and clot formation by blocking the action of vitamin K, leading to decreased levels of vitamin K–dependent factors (F II, F VI, F IX, and F X). They are routinely used for anticoagulation to prevent recurrent thromboembolic events, such as pulmonary embolism, venous thrombosis, stroke, and myocardial infarction. They are also used commonly in patients with atrial fibrillation, and in patients with prosthetic heart valves.[157]

Daily doses of 2.5–7.5 mg warfarin are typically required to maintain adequate anticoagulation. PT/INR is used to monitor anticoagulation levels, with target therapeutic ranges varying based on medical indication, with PT of 18–30 seconds or INR of 1.5–4.0, but seldom above 3.5. Patients with paroxysmal atrial fibrillation and porcine heart valves require minimal anticoagulation (INR target 1.5–2.0), venous thrombosis is managed with intermediate-range coagulation (INR 2.0–3.0), whereas mechanical prosthetic heart valves and hypercoagulable states require more intense anticoagulation (INR target 3.0–4.0).[156]

VKA therapy requires continual laboratory monitoring, (i.e., typically every 12 weeks), as fluctuations can occur. It has a longer duration of action, with coagulant activity in blood decreased by 50% in 12 hours and 20% within 24 hours of therapy initiation. Coagulation returns to normal levels in approximately 2–4 days following discontinuation of coumarin drugs.

Coumarin drugs are particularly susceptible to drug interactions. Drugs that potentially increase warfarin potency (i.e., elevate the INR) do so by either inhibiting the cytochrome P450 enzymes in the liver that break down the drug, or by altering gut bacterial flora that affect GI absorption of the drug. Drugs that increase potency include metronidazole, penicillin, erythromycin, cephalosporins, tetracycline, fluconazole, ketoconazole, chloral hydrate, and propoxyphene. Those that reduce its potency (i.e., decrease the INR) include barbiturates, ascorbic acid, dicloxacillin, and nafcillin.[158] In addition, a synergistic antihemostatic

effect is seen when VKAs are used in combination with ASA or NSAIDs.

Warfarin is among the top 10 drugs with the largest number of serious complications, including death, as reported to the US FDA, with intracranial hemorrhage being the most feared complication due to its morbidity and mortality.[159] An observational study of over 100,000 outpatient adults on warfarin therapy showed an overall rate of 3.8% of bleeding episodes that required a hospital visit.[160] The anticoagulant effect of VKAs may be reversed immediately by infusion of FFP or PCC, or over a longer period of time by administration of vitamin K.

Direct Oral Anticoagulants

DOACs, also referred to as NOACs (e.g., dabigatran, apixaban, rivaroxaban, edoxaban, and betrixaban), have been recommended for prevention of pulmonary embolism and deep vein thromboses, or for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. They are favored over warfarin mainly due to equivalent efficacy, more targeted action, predictable and stable anticoagulant effect at regular fixed dosages (thereby eliminating the need for regular monitoring), shorter half-lives, fewer drug and food interactions, and the significantly decreased incidence of intracranial hemorrhage.[161] There are two main types of DOACs based on their mechanisms: direct thrombin (or F IIa) inhibitors, and F Xa inhibitors.

Dabigatran (Pradaxa) is a competitive and reversible F IIa inhibitor, with an incidence of major bleeding episodes that is decreased or similar to that of warfarin.[162,163] While not routinely monitored, elevated thrombin time, accompanied by an elevated aPTT, is consistent with therapeutic levels of the drug. Idarucizumab (Praxbind) is an antidote to dabigatran, the only one available for the DOACs.

The direct F Xa inhibitors include rivaroxaban, apixaban, edoxaban, and betrixaban, and are desirable due to their rapid onset of action. While PT may be prolonged in patients treated on rivaroxaban, it is not useful for monitoring the effects of apixaban. Moreover, aPTT is not useful in detecting the therapeutic level of these drugs. The main drawback to these medications is the lack of specific antidotes, which are currently in the development stages.

PCC has been shown to reverse the prolongation of PT in those treated with rivaroxaban, but not dabigatran,[164] and there are some data supporting the use of rFVIIa to reverse the effects of both of these drugs.[165] Current recommended algorithms for management of severe bleeding episodes due to these new oral anticoagulants include cessation of the drugs, local hemostatic measures at the source of bleeding, volume replacement, and transfusion of blood products if needed.[166]

Medical Management of Coagulation Disorders

Medical intervention for individuals with inherited coagulation disorders is for active bleeding due to an injury, preparation for an invasive procedure, or for prophylaxis for spontaneous bleeding (Table 18-7). For hemophilia, prophylactic factor replacement therapy has been shown to be effective for reducing bleeding, specifically intracerebral hemorrhage, and long-term complications such as chronic arthropathy, hospitalizations, and absenteeism from school and work.[167] However, there are risks, including high costs, burdens of IV infusions, risk of thrombosis and inhibitor development, and interference with daily life. All of the available products are effective, with the choice based on safety (specifically from viral infections such as HIV, hepatitis B and C virus), purity, risk of inhibitor development, product half-life, and cost. In addition to factor concentrates, a new class of non-blood-product prophylactic emicizumab (Hemlibra) administered subcutaneously up to every 4 weeks, has shown promise for preventing joint bleeding and deterioration of joint status.[168]

Fresh Frozen Plasma

FFP is prepared from whole blood or apheresis and frozen within 8 hours of collection. It is frozen at -18 to -30 °C, and is usable for 1 year from the date of collection. Standard FFP units from a single unit of whole blood have a volume of approximately 200–250 mL. It is indicated for coagulation factor replacement during management of major bleeding due to warfarin, vitamin K deficiency, liver disease, DIC, and rare inherited coagulation disorders (e.g., deficiencies of F XIII, F X, F VII, F V, F II). It is not used to correct excessive anticoagulation due to medications or other causes of prolonged INR in the absence of bleeding. However, for cases in which the INR is elevated, and an invasive procedure is required in the near future, transfusion of FFP is a consideration.

FFP should not be used as primary therapy to replace specific coagulation factors (e.g., in the case of hemophilia) because of their disadvantages of potential viral transmission and the large fluid volumes needed to raise factor levels adequately for hemostasis. FFP contains all coagulation factors in nearly normal concentrations and may aid hemorrhage control in a patient with mild hemophilia B. In the average-size patient, 1 unit of FFP raises F IX levels by 3%. Postoperative bleeding in mild to moderate F X deficiency can be managed with FFP, and PCCs may be held in reserve for severely deficient patients.[169] The typical dose of FFP is approximately 10–15 mL/kg (i.e., approximately 3–5 units) in most adults; however, this represents a significant volume challenge of 750–1250 mL of plasma, which can precipitate pulmonary edema.

Table 18-7 Principal products for systemic management of patients with bleeding disorders.

Product	Description	Source	Common Indications
Platelets	"One pack" = 50 mL; raises count by 6000	Blood bank	<10,000 in nonbleeding individuals; <50,000 presurgical;<50,000 in actively bleeding individuals; nondestructive thrombocytopenia
Fresh frozen plasma	Unit = 150–250 mL 1 h to thaw Contains F II, F VII, F IX, F X, F XI, F XII, F XIII and heat-labile F V and F VII	Blood bank	Undiagnosed bleeding disorder with active bleeding; severe liver disease; when transfusing >10 units blood Immune globulin deficiency
Cryoprecipitate	Unit = 10–15 mL Contains F VIII and F XIII, vWF, and fibrinogen	Blood bank	Hemophilia A, von Willebrand disease, when factor concentrates/DDAVP are unavailable Fibrinogen deficiency
F VIII concentrate (purified antihemophilic factor)*	Unit raises F VIII level by 2% Heat treated contains vWF Recombinant and monoclonal technologies are pure F VIII	Pharmacy	Hemophilia A, with active bleeding or presurgical; some cases of von Willebrand disease
F IX concentrate (PCC)*	Unit raises F IX level by 1–1.5% Contains F II, F VII, F IX, and F X Monoclonal F IX is only F IX	Pharmacy	Hemophilia B, with active bleeding or presurgical PCC used for hemophilia A with inhibitor
DDAVP	Synthetic analogue of antidiuretic hormone 0.3 µg/kg IV or SQ Intranasal application	Pharmacy	Active bleeding or presurgical for some patients with von Willebrand disease, uremic bleeding, or liver disease
ε-Aminocaproic acid	Antifibrinolytic 25% oral solution (250 mg/mL) Systemic: 75 mg/kg every 6h	Pharmacy	Adjunct to support clot formation for any bleeding disorder
Tranexamic acid	Antifibrinolytic 4.8% mouth rinse—not available in US Systemic: 25 mg/kg q8h	Pharmacy	Adjunct to support clot formation for any bleeding disorder

DDAVP, desmopressin acetate; F, factor; IV, intravenously; PCC, prothrombin complex concentrate; SQ, subcutaneously; vWF, von Willebrand factor.

Additional risks of plasma exposure include infection and allergic reactions. Infection risks for FFP are the same as that for most whole blood products, which include (with estimated incidences in the United States): hepatitis B virus (1:1 million), HCV (1:1.2 million), human T-lymphotropic virus (1:2.7 million), and HIV (1:1.5 million), with other considerations including syphilis, West Nile virus, Zika virus, CMV, and *Trypanosoma cruzi*.

Cryoprecipitate

Cryoprecipitate is the cold insoluble precipitate remaining after FFP is thawed at 4 °C. A typical bag (1 unit in a 10–15 mL volume) of cryoprecipitate contains approximately 80–150 units of F VIII, 50–75 units of F XIII, 100–150 units of VWF, and 150–250 mg of fibrinogen. Cryoprecipitate is widely used for surgical bleeding and trauma when the fibrinogen level is low (e.g., DIC, liver disease, fibrinogen disorders) and for uremic bleeding. Other uses of cryoprecipitate include management of postpartum hemorrhage, and as a part of massive transfusion protocols. Clinical use of cryoprecipitate has declined or become obsolete in some places due to the availability of specific coagulation factor concentrates, fibrinogen concentrates, and/or recombinant factor products that have a lower risk of complications. It is no longer routinely used to treat hemophilia A, VWD, and F XIII deficiency, except in unusual circumstances.

Desmopressin acetate

DDAVP (1-deamino-8-D-arginine vasopressin) is thought to stimulate endogenous release of F VIII and VWF from blood vessel endothelial cell storage sites. This synthetic vasopressin analog is now considered the treatment of choice for bleeding events in patients with these bleeding diatheses, owing to its absence of viral risk and lower cost. It provides adequate transient increases in coagulation factors in some

patients with mild to moderate hemophilia A and type I VWD, avoiding the need for plasma concentrates.[129] However, DDAVP is ineffective for individuals with severe hemophilia A.

DDAVP can be given at a dose of 0.3 μg/kg body weight by IV or subcutaneous route or as intranasal spray application of DDAVP (Stimate), with 2 sprays for adults weighing over 50 kg and 1 spray (150 μg) for children and adults under 50 kg. It should be given within 1 hour prior to dental extractions or surgery or to treat spontaneous or traumatic bleeding episodes, resulting in approximately a threefold increase in VWF and F VIII.[131] A DDAVP trial or test dose response may be indicated prior to extensive surgery to evaluate the level of drug effect on assayed F VIII activity in the individual patient. Prolonged use of DDAVP (such as for 3 or more days) results in exhaustion of F VIII storage sites and diminished hemostatic effect, therefore antifibrinolytic agents are useful adjuncts to DDAVP therapy.

Factor Replacement Therapy

Since partially purified F VIII and F IX complex concentrates prepared from pooled plasma were first used in the late 1960s and 1970s, multiple methods of manufacturing products with increased purity and reduced risk of viral transmission have been developed, including intermediate-purity products prepared by heat or solvent/detergent treatment. Included in this group are high-purity F VIII products manufactured using recombinant or monoclonal antibody purification techniques, and the newer extended half-life F VIII and F IX products made with crystallizable fragment fusion technology or PEGylation.[170] All available factor replacement products are administered IV, with the majority requiring reconstitution of powder with sterile water.

F VIII concentrates are dosed by units, with 1 unit of F VIII being equal to the amount present in 1 mL of pooled fresh normal plasma. The plasma level of F VIII is expressed as a percentage of normal. Since 1 unit of F VIII concentrate per kg of body weight raises the F VIII level by 2%, a 70 kg patient would require infusion of 3500 units to raise his factor level from <1 to 100%. A dose of 40 U/kg F VIII concentrate typically is used to raise the F VIII level to 80%–100% for management of significant surgical or traumatic bleeding in a patient with severe hemophilia. Additional outpatient doses may be needed at 12-hour intervals, or continuous inpatient infusion may be established.

Highly purified recombinant and monoclonal F IX concentrates are the treatment of choice for hemophilia B patients undergoing surgery. F IX complex concentrates or PCCs, which contain F II, F VII, F IX, and F X, are also widely used for patients with hemophilia B. One unit of PCC or higher-purity F IX concentrates given by bolus per kg body weight raises the F IX level by 1%–1.5%. Thus, a dose of 60 U/kg of F IX concentrate typically is needed to raise the F IX level to 80%–100% for management of severe bleeding episodes in a patient with a severe F IX deficiency. Repeat outpatient doses may be needed at 24-hour intervals.

Properly supervised home therapy, for which patients self-treat with factor concentrates at the earliest evidence of bleeding, is a cost-effective method offered to educable and motivated patients by some medical centers. Complications of factor replacement therapy include allergic reactions, viral disease transmission (hepatitis B and C, CMV, and HIV), thromboembolic disease, DIC, and development of antibodies to factor concentrates. Since 1987, with viral screening of donated plasma, there have been no transfusion-related HIV seroconversions in the United States.

Development of F VIII or F IX inhibitors is a significant complication. These pathologic circulating antibodies of the IgG class, which specifically neutralize F VIII or F IX procoagulant activity, arise as alloantibodies in some patients with hemophilia. Inhibitors are more common for F VIII deficiency, where it is estimated that 20%–30% with severe and 5%–10% with mild to moderate disease have inhibitors compared to less than 5% of those with severe hemophilia B.[171] Inhibitor level is quantified by the Bethesda inhibitor assay and is reported as Bethesda units (BU).

The inhibitor titer and responsiveness to further factor infusion (responder type) dictate which factor replacement therapy should be used. Patients with inhibitors are classified according to titer level—low (<5 BU/mL) or high (>5 BU/mL)—and also by responder type. Low responders typically maintain low titers with repeated factor concentrate exposure, whereas high responders show a brisk elevation in titer due to the amnestic response and are the most challenging to manage. Patients with low inhibitor titers are usually low responders and those with high titers are often high responders.

For hemorrhage with hemophilia A patients, activated PCC (e.g., FEIBA [factor eight inhibitor bypassing activity; anti-inhibitor coagulant complex]) or rFVIIa (NovoSeven), are the therapies of choice. The standard dose of rFVIIa is 90 μg/kg to achieve plasma FV II activity levels of 17–24 IU/mL with a 2.5-hour half-life, creating a 2–3-hour treatment dosing interval, in bleeding patients.[172] A new antibody, emicizumab (Hemlibra), binds fragments of F X/XA and F IX/IXa and has been approved for routine prophylaxis in patients with F VIII inhibitors.[171] Immune tolerance protocols may be used in some inhibitor patients in an attempt to eradicate inhibitors.[173]

Dental Management of Coagulation Disorders

Determination of factor replacement requirements should be accomplished in consultation with the patient's

hematologist, and is dependent on the invasiveness of the procedure. Only an estimated 2% of hemophilic patients experience one or more delayed bleeding episodes after dental treatment when managed in a hemophilia treatment center.[174] Appropriate precautionary measures now allow surgery to be performed safely, with no significantly greater risk of bleeding than in patients without hemophilia.[175]

For surgical hemostasis, clinical practice guidelines recommend target replacement factor activity levels of 40%–50% of F VIII (dose 20–25 U/kg) and F IX (dose 40–50 U/kg) for 1–2 days, in conjunction with antifibrinolytics.[176,177] Recommended minimum factor level during the healing phase is 20%. Higher hemostatic factor levels are needed for larger wounds from extraction of multiple or multirooted teeth, or when gingival inflammation, bleeding, tooth mobility, or apical lesions are present. Special consideration is made for the more significant risks associated with extraction of impacted mandibular third molars due to the potential for retropharyngeal bleeding and airway compromise. Factor activity levels required for postextraction hemostasis have been reported to vary from 3.5% to 25% for deciduous teeth and 5.5% to 20% for permanent teeth. Gingival bleeding unresponsive to antifibrinolytics requires 20%–30% clotting F VIII or F IX.

Three methods of replacement therapy have been employed to maintain circulating factor levels during surgical and healing phases. These include intermittent replacement therapy, continuous IV factor infusion therapy, and a single preoperative factor concentrate infusion combined with an antifibrinolytic mouthwash.[178] When single-bolus infusion is used for outpatient procedures, transfusion recommendations generally aim for replacement of missing coagulation factors to levels of 50%–100%. This accounts for the possible failure of factor activity to rise to target levels, and variable plasma half-lives (8–12 hours for F VIII, and 18–24 hours for F IX). F VIII levels may be sufficiently raised by DDAVP in some patients with mild to moderate hemophilia A and VWD to allow dental extractions without transfusion. For extensive surgery, additional postoperative factor maintenance may be indicated, accomplished by infusion of factor concentrates, DDAVP, cryoprecipitate, or FFP.

Postsurgical bleeding due to fibrinolysis commonly starts 3–5 days after surgery and can usually be controlled by local measures and use of antifibrinolytics. Continual oozing from unstable fibrinous clots (i.e., "liver clots") may require their removal and the repacking of the extraction socket with local hemostatic agents. The use of fibrin sealants has allowed reduction in factor concentrate replacement levels in hemophiliacs undergoing dental surgeries when used in combination with antifibrinolytics.[179,180,181] However, the use of fibrin glue does not obviate the need for factor concentration replacement in severe hemophiliacs.[182]

Periodontal surgical procedures warrant elevating circulating factor levels to 50% and use of post-treatment antifibrinolytics. Periodontal packing material aids in hemostasis and protects the surgical site; however, it may be dislodged by severe hemorrhage or subperiosteal hematoma formation.

Dental Management of Patients on Anticoagulant Therapy

Management of the dental patient on anticoagulant therapy involves consideration of the degree of anticoagulation achieved as gauged by the laboratory values, the dental procedure planned, and the level of thromboembolic risk for the patient.[183] In general, higher INRs result in higher bleeding risk from surgical procedures.[184]

Vitamin K Antagonists

It is generally held that nonsurgical dental treatment can be accomplished without alteration of the anticoagulant regimen, provided that the PT/INR is not well above the therapeutic range and trauma is minimized.[185,186,187] Some controversy exists over the management of anticoagulated patients for oral surgical procedures.[188,189,190] Patients who discontinue warfarin preoperatively are exposed to 3–4 days at subtherapeutic anticoagulation levels postoperatively after immediate resumption of therapy. Risks of a life-threatening thromboembolic event are 3–5-fold greater than that of significant uncontrollable postoperative bleeding.[191] The American Heart Association and American College of Cardiology scientific statement recommends that for patients undergoing dental procedures, tranexamic acid or EACA (Amicar) mouthwash can be applied without interrupting anticoagulant therapy.[192] The 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend continuing VKAs with coadministration of oral prohemostatic agent or stopping VKAs 2–3 days before minor dental procedures.[193] Systematic reviews and meta-analyses of randomized controlled trials examined the bleeding potential in dental practice of patients on warfarin therapy.[194,195] Among all patients, there were no major bleeding episodes, and there were no differences in the incidence of clinically significant minor bleeding episodes between those who continued their regular dose of warfarin and those who discontinued or altered their dose of warfarin, with local and oral hemostatic agents showing hemostatic benefit.

Preparation of the anticoagulated patient for surgical procedures depends on the extent of bleeding expected and the thromboembolic risk. For surgical procedures, physician consultation is advised in order to determine the patient's most recent PT/INR level and the best treatment approach

based on the patient's relative thromboembolic and hemorrhagic risks. When the likelihood of thrombotic and embolic complications is small and hemorrhagic risk is high, warfarin therapy can be discontinued briefly by the physician at the time of surgery, with reinstitution within a day postoperatively.[181,196,197] Warfarin's long half-life of 42 hours necessitates dose reduction or withdrawal 2 days prior to surgery in order to return the patient's PT/ INR to an acceptable level for surgery.[181,198] For patients with moderate thromboembolic and hemorrhagic risks, warfarin therapy can be maintained in the therapeutic range with the use of local measures to control postsurgical oozing.[199,200]

For surgical treatment for those with a supratherapeutic INR of >3.5–4.0, either deferral, dose modification, or proceeding with precautions (e.g., in a hospital setting with physician support) is considered. With an INR <3.5–4.0, minor surgical procedures with minimal anticipated bleeding may require local measures, but no dose modification. When moderate to significant bleeding is expected (multiple extractions or removal of third molar teeth), local measures should be used and INR reduction may be considered in consultation with the patient's physician. High-risk cardiac patients undergoing high-bleeding-risk surgical procedures may be managed with LMWH bridging. LMWH is a less costly alternative to IV heparin substitution therapy, rarely used today, that does not require hospital admission (e.g., enoxaparin). Using this management technique, a LMWH is substituted for warfarin a few days before surgery, and it is withheld from the patient for only a few hours on the day of the surgery.[201]

Use of additional local hemostatic agents such as microfibrillar collagen, oxidized cellulose, or topical thrombin is recommended for anticoagulated patients. Fibrin sealant has been used successfully as an adjunct to control bleeding from oral surgical procedures in therapeutically anticoagulated patients with INRs from 1.0 to 5.0, with minimal bleeding complications.[202] Use of antifibrinolytics may have value in control of oral wound bleeding, thereby alleviating the need to reduce the oral anticoagulant dose.[203] Tranexamic acid solution used as an mouthwash has proven effective in control of oral surgical bleeding in patients with INRs between 2.1 and 4.8, and is slightly superior when compared to an autologous fibrin glue preparation.[201,204,205] As previously discussed, the use of medications that interact with and alter warfarin's anticoagulant effectiveness is to be avoided.

Heparin

Continuous IV unfractionated heparin, which has the greatest hemorrhagic potential among the heparin techniques, is discontinued 6–8 hours prior to surgery to allow adequate surgical hemostasis. In general, oral surgical procedures can be carried out without great risk of hemorrhage when local hemostatics are used in a patient receiving LMWH subcutaneously; however, on consultation, the patient's physician may recommend withholding the scheduled injection only a few hours prior to the operation. One small retrospective study found no postoperative bleeding events after invasive dental procedures for patients on LMWH alone, with several instances in patients who were concurrently on LMWH and warfarin.[206] If a bleeding emergency arises, the action of heparin can be reversed by protamine sulfate. Dosage for unfractionated heparin reversal is 1 mg protamine sulfate IV for every 100 units of active heparin. If given within 8 hours of the LMWH injection, then the maximum neutralizing dose of 1 mg protamine/100 units of LMWH given in the last dose is used.

Direct Oral Anticoagulants

The Scottish 2015 guideline recommends that the provider have a discussion with the patient about possible benefits and harms for continuing or interrupting medications and consider short-term interruption of DOACs only for high-risk invasive dental procedures (e.g., >3 extractions, flap surgery, periodontal surgery, crown lengthening, biopsies).[207] Because of the short half-lives of these agents, the recommendations entail morning procedure appointments, in which the morning dose or daily dose is skipped, and then the evening or next-day dose is resumed, in the case of twice-a-day medications (e.g., apixaban or dabigatran) and once-a-day medications (e.g., rivaroxaban), respectively. Additional advice includes treatment early in the day and beginning with a limited treatment area (i.e., 1–2 teeth) to allow hemostasis monitoring and reassessment, and use of local hemostatic measures.[207] A 2019 systematic review evaluated the literature concerning the dental management of patients on DOACs, assessing for the incidence of postoperative bleeding complications.[208] They found that there were no differences in the incidence and severity of postoperative bleeding complications in patients who continued DOACs versus those that discontinued DOACs prior to dental procedures, including extractions, in addition to the absence of any thromboembolic events recorded.

GENERAL DENTAL MANAGEMENT CONSIDERATIONS

Dental modifications for patients with bleeding disorders depend on both the type and invasiveness of the dental procedure and the type and severity of the bleeding disorder. Thus, little or no modification is needed for patients with mild coagulopathies prior to dental procedures with limited consequences from bleeding. More modification is needed for those with severe coagulopathies or prior to

dental procedures anticipated to have great risks of bleeding. When there is greater concern for significant bleeding, the goal of management is to restore the hemostatic system preoperatively to an acceptable range while utilizing adjunctive and/or local measures. For reversible or acute hemostatic disorders, it may be best to treat the primary illness or defect in order to allow the patient to return to a manageable bleeding risk for the dental treatment period. With respect to therapeutic alterations in hemostasis due to medications (e.g., clopidogrel, warfarin, dabigatran), local hemostatic measures usually suffice; however, there are limited instances in which drug discontinuation or dose alteration may be recommended and accomplished by the patient's physician. For irreversible inherited coagulopathies, the missing or defective element may need to be replaced from an exogenous source. Assessment of the coagulopathy and delivery of appropriate therapy prior to dental procedures are best accomplished in consultation with a hematologist and may dictate treatment in specialized hospital facilities.[209]

Local Hemostatic Measures

Local hemostatic agents and techniques include pressure, surgical packs, vasoconstrictors, sutures, surgical stents, topical thrombin, and use of absorbable hemostatic materials (Table 18-8). Although having no direct effect on hemostasis, primary wound closure aids patient comfort, decreases blood clot size, and protects clots from masticatory trauma and subsequent bleeding.[210] Sutures can also be used to stabilize and protect packing, with resorbable and nonresorbable suture materials shown to be equally effective. Microfibrillar collagen fleeces (e.g., Avitene, Helitene) aid in hemostasis when placed against the bleeding bony surface of a well-cleansed extraction socket. This acts to attract platelets, triggering aggregation of platelets into thrombi in the interstices of the fibrous mass of the clot.[211] Surgifoam and Gelfoam are absorbable gelatin compressed sponges with intrinsic hemostatic properties. A collagen absorbable hemostat manufactured as a 3 in. × 4 in. sponge (INSTAT) or fabricated as a nonwoven pad or sponge (Helistat, Gelfoam, Ultrafoam) is also a useful adjunct.

Topical thrombin (Thrombogen) directly converts fibrinogen in blood to fibrin, and is an effective adjunct when applied directly to the wound or carried to the extraction site in a nonacidic medium on oxidized cellulose. Surgical acrylic stents may be useful if carefully fabricated to avoid traumatic irritation to the surgical site.

Fibrin sealants or fibrin glue is a biologic tissue adhesive that simulates the final stages of coagulation and has been used effectively as an adjunct with adhesive and hemostatic effects to control bleeding at wound or surgical sites.[212] Commercially available as Tisseel, it has been useful in periodontal surgery, or even as an alternative to sutures.[213]

Diet restriction to full liquids for the initial 24–48 hours, followed by intake of soft foods for 1–2 weeks, will further protect the clot by reducing the mechanical trauma from chewing.

Table 18-8 Local hemostatic agents.

Brand Name	Generic Name or Description
Gelfoam (Pfizer, New York, USA) Surgifoam (Ethicon, Somerville, NJ, USA)	Absorbent gelatin sponge material
INSTAT (Ethicon)	Collagen absorbable sponge
Surgicel (Ethicon)	Oxidized cellulose
Thrombogen (Ethicon)	
Avitene (Davol, Cranston, RI, USA) Helitene (Integra Life Sciences, Plainsboro, NJ, USA)	Microfibrillar collagen fleeces
Bleed-X (QAS, Orlando, FL, USA)	Microporous polysaccharide hemispheres
Tisseel VH (Baxter, Deerfield, IL, USA) Tissucol (Termo trattato, Wien, Austria)	Fibrin sealant
Cyklokapron (Pfizer)	Tranexamic acid
Amicar (Wyeth-Ayerst, Wayne, PA, USA)	Episilon-aminocaproic acid

Antifibrinolytics

Antifibrinolytic drugs such as ε-aminocaproic acid (EACA; Amicar 25% syrup) and tranexamic acid (AMCA; Lysteda, Cyklokapron) inhibit fibrinolysis by blocking the conversion of plasminogen to plasmin, resulting in clot stabilization. They are very useful for oral procedures because fibrinolysis is highly active on mucosal surfaces. Products are available for use systemically (oral or IV) and/or topically, as a mouthwash. Postsurgical use of EACA has been shown to significantly reduce the quantity of factor required to control bleeding when used in conjunction with presurgical concentrate infusion sufficient to raise plasma F VIII and F IX levels to 50%.[178,214,215] A regimen of 50 mg/kg of body weight EACA given topically and systemically as a 25% (250 mg/mL) oral rinse every 6 hours for 7–10 days appears adequate as an adjunct. Tranexamic acid (4.8%) oral rinse, not commercially available in the United States, was found to be 10 times more potent than EACA in preventing postextraction bleeding in hemophiliacs, with fewer side effects.[216,217] Systemic antifibrinolytic therapy can be given orally or IV as EACA 75 mg/kg

(up to 4 g) every 6 hours or AMCA 25 mg/kg every 8 hours until bleeding stops.[176] For the treatment of acute bleeding syndromes due to elevated fibrinolytic activity, it is suggested that 10 tablets (5 g) or 4 teaspoons of 25% syrup (5 g) of Amicar be administered during the first hour of treatment, followed by a continuing rate of 2 tablets (1 g) or 1 teaspoon of syrup (1.25 g) per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding has been controlled. Amicar syrup–soaked gauze packs, used for application of pressure to wound sites, are also often successful at assisting hemostasis.

Susceptibility to Infection

Susceptibility to infection among patients with congenital bleeding disorders is not a significant concern. However, hemophiliacs may have had a total joint replacement due to bleeding into weight-bearing joints, for which some authorities would recommend antibiotic prophylaxis prior to invasive dental procedures;[218] however, hemophilic arthropathy as cause of orthopedic implants does not meet current guidelines for elevated risk.[216] Should a hematoma form as a result of an anesthetic injection, other dental or intubation trauma, or spontaneously, it should be observed for clinical signs of infection, and if these develop use of a broad-spectrum antibiotic may be indicated during resolution.[219] If bleeding results from bone marrow–suppressive systemic disease or chemotherapeutic drug use, antibiotics may be used to prevent infection from bacteremia-inducing dental procedures when production of mature functional neutrophils is substantially diminished.

Pain Control and Local Anesthesia

The use of ASA and other NSAIDs for pain management is generally avoided in patients with bleeding disorders, due to inhibition of platelet function and potentiation of bleeding episodes.

Caution must be exercised when administering local anesthetic via nerve-block injections in hemophiliacs, as there is a risk of hematoma formation when anesthesia is administered in a highly vascularized area. Nerve blocks might be avoided by use of nitrous oxide–oxygen analgesia for some restorative procedures. Local anesthetic procedures in hemophiliacs that do not require preoperative factor infusion include buccal infiltration, interpapillary injection, endodontic (root canal) treatment, and intraligamentary injections.[220] Patients on anticoagulants and with platelet disorders generally are not at increased risk from block anesthesia.

Block injections place anesthetic solutions in highly vascularized, loose connective tissue with no distinct boundaries, where formation of a dissecting hematoma is possible, occurring in 8% of hemophilic patients not treated with prophylactic factor replacement prior to mandibular block injection (Figure 18-10).[221] Extravasation of blood into the soft tissues of the oropharyngeal area in hemophiliacs can produce gross swelling, pain, dysphagia, respiratory obstruction, and risk of death from asphyxia. For routine anesthetic blocks, minimum clotting factor levels of 20%–30% are required.[222] In addition, an anesthetic with vasoconstrictor should be used. Intramuscular injections should also be avoided due to the risk of hematoma formation.

Ability to Withstand Care

Patients with bleeding disorders, appropriately prepared preoperatively, are generally able to tolerate invasive dental procedures, although consultation with the patient's physician is recommended for guidance on medical management for higher-risk surgical procedures.

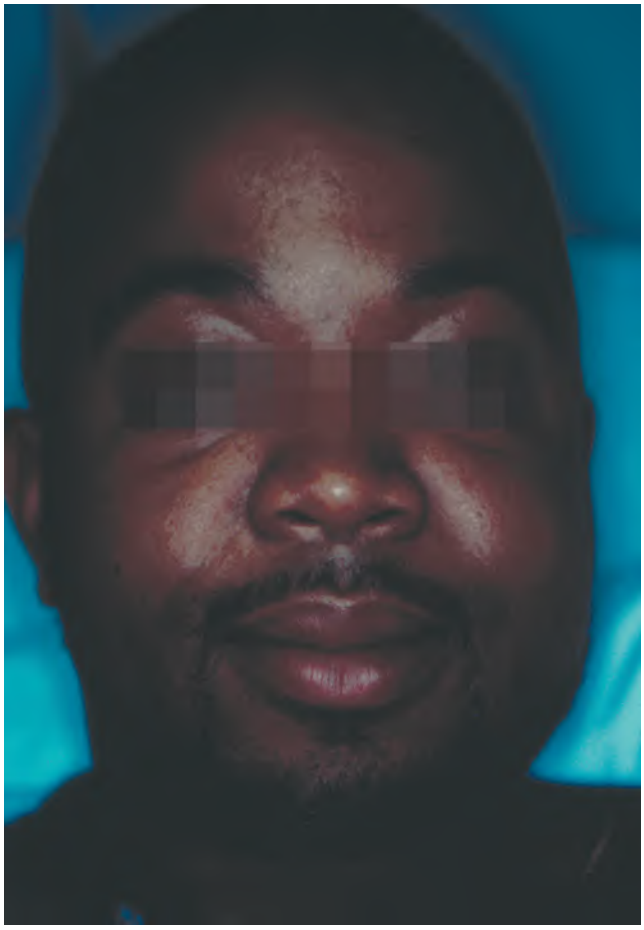

Figure 18-10 A 24-year-old man with severe hemophilia A and low-titer inhibitor, 3 days after inferior alveolar nerve block–induced parapharyngeal hemorrhage. The patient presented with difficulty swallowing and pending airway compromise 8 hours after nerve block. Subsequent treatment with PCCs over 3 days controlled the bleeding and began the resolution of facial swelling.

Extended dental treatment sessions or dental treatment in the operating room under general anesthesia may help to maximize treatment accomplishments at one visit and thereby minimize the risk and cost from some medical management protocols for severe bleeding disorders (e.g., coagulation factor replacement for severe hemophiliacs, warfarin withdrawal–heparinization approach for patients at high risk of thrombosis). The general anesthesia approach may also be useful when patient cooperation or anxiety prohibits outpatient clinic or office treatment, or the patient has extensive treatment needs. Although oral endotracheal intubation creates an access challenge for the dentist, it is preferred over nasal endotracheal intubation with its risk of inducing a nasal bleed.

Preventive and Periodontal Therapies

Periodontal health is of critical importance for the patient with a coagulopathy, because hyperemic gingiva contributes to spontaneous and induced gingival bleeding. Periodontitis is a leading cause of tooth morbidity and often necessitates extraction(s). Individuals with bleeding diatheses are unusually prone to oral hygiene neglect due to fear of toothbrush-induced bleeding; however, regular oral hygiene can be accomplished without risk of significant bleeding. Periodontal probing and supragingival scaling and polishing can generally be done routinely without modification. Careful subgingival scaling with fine scalers rarely warrants replacement therapy. Inflamed and swollen tissues are best treated initially with chlorhexidine oral rinses, or by superficial gross debridement with ultrasonic or hand instruments to allow gingival shrinkage prior to deep scaling. Deep subgingival scaling and root planing should be performed by quadrant to reduce the gingival area exposed to potential bleeding. Locally applied pressure and post-treatment antifibrinolytic oral rinses are usually successful in controlling any protracted bleeding.[223,224] Surgical periodontal therapy is considered to have a high risk of bleeding, if it involves raising a flap.[225] However, expert opinion recommends that treatment may continue for those on anticoagulant therapy, if INR is within the therapeutic range in the case of VKAs.

Restorative, Endodontic, and Prosthodontic Therapy

General restorative, endodontic, and prosthodontic procedures do not result in significant bleeding beyond the ability to control with local measures. Rubber dam isolation is advised to minimize the risk of lacerating soft tissue in the operative field and to avoid creating ecchymoses and hematomas with high-speed evacuators or saliva ejectors. It is important to select a rubber dam clamp that does not traumatize the gingiva. Matrices, wedges, and a hemostatic gingival retraction cord may be used with caution to protect soft tissues and improve visualization when subgingival extension of cavity or crown preparation is necessary. Cold water or antifibrinolytic-impregnated gauze pressure may aid in hemostasis.

Endodontic therapy is often the treatment of choice over tooth extraction for patients with severe bleeding disorders, due to the higher risk of hemorrhage from the latter. As always, instrumentation and filling beyond the apical seal should be avoided. Application of epinephrine intrapulpally to the apical area is usually successful in providing intrapulpal hemostasis. Endodontic surgical procedures require the same factor replacement therapy as do oral surgical procedures.

Removable prosthetic appliances can be fabricated without complications, but the postdelivery appointments are important to prevent against mucosal trauma. Denture trauma should be minimized by prompt and careful postinsertion adjustment.

Pediatric Dental Therapy

The pediatric dental patient occasionally presents with prolonged oozing from exfoliating primary teeth. In a child with factor deficiencies, administration of factor concentrates and extraction of the deciduous tooth with curettage may be necessary for patient comfort and hemorrhage control. One suggestion is the extraction of mobile primary teeth using periodontal ligament anesthesia without factor replacement after 2 days of vigorous oral hygiene to reduce local inflammation.[226] Hemorrhage control is obtained with gauze pressure, and hemostasis is achieved in 12 hours. Pulpotomies can be performed without excessive pulpal bleeding. Stainless-steel crowns should be prepared to allow minimal removal of enamel at gingival areas.[227]

Orthodontic Therapy

Orthodontic treatment can be provided with little modification. Care must be observed to avoid mucosal laceration by orthodontic bands, brackets, and wires. Bleeding from minor cuts usually responds to local pressure. Properly managed fixed orthodontic appliances are preferred over removable functional appliances for the patient with a high likelihood of bleeding from chronic tissue irritation. The use of extraoral force and shorter treatment duration further decrease the potential for bleeding complications.[228]

Dental Implants

Surgery for dental implant placement is approached with preparation in a similar manner as dental extractions, including

augmentation of hemostasis before surgery and postoperative use of antifibrinolytic and other topical approaches.[229]

Dental Surgery (Extractions)

Dental surgical management draws on disease-specific approaches to management of the underlying bleeding diathesis, some of which were discussed in the medical management section. All patients with bleeding disorders should be specifically educated about possible prolonged intraoral bleeding and intraoral and extraoral ecchymosis as part of informed consent. Risks and benefits of preoperative and postoperative management strategies should be discussed among physician, dentist, and patient to allow shared decision-making.

NOTE

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19

Immunologic Diseases

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THE IMMUNE SYSTEM: PROTECTION FROM PATHOGEN CHALLENGE

A significant number of oral diseases result from defects or deficits in the immune system. The immune system is extremely complex, but is composed of both the innate and adaptive immune systems, served by diverse cell types that have the primary function of defending the body against infection. To achieve this, the immune system has to distinguish between self and non-self and identify foreign invaders as distinct from self.[1] In this way, the immune system can recognize and clear invading pathogens such as viruses, bacteria, or parasites, but tolerate antigens derived from innocuous proteins, and self-antigens as well as commensal microbiota. When responding to an invading pathogen, the immune system is responsible for coordinating an effective immune response, which will not only neutralize the invading pathogen, but remove dead or damaged cells and turn itself off once the pathogen has been removed. Furthermore, the immune system is tasked with mediating responses to injury, cell death, and tumor surveillance. An appropriately functioning immune system is vital for life and its importance is highlighted by the fact that its dysfunction underpins a plethora of diseases, ranging from infection to cancer and autoimmunity; within the oral cavity, immune system dysfunction contributes to the pathology of gingivitis, periodontitis, oral infections, and autoimmune manifestations of systemic or local disease.

Immune responses in humans, and indeed all vertebrates, are mediated by two distinct yet connected systems: the *innate* and the *adaptive* immune systems.[2] The innate immune system is immediately activated upon injury or pathogen encounter. This activation occurs in a nonspecific manner, but is often capable of independently eliminating the invading insult. However, when the innate immune response is unable to control the insult, it will recruit and activate an adaptive immune response. The adaptive immune system is highly targeted, not only ensuring that the right type of immune response is activated for the type of infection, for example viral verses parasitic, but also becoming targeted to the specific invader. Moreover, it will later provide memory for the specific pathogen, allowing a faster, more effective immune response to be mounted upon any subsequent encounter with the same pathogen. The two systems are heavily connected. However, the innate immune system is absolutely vital for effective protection against injury and infection, particularly at mucosal sites.

THE IMMUNE SYSTEM OF THE MOUTH

Successful defense of oral mucosal barriers requires secretion of saliva, an effective epithelial barrier, and activation of innate and adaptive immune cells. Indeed, we consider saliva, a mucosal barrier, and the immune cell network to be the pillars of the oral immune system (Figure 19-1).

Saliva

Saliva, the extracellular fluid secreted by salivary glands in the mouth, plays a critical role in immune protection at the oral mucosal barrier. Saliva contains 99% water, but also electrolytes, enzymes for digestion (amylase, lipase), mucus, and antimicrobial components. Key antimicrobial components in saliva are secretory immunoglobulin (Ig) A, microbiocidal enzymes such as lysozyme, lactoperoxidase, lactoferrin, proline-rich proteins, and antimicrobial peptides (histatins, defensins, secretory leukocyte protease inhibitor [SLPI]). Saliva provides constant lubrication and ensures the health and integrity of the mucosal barrier. Indeed, patients with reduced or absent saliva (dry mouth to hyposalivation) suffer from mucosal inflammation and ulcerations, which lead to pain and difficulty eating. Saliva also clearly provides effective antimicrobial defense, particularly toward specific microbial pathogens. In fact, patients with xerostomia present predominantly with oral candidiasis (a mucosal infection with *Candida albicans*) as well as severe to rampant dental infections with "cariogenic" (dental caries–causing) bacteria, such as *Streptococcus mutans*.

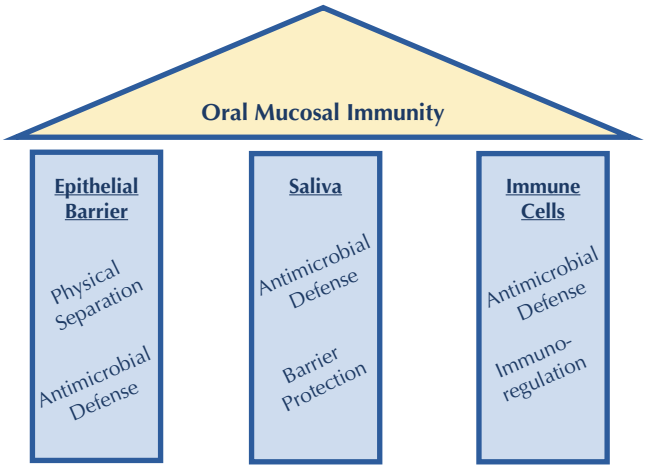

Figure 19-1 Epithelial barrier, saliva, and immune cell network are the three pillars of oral mucosal immunity, providing physical separation, antimicrobial defense, and immuno-regulation to achieve a balance between host and environment.

Oral Epithelium

The oral epithelial barrier is a key interface of the human body with the external environment, providing physical, structural, and immunologic protection to infectious challenge. The oral mucosa is lined with a multilayer squamous cell epithelium. This epithelium is fortified to a different extent depending on the area of the oral cavity and its functional needs. In the hard palate, dorsum of tongue, and gingiva, the epithelium is fully keratinized to withstand the constant mechanical damage induced during mastication. However, the majority of the oral epithelial barrier is composed of lining epithelium, a multilayered squamous cell epithelium with minimal keratinization. Such epithelium lines the buccal mucosa, the labial mucosa, the gingival crevice, and the floor of the mouth. These areas are more exposed to the outside environment, not only because of minimal keratinization, but because some of them have thinner epithelium and increased vascularity (such as the floor of the mouth).

However, possibly the most exposed and vulnerable site of the oral mucosal barrier is the junctional epithelium (the connection between teeth and mucosa). The junctional epithelium, which directly attaches to the surface of the tooth, is only three to four cells thick at its narrowest points near the teeth and is nonkeratinized. This means that the junctional epithelium is a weak point in the oral mucosal barrier. However, by being nonkeratinized, it is permeable, and therefore serves as the primary pathway for the transmigration of immune cells, particularly neutrophils, and fluid into the oral space. This fluid, termed gingival crevicular fluid, contains host-defensive proteins that are then at a high concentration on the external side of the junctional epithelium. Thus, the oral epithelium is locally specialized, providing a physical barrier protecting underlying tissues. Alongside this, oral epithelial cells are key sources of pro-inflammatory cytokines and chemokines and directly respond to pathogens; as such, disruption of the epithelium constitutes a risk factor for infection and aberrant inflammation.

Immune Cells

The oral cavity is constantly exposed to environmental stimuli, including a resident commensal bacterial community, continuous damage from mastication, and pathogen challenge. The ceaseless nature of these local triggers requires active immune surveillance within the mouth. This means that in addition to saliva and specialized epithelium, immune cells are resident even within healthy oral mucosa to ensure effective barrier defense, regulation, and healing. Here we will introduce the main mediators of the immune system, first those of the innate and then the adaptive immune system, outlining how these systems play key roles in safeguarding health and driving pathology.

Innate Immunity

The major innate immune cells present within the oral mucosa are *neutrophils*. These are short-lived (24–48 hours) cells that make up about 70% of peripheral blood white blood cells. Neutrophils are activated by bacterial products, exhibiting profound antimicrobicidal activity, through ingestion of bacteria (phagocytosis) and release of soluble and nonsoluble components that can trap and kill extracellular pathogens.[3] These cells are rapidly mobilized to sites of pathogen invasion, being the first innate immune cells to extravasate from blood vessels, via a well-defined series of events, and migrate toward the infection. Here, neutrophils release reactive oxygen species (ROS), granules containing cytotoxic compounds and antimicrobial peptides, and neutrophil extracellular traps (NETs), which combined create an environment proficient at pathogen killing, degradation, and removal.

Even in health, neutrophils constitute the majority of immune cells present in the gingival oral barrier. Neutrophils constantly traffic from the circulation, through gingival tissue and junctional epithelium, into the gingival crevice. It has been demonstrated that about 30,000 neutrophils undertake this journey every minute in humans, and as such neutrophils can be found within the oral cavity.[4] The functional contributions of neutrophils outside the tissue, within the oral cavity, remain to be defined, but it is clear that effective neutrophil surveillance of the gingival barrier is vital for oral health, as oral inflammation routinely occurs when neutrophil functions and numbers are dysregulated.

Other innate immune cells resident within the oral mucosa include mononuclear phagocytes, phagocytic cells including *monocytes*, *macrophages*, and *dendritic cells* (DCs).[5] The main function of monocytes, and their macrophage progeny, is to internalize pathogens and dead/dying cells and degrade them in an organelle that has a low pH and is filled with hydrolytic enzymes: the phagosome. In this way, monocytes and macrophages are considered functionally plastic, as they mediate key roles in both pathogen protection, but also tissue repair and healing. At other mucosal sites, macrophages are crucial for the maintenance of barrier homeostasis, adopting barrier-specific functions that support health. For example, in the gastrointestinal tract, macrophages constitutively produce the anti-inflammatory cytokine interleukin (IL)-10. However, the functional characteristics and importance of macrophages within the oral barrier remain to be determined.

The main function of DCs is to internalize and process foreign particles to generate small peptide antigens that can be presented on their cell surface to T cells. Therefore, DCs are considered "professional" *antigen-presenting cells* (APCs) and are key initiators of the adaptive immune response. Upon activation, barrier-resident DCs become more effective at processing and presenting antigens and drain to local lymph nodes, where they interact with, and activate, T cells. *Langerhans cells* are perhaps the best studied of the oral DCs, residing in the oral epithelium, but multiple populations of DCs have been described, each of which exhibits enhanced capabilities at initiating specific types of T-cell response. Although the DC populations at certain oral barriers have been well characterized, we are only just beginning to understand how distinct subsets contribute to the mounting of effective T-cell responses within the oral cavity.

The *complement system* is a major arm of innate immunity that enhances pathogen clearance by promoting pathogen phagocytosis, antigen presentation, and immune cell activation, and can also attack the cell surface of any invader. The complement system consists of multiple plasma proteins (C1-9), pattern-recognition molecules, and proteases that operate in a cascade to opsonize pathogens and induce proinflammatory responses. As such, complement plays a vital role in promoting effective immune responses upon pathogen challenge. However, complement can also become dysregulated and has been shown to contribute to pathology in diseases such as cancer and autoinflammatory diseases; in particular, excessive complement activation is seen in patients with periodontitis.

Alongside these key innate immune mediators are populations of cells that exhibit characteristics of both the innate and adaptive immune systems. These include *innate lymphoid* cells (ILCs), *natural killer* (NK) cells, and *γδ-T* cells. Although lymphocytes, these cells are not activated by peptide antigens and instead rapidly respond to signals of tissue and cellular perturbation, either producing an array of immunomodulatory cytokines or inducing cell death of infected cells. In mediating such functions, ILCs, NK, and γδ-T cells are all at low frequencies in peripheral blood but are enriched at mucosal barrier sites. Within the oral cavity all these immune cells have been identified,[6] with specialized populations of ILCs and NK cells present in salivary glands and oral barrier-resident γδ-T cells being shown to safeguard gingival immune homeostasis and limit periodontitis development.

Adaptive Immunity

Activation of innate immunity culminates in the development of highly specific immune responses, which are antigen specific and coordinated by cells of the adaptive immune system, specifically *lymphocytes*. There are two types of lymphocytes, *B cells* and *T cells*, which express genetically rearranged and extremely diverse antigen receptors. These receptors allow the B or T cell to be activated in an antigen-specific manner, thus imparting the specificity exhibited by these cells.

The B-cell receptor is a surface-bound immunoglobulin molecule, which recognizes both linear and conformation antigens. Recognition of antigen via this immunoglobulin receptor, alongside some additional activation signals, allows B cells to start producing soluble immunoglobulins, also known as *antibodies*. Antibodies can neutralize pathogens, for instance bind to viruses and prevent cell entry, activate immune cells, and activate the complement cascade. Initially B cells will produce IgM; however, as the immune response develops, B cells undergo class switching, a genetic rearrangement that allows B cells to produce other antibody isotypes: IgG, IgA, IgD, or IgE. The different isotypes have distinct constant regions that do not participate in antigen binding, but instead are important for the effector function of the antibody. For example, IgE will preferentially bind to antibody receptors expressed on mast cells, triggering the release of histamine during parasitic worm infection and allergy. IgG is the dominant antibody found in plasma and can be transported across the placenta to impart a degree of fetal protection.

The mouth is part of the mucosal immune system, embracing all mucosal epithelium including that of the gut, lungs, respiratory and genital tracts, breast, and eyes and with a total surface area of 400 m^2. The surfaces are protected by mucins but adaptively by secretory IgA, which can be induced by immunization in the gut or nose and independently from serum IgA. Thus, antibodies found in secretions, such as saliva or bronchial secretions, are usually IgA (or sometimes IgM) produced by plasma cells within mucosal tissues. The IgA secreted by plasma cells in the lamina propria links to the secretory component, which facilitates antibody transport through the secretory epithelium. Mucosal IgA is mainly dimeric, in contrast to serum IgA. It protects by virus or enzyme neutralization, by aggregation of bacteria, and by preventing adherence of pathogens to the host.

Oral commensal bacteria-specific antibodies, predominantly IgA, can be detected in the oral fluids of even healthy individuals and certain oral commensals have been shown to be coated in IgA. In addition, autoantibodies in various autoimmune diseases can be detected in saliva, which can be used as a diagnostic fluid. Serum antibodies against oral commensal bacteria have also been detected, and there are some indications that they may help regulate the bacterial communities on the surfaces of the teeth and more generally within the oral cavity, acting via crevicular fluid.

For T cells to become activated, antigen must be processed and bound to a class I or class II major histocompatibility complex (MHC) molecule on the surface of an APC. Antigens recognized by the T-cell receptor are short linear peptide sequences, which are recognized in the context of the MHC in which they are presented. In terms of T-cell activation, encounter of cognate antigen bound to MHC is considered "signal 1," but an additional signal is required for full T-cell activation. "Signal 2" is co-stimulation, whereby ligand-receptor pairs on the surface of the T cell and APC interact to further promote T-cell activation; in this way T-cell activation is strictly controlled.

There are two types of T cells: $CD4^+$ and $CD8^+$ T cells. *$CD8^+$ T cells* are activated by peptide antigens of intracellular origin (therefore most likely viral antigens), which are presented by MHC class I molecules. Activated $CD8^+$ T cells proliferate and differentiate to become *cytotoxic lymphocytes* (CTLs), which are highly effective killing machines capable of inducing the cell death of multiple target cells presenting their specific antigen. *$CD4^+$ T cells* are activated by peptides bound to MHC class II molecules, whereupon they differentiate into different subsets of T-helper (Th) cells.[7] $CD4^+$ T cells can be considered to require a "signal 3," which drives the activated $CD4^+$ T cell to differentiate into either a Th1, Th2, Th17, or regulatory T cell (Treg). Th1 and Th2 cells were the first $CD4^+$ T cell subsets identified in the 1980s. *Th1 cells* help promote the clearance of bacteria and viruses, whereas *Th2 cells* are generated in response to parasitic worm infections and help fight off these large extracellular pathogens. Th1 cells predominantly produce the cytokine IFNγ, which activates macrophages, making them more effective at phagocytosing and killing pathogens and supports $CD8^+$ T cell differentiation into CTLs. Th2 cells predominantly produce the cytokines IL-4 and IL-13. These cytokines subsequently promote a coordinated immune response that clears worm infection by promoting eosinophil recruitment and epithelial shedding.

More recently, *Th17 cells* have been identified, which are distinguished by their production of the cytokines IL-17A and IL-17F.[8] This subset is vital for defending against fungal infection, and individuals with defects in the generation or function of this subset frequently present with persistent candidiasis. Th17 cells promote neutrophil recruitment to the site of infection and also enhance the production of antimicrobial peptides by epithelial cells. The final classical subset of $CD4^+$ T cells is *Tregs*; unlike the other subsets, Tregs do not promote effective immunity, but instead play key roles in the suppression of immune responses. Tregs are defined by the expression of the transcription factor Foxp3 (or scurfin) and have been shown to be vital mediators of peripheral tolerance. Their importance to health is highlighted by the severe autoinflammatory disease that results in their absence; individuals with mutations in the *Foxp3* gene develop IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked), a lymphoproliferative disease in which self-reactive T cells target multiple bodily organs and inappropriate T-cell responses are mounted to harmless antigens. Indeed, defects in Treg numbers and function have been identified in patients with a plethora of different inflammatory diseases. Of note from a therapeutic standpoint is that in experimental systems, increases in Tregs have been shown to limit the pathology of autoinflammatory diseases, including periodontitis.

Following the clearance of any invading organism, most activated, differentiated T-cell populations undergo apoptosis as pathogen-derived antigens are removed. However, a subset of antigen-specific T cells survives and persists long-term after pathogen clearance. These are known as *memory T cells* and remain within the body to rapidly respond should reinfection with the same pathogen occur. Different types of memory T cells exist. Some continuously circulate through the body similar to naïve T cells, awaiting reactivation. Others become resident in the tissues in which the pathogen challenge occurred. In this way, mucosal barriers show increased proportions of resident memory T cells, which promote rapid effector responses and site-specific protection against pathogens.

Within oral barriers, most resident T cells exhibit a memory phenotype, and most are $CD4^+$ T cells. In health, resident effector $CD4^+$ T cells predominantly produce the cytokine IFNγ, as outlined earlier, the canonical Th1 cytokine. Alongside these effector cells, resident within the oral mucosa are Tregs, presumably to help regulate local inflammatory reactions. At other barrier sites, most notably the gastrointestinal tract and skin, Th17 cells are resident during health, help the host establish an appropriate dialogue with the commensal bacterial community, and also promote epithelial barrier function. This is not the case in the oral cavity, where Th17 numbers are low in healthy tissues but are dramatically expanded during periodontitis.[8] Indeed, emerging studies indicate that Th17 cells are key mediators of pathology in periodontitis, and that targeting these cells could provide a novel opportunity in the treatment of this disease.

Maintenance of Immune Homeostasis in the Oral Cavity

Maintenance of immunologic health within the oral cavity is an active process, with local immune mediators of both the innate and adaptive arms of the immune system acting in coordination to reinforce barrier integrity and prevent pathogen invasion.[9] This local immune activity will also shape and constrain the local commensal bacterial community.

Ongoing studies have begun to delineate the immune populations present at distinct oral sites and what is becoming clear is that a unique immune network polices oral mucosal barriers compared to other mucosal barrier sites. The unique aspects of immune functioning at oral barriers likely reflect the need for specific immune activities that are required to maintain homeostasis at these sites. For example, given that oral mucosal sites constantly experience mechanical damage as a result of mastication, there is a requirement for rapid and continuous healing; immune mediators within the oral cavity would promote this. The unique nature of the oral immune network can most readily be seen in the high numbers of neutrophils present at this site, as well as the continuous recruitment and extravasation of neutrophils through the oral epithelium that occur during health. Indeed, the continuous extravasation of neutrophils through the oral epithelium does not happen across any other healthy mucosal barrier. Ultimately, the combined activities of both innate and adaptive immune cells are required for effective defense of oral barriers. The complex nature of this defensive network is readily highlighted by the plethora of oral pathologies that result when any aspect of it malfunctions.

PRIMARY IMMUNODEFICIENCIES

Primary immunodeficiencies (PIDs, also known as inborn errors of immunity) include a group of more than 300 genetic disorders, which are typically caused by single-gene mutations and impair specific mechanisms of immune function. Although PIDs were previously thought to be very rare conditions, they are now known to affect 1 of every 1200–2000 individuals, with growing prevalence due to increased testing and recognition. The clinical presentation of PIDs is variable and often includes severe or unusual infections with a single type of infectious agent. Importantly, autoimmunity, autoinflammation, and malignancy are increasingly recognized as signs of PID disease. In 2015 the expert committee of the International Union of Immunological Societies (IUIS) developed an updated classification scheme[10] to categorize PID diseases into nine categories based upon the segment of the immune system affected, and it provides a clinically oriented strategy for disease categorization that can facilitate diagnosis and management.[11]

Multiple PIDs present with significant oral manifestations, ranging from oral infections to severe periodontal disease, craniofacial anomalies, and malignancy. Recognition of such disease is key in oral medicine, as such patients often present with significant and challenging clinical needs and therefore diagnosis and disease understanding are necessary to provide specialized care in coordination with a multidisciplinary team of experts. From a scientific standpoint, understanding and characterization of relevant diseases provide insights into the role of specific arms of the immune system in oral health and disease.

This chapter will introduce the basic current classification scheme for PIDs, and present the main features of each major category as well as examples of genes implicated in these diseases (Table 19-1). PIDs with significant oral manifestations will be given increased attention and summarized in the text and in table format (Table 19-2).

Table 19-1 Major categories of primary immunodeficiencies.

Immune FunctionAffected	Genes Affected (Examples)	Clinical Phenotype
1) **Immunodeficiencies affecting cellular and humoral immunity**		
TB^+ SCID	*IL2RG, JAK3, IL7R, CD3D CD3E*	Broad range of life-threatening infections
TB- SCID	*RAG1, RAG2*	As above
CID	*CD40, CD40L, TAP1, TAP2 DOCK8*	Broad range of infections, Milder than SCID
2) **Combined immunodeficiencies with associated syndromic features**		
CID congenital thrombocytopenia	*LOF WAS*	CID with low platelets
CID due to DNA repair defects (e.g., ataxia telangiectasia)	*ATM*	CID with intrauterine growth restriction, facial dysmorphisms
CID due to thymic defects with additional congenital anomalies (e.g. Di George syndrome)	*22q11.2* deletion	CID with structural heart defects, hypoparathyroidism, facial dysmorphisms
CID with immuneosseous dysplasia		CID with skeletal anomalies
Hyper-IgE syndromes (HIES)	*LOF STAT3*	CID with hyper-IgE, AD-HIES, or Job's syndrome (oral features)

Table 19-1 (Continued)

Immune FunctionAffected	Genes Affected (Examples)	Clinical Phenotype
Dyskeratosis congenita (DKC), myelodysplasia, defective telomere	Multiple gene targets	CID with syndromic features DKC is associated with risk for oral cancer
3) **Predominantly antibody deficiencies**		
All serum Ig isotypes affected	*BTK, CD79A, CD79B*	Severe bacterial infections
At least two serum Ig isotypes affected	*CD19, CD20, BAFF-R*	Recurrent infections
Severe reduction in IgG/IgA	*UNG*	Recurrent infections
Specific isotype or functional		May be asymptomatic
4) **Diseases of immune dysregulation**		
Regulatory T-cell defects	*FOXP3, IL2RA, CTLA4*	Multiorgan inflammation and autoimmunity
Autoimmune lymphoproliferative syndrome (ALPS)	*FASLG, FADD, TNFRSF6*	Spenomegaly, adenopathies, autoimmune cytopenias
Immune dysregulation with colitis	*IL10, IL10RA, IL10RB*	Colitis
Familial hemophagocytic lymphohistiocytosis syndromes (e.g. Chédiak–Higashi syndrome)		Fever and cytopenias
Autoimmunity with/without lymphoproliferation (e.g., APECED)	*AIRE, ITCH*	Autoimmunity
5) **Congenital defects of phagocyte number or function**		
Congenital neutropenias	*HAX1, ELANE/ELA2*	Infections, periodontitis
Defects in neutrophil motility	*ITGB2, CTSC, FPR1, RAC2*	Infections, periodontitis
Defects in myeloid respiratory burst	*CYBB, CYBA, NCF1, NCF2*	Infections, hyperinflammatory phenotype
Nonlymphoid defects	*GATA2*	Mycobacterial susceptibility
6) **Defects in intrinsic and innate immunity**		
Mendelian susceptibility to mycobacterial disease (MSMD)	*IL12RB1, IL12B, INFGR1/2, TYK2*	Mycobacterial infections and *Salmonella*
Epidermodysplasia verruciformis (e.g. WHIM)	*TMC6, TMC8, CORO1A, CXCR4*	HPV infections
Predisposition to severe viral infection (NK/T-cell defects)	*STAT1/2, IFNAR2*	HSV, EBV, HHV, VZV
Herpes simplex encephalitis		Encephalitis
TLR signaling pathway deficiency	*IRAK1/4, MYD88*	Pyogenic bacterial infections
Predisposition to invasive fungi	*CARD9*	Invasive candidiasis
Predisposition to mucocutaneous fungal disease	*RORC, IL-17RA, IL17F* *IL17RC, TRAF3IP2*	Mucocutaneous candidiasis
7) **Autoinflammatory disorders**		
Type I interferonopathies	*PSMB8*[a]	Fever, contractures, panniculitis
Defects affecting the inflammasome	*MEFV, NLRP3, NLRP12, NLRP1*	Fevers, inflammatory tissue lesions (IBD or arthritis), rashes
Non-inflammasome-related conditions	*PSTPIPI, IL1RN*	Inflammatory tissue lesions
8) **Complement deficiencies**		
Affecting early complement components	*C1-C4* *C1R-C1S*	SLE Periodontitis
Terminal classic components	*C5-C9*	Neisserial infections
9) **Phenocopy of PID**		
Autoimmune lympho-leuko proliferation	*TNFRSF6, KRAS, NRAS*	Splenomegaly, lymphadenopathy, cytopenia
Autoantibody diseases	*AIRE*	Infections due to antibodies to cytokines

AD-HIES, autosomal dominant hyper-immunoglobulin E syndrome; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; CID, combined immunodeficiencies; EBV, Epstein–Barr virus; HHV, human herpesvirus; HPV, human papillomavirus; HSV, herpes simplex virus; IBD, inflammatory bowel disease; Ig, immunoglobulin; NK, natural killer; PID, primary immunodeficiency; SCID, severe combined immunodeficiency; SLE, systemic lupus erythematosus; TLR, toll-like receptor; VZV, varicella-zoster virus; WHIM, warts, hypogammaglobulinemia, recurrent infections, and myelokathexis.

Table 19-2 Common oral manifestations in primary immunodeficiency.

Oral Manifestations	Immune Mechanism Involved	Specific Mutations/Syndromes
Recurrent herpetic infections Human papilloma viruses	T-cell/NK T-cell function	Tapasin genes/MHCI deficiency MHCII deficiency Deletion chromosome 22q11.2/ DiGeorge *DOCK8* *WAS*/Wiskott–Aldrich syndrome SCID
Odontogenic infections	B cells	*BTK*/BTK deficiency Select IgG deficiencies
Chronic mucocutaneous candidiasis	Defects in IL-17-dependent responses Hyperinflammatory syndromes	*STAT3*/AD-HIES *RORC* *IL-17RA* *IL17F* IL17RC *TRAF3IP2* *AIRE*/APECED *GOF STAT1*
Aggressive periodontitis in children and young adults	Neutropenia Defects in neutrophil motility	*ELANE* *WAS*/X-linked neutropenia *HAX1* *COH1*/Cohen syndrome *LYST*/Chédiak–Higashi syndrome *CXCR4 GOF (WHIM)* *ITGB2*/LAD-1 *CTSC*/Papillon–Lefèvre *FPR1*/LJP
Recurrent oral ulcers	Autoinflammatory syndromes (periodic fevers, PFAPA, and others) Neutropenia/defects in neutrophil motility/function PID with HSV susceptibility	*DIRA, A20, GOF STAT1* *ELANE*, LAD, CGD CID, *DOCK8*
Head and neck squamous cell carcinoma	Immunodeficiencies with severe HPV susceptibility Other	*WHIM, DOCK8* CID Epidermodysplasia verruciformis **Dyskeratosis congenita**

AD-HIES, autosomal dominant hyper-immunoglobulin E syndrome; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; CGD, chronic granulomatous disease; CID, combined immunodeficiencies; HPV, human papillomavirus; HSV, herpes simplex virus; Ig, immunoglobulin; LAD, leukocyte adhesion deficiency; LJP, localized juvenile periodontitis; NK, natural killer; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis; PID, primary immunodeficiency; SCID, severe combined immunodeficiency.

Immunodeficiencies Affecting Cellular and Humoral Immunity (T Cells/B Cells)

This group of diseases significantly affects adaptive immune responses by impairing the development and function of T cells and B cells. They are also called combined immunodeficiencies (CIDs), as they tend to affect the development and function of multiple cellular subtypes.[11,12] The most severe example of CID is severe combined immunodeficiency (SCID). Patients with this condition are born with almost no T cells. Although many patients with SCID may have B cells, antibody production is absent because there is no T-cell help. Patients present within the first few months of life with life-threatening infections. Without curative therapy (hematopoietic stem-cell transplantation or gene therapy), patients typically die from overwhelming infection before 1 year of age. Other CIDs are somewhat arbitrarily distinguished from SCID in that they typically do not lead to death in the first year of life and typically have higher T-cell

numbers and T-cell function compared with SCID. Patients with CID defects can present with a broad range of infections, including viral, fungal, and/or bacterial infections. Such patients are also susceptible to opportunistic infections (e.g., *Pneumocystis jirovecii* pneumonia) and infections from live vaccinations (e.g., measles, mumps, and rubella [MMR] and varicella).

This category includes SCID, both with absence of T cells and NK cells but presence of B cells (T^-B^+) as well as without T or B cells (T^-B^-); and milder forms of CID. Mutations associated with T^-B^+ typically affect the maturation and survival of T cells and NK T cells by affecting either cell development or signaling through the T-cell receptor (*CD3D*, *CD3E*), and T/NK cell survival and activation (*IL2RG, IL7R*, *JAK3*).[13] Mutations leading to T^-B^- SCID include those affecting the rearrangement of the T-cell receptor and of immunoglobulins (*RAG1/ RAG2*). Milder forms of non-SCID CID are caused by MHCI/II deficiencies (*TAP1*, *TAP2*), *CD40* deficiency, or *Dock8* deficiency.[13]

DOCK8

DOCK8 deficiency has been reported to present with significant oral manifestations. It is caused by loss-of-function (LOF) mutations in the *DOCK8* gene, which encodes a guanine nucleotide exchange factor that regulates the actin cytoskeleton and is highly expressed in lymphocytes. Patients have impaired B-, T-, and NK T-cell survival and long-lived memory responses.[14] Clinically such patients present with eczema, recurrent respiratory as well as persistent mucocutaneous viral infections: varicella-zoster virus (VZV), molluscum contagiosum, herpes simplex virus (HSV), and human papillomavirus (HPV). Persistent infection, particularly with HPV, leads to increased risk of cancer (typically viral-driven, squamous cell carcinomas), which affects up to 17% of patients. In the oral cavity, severe HPV and HSV infections have been reported in DOCK8 patients as well as susceptibility to HPV-associated squamous cell carcinoma (Figure 19-2).

Combined Immunodeficiency with Syndromic Features

This category includes diseases in which patients are affected by combined immunodeficiency in conjunction with other clinical features outside the immune system, such as congenital anomalies and manifestations in the skeletal system. It includes the following subcategories:

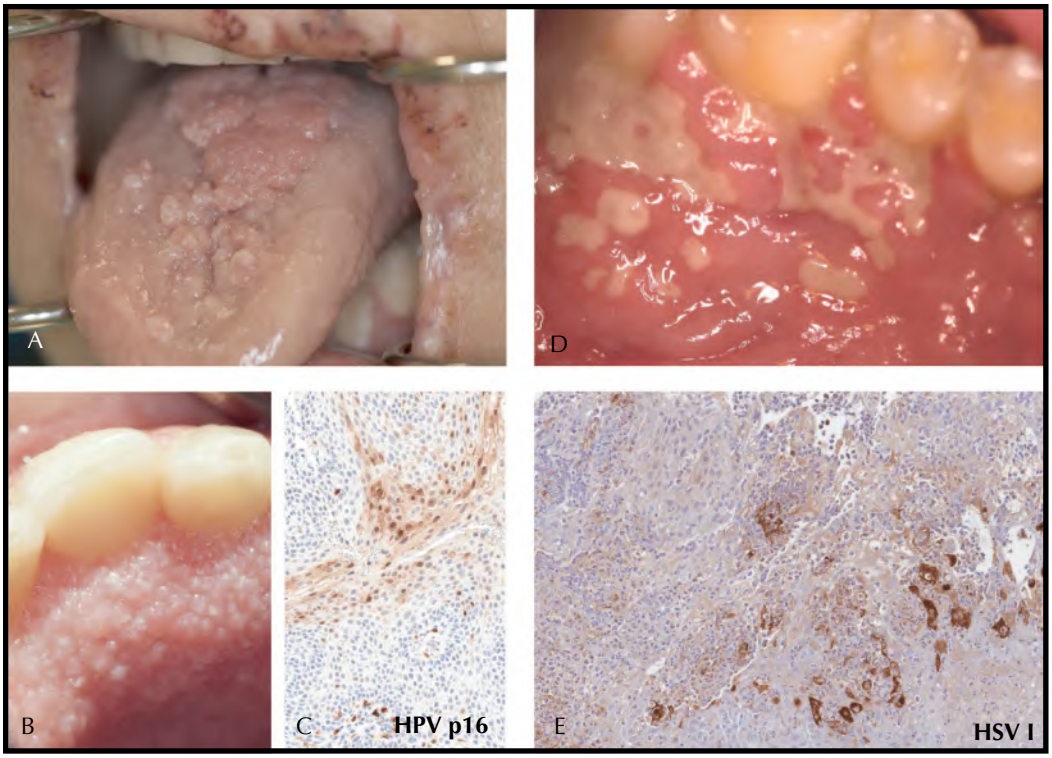

Figure 19-2 Oral mucosal viral infections in patients with DOCK8 deficiency. Patient 1 (A–C) suffers from severe oral human papillomavirus (HPV) infections despite antiviral treatment. Widespread condylomas are apparent throughout the tongue dorsum (A) and on the palate (B). Histopathologic evaluation of palatal lesions reveals p16 positivity indicative of HPV infection (C, brown staining). Patient 2 (D–E) suffers from oral herpes simplex virus 1 (HSV-1) infection. A nonhealing palatal ulcer is shown (D), which upon biopsy and immunohistochemical staining revealed HSV-1 positivity (E).

- *CID with congenital thrombocytopenia*. Disorders in this subcategory are characterized by CID with low platelets as a key clinical feature. A classic example is Wiskott–Aldrich syndrome (WAS, LOF mutation), characterized by thrombocytopenia with small platelets, bloody diarrhea, and eczema.[15]
- *CID due to DNA repair defects*. DNA repair defects can result in both T- and B-cell abnormalities because it is essential for V(D)J recombination to generate T-cell/B-cell diversity and for effective class-switch recombination. In addition to a CID phenotype, many of these conditions such as ataxia telangiectasia (caused by *ATM* mutations) are characterized by other clinical features including intrauterine growth restriction (IUGR), facial dysmorphisms, and increased radiosensitivity.
- *CID due to thymic defects with additional congenital anomalies*. Genetic disorders in this category result in impaired development of the thymus, which ultimately affects T-cell development and can result in CID. One of the most common (1:3000 live births) and well-characterized syndromes with underlying immunodeficiency is DiGeorge (*22q11.2* deletion) syndrome. This syndrome is characterized by structural heart defects, hypoparathyroidism (resulting in hypocalcemia), characteristic facial features, and T-cell immunodeficiency.
- *CID with immuneosseous dysplasia*. These disorders are characterized by CID features with skeletal abnormalities.
- *Hyper-IgE syndromes (HIES)*. These disorders are all characterized by CID and elevated IgE. One well-characterized such PID with documented oral/craniofacial features is autosomal dominant hyper-IgE syndrome (AD-HIES/Job's syndrome). AD-HIES is caused by LOF mutations in the signal transducer and activator of transcription (STAT) 3 gene. Clinical manifestations occurring in >75% of patients are recurrent staphylococcal abscesses, recurrent airway infections, and increased concentration of IgE in serum.[16] Patients also present with atopy and skeletal manifestations. In the craniofacial/oral region, manifestations include characteristic facial features, retention of primary teeth, and recurrent oral candidiasis (Figure 19-3).
- *Dyskeratosis congenita (DKC), myelodysplasia, defective telomere maintenance*. Telomeres are structures that prevent the loss of genetic material that normally occurs with every cell division. Without proper telomere maintenance, cell senescence and apoptosis can occur, especially in highly proliferative cell types such as lymphocytes. As such, in the presence of defects in telomere maintenance, patients can present with CID combined with syndromic features affecting the skin, nails, and hair and leading to lung fibrosis and enteropathy.[17] Such patients also have an increased risk for malignancy, including *increased risk for oral cancer*, and therefore oral cancer screening becomes particularly significant for this patient population.

Predominantly Antibody Deficiencies

B cells differentiate into plasma cells that produce antibodies or immunoglobulins. Human antibodies are classified into five isotypes (IgM, IgD, IgG, IgA, and IgE) according to their H chains, which provide each isotype with distinct characteristics and roles. IgG is the most abundant antibody isotype in the blood (plasma), accounting for 70–75% of human immunoglobulins. Antibody deficiencies are categorized into the following:

- Severe reduction in all serum Ig isotypes with absent B cells (e.g., *BTK* deficiency Bruton's agammaglobulinemia, Igα and Igβ deficiency due to *CD79A/B* mutations).
- Severe reduction in at least two serum Ig isotypes with normal or low numbers of B cells (e.g., B-cell deficiencies including mutations in *CD19*, *CD20*, and *BAFF-R*).
- Severe reduction in serum IgG and IgA with increased IgM and normal numbers of B cells (*UNG* deficiency).
- Isotype or light-chain deficiencies with normal numbers of B cells (such as Ig heavy-chain mutations, K chain deficiency, and isolated IgG subclass deficiencies).

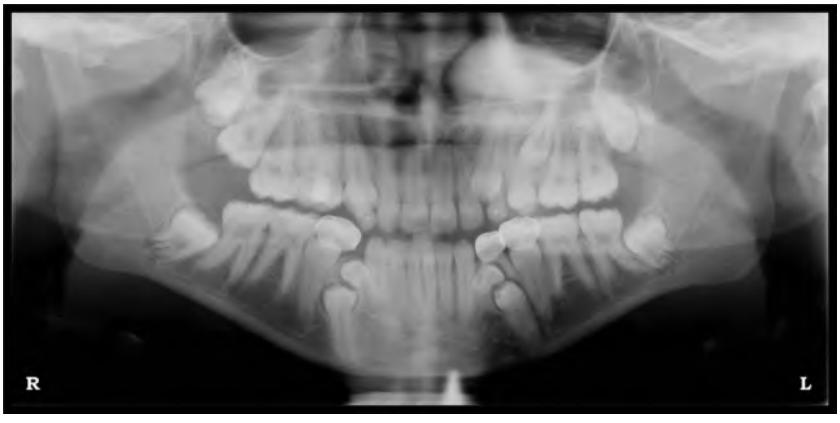

Figure 19-3 Retention of primary dentition is a hallmark oral sign for autosomal dominant hyper-immunoglobulin E syndrome (AD-HIES or Job's syndrome). Panoramic radiograph of a 25-year-old patient with AD-HIES (*GOF STAT3*). Multiple primary teeth are still present. Permanent mandibular premolars have failed to erupt despite normal tooth development. In such patients, timely removal of primary teeth allows for eruption of the permanent dentition.

Patients with antibody deficiency commonly present with recurrent bacterial infections of the upper and lower respiratory tracts (ear infections, sinus infections, and pneumonia, including odontogenic infections) from encapsulated bacteria, such as *Streptococcus pneumoniae*. However, more invasive bacterial infections such as sepsis, meningitis, and osteomyelitis can occur. These patients have also been reported to be susceptible to severe odontogenic infections.

Diseases of Immune Dysregulation

It is increasingly recognized that numerous PIDs present with features of dysregulated inflammatory responses that often lead to autoimmune phenomena, including cytopenias and solid organ autoimmunity, in addition to lymphoproliferation and malignancy. The treatment of immune disorders with coexisting immune deficiency and immune dysregulation is challenging, as it requires careful balancing of immunosuppression and control of infection. Subcategories of PID with immune dysregulation include the following:

- *Regulatory T-cell defects.* Tregs play a critical role in peripheral tolerance by suppressing autoreactive and activated T cells. Reduced or impaired function of Tregs results in systemic autoimmunity. Examples in this category include IPEX (due to *FOXP3* mutations), CD25 deficiency (*IL2RA*), and cytotoxic T-lymphocyte-associated antigen 4 (*CTLA4*) deficiency.
- *Autoimmune lymphoproliferative syndrome* (ALPS). ALPS results from defects in the
  Fas/Fas ligand (FasL) pathway. This pathway normally eliminates autoreactive lymphocytes. Relevant mutations include *FASLG*, *FADD*, and *TNFRSF6*.[18]
- *Immune dysregulation with colitis*, classically associated with *IL10* and *IL10RA/RB* mutations.
- *Familial hemophagocytic lymphohistiocytosis syndromes* are linked to decreased NK and CTL cells with increased activation of T cells. One disease in this category, Chédiak–Higashi Syndrome, is linked to severe periodontitis; it is caused by mutations in the lysosomal trafficking regulator gene (*CHS1*/*LYST*).[19] Beyond aberrant inflammatory responses, these patients present with significant neutrophil defects, including destruction of neutrophils early in myelopoiesis, decreased chemotactic responses, and impaired diapedesis. Neutrophil defects in these patients have been linked to susceptibility to periodontal disease.
- *Autoimmunity with/without lymphoproliferation*, as seen in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED; mutations in *AIRE*) and ITCH syndrome (*ITCH* mutations). APECED is of increased interest to the oral medicine provider as these patients present with dental enamel defects, susceptibility to oral candidiasis, and have been reported to have an increased risk for oral squamous cell carcinoma.

Congenital Defects of Phagocyte Number and/or Function

Phagocytes such as neutrophils and macrophages act as a first line of defense to protect the body from harmful bacteria and fungi by phagocytosis and destruction of these pathogens and through initiation and engagement of adaptive immune responses. Through phagocytosis and release of immune mediators, these cells also play crucial roles in wound healing as well as in the resolution of inflammation.

Main subcategories in this section include the following:

- Congenital neutropenia (due to defective neutrophil development).
- Defects in neutrophil motility.
- Defects in myeloid respiratory burst.
- Nonlymphoid defects (which include defects in the development of monocyte/macrophages due to *GATA2* mutations). Congenital neutrophil defects as well as defects in neutrophil motility and function have been linked to severe aggressive periodontitis at a young age as well as recurrent oral ulcerations, and thus specific examples of these diseases are discussed here.

Congenital Neutropenia

Congenital neutropenia is caused by mutations in genes affecting granulopoiesis (development of neutrophils in the bone marrow), such as mutations in *HAX1* (Kostman syndrome), in the elastase *ELA2/ELANE* gene, or in the (HCLS) 1-associated gene X1. Patients with such mutations have peripheral neutrophil counts below 0.5×10^9/L (1.5– 1.8×10^9/L in health) and frequent bacterial/fungal infections, as well as severe periodontitis that begins in childhood. Granulocyte colony-stimulating factor (G-CSF) treatment leads to improvement of infection susceptibility with varying results in the resolution of periodontitis. Hematopoietic stem-cell transplant has been shown to reverse the phenotype of periodontitis in these patients.

Leukocyte Adhesion Deficiency I

Leukocyte adhesion deficiency 1 (LAD-1) is a rare disorder of leukocyte adhesion and transmigration, which results from mutations in the *ITGB2* gene encoding for the β2 integrin component, CD18. Deficiency in CD18 prevents neutrophil adhesion to endothelial surfaces and extravasation into tissues. This results in severe tissue neutropenia. Patients with LAD-1 suffer from recurrent infections, defective wound healing, and in the oral cavity present with severe to aggressive periodontitis and recurrent oral ulcers.[20] Periodontitis in these patients has been shown to be recalcitrant to standard-of-care treatment with loss of dentition in the teenage years (Figure 19-4).

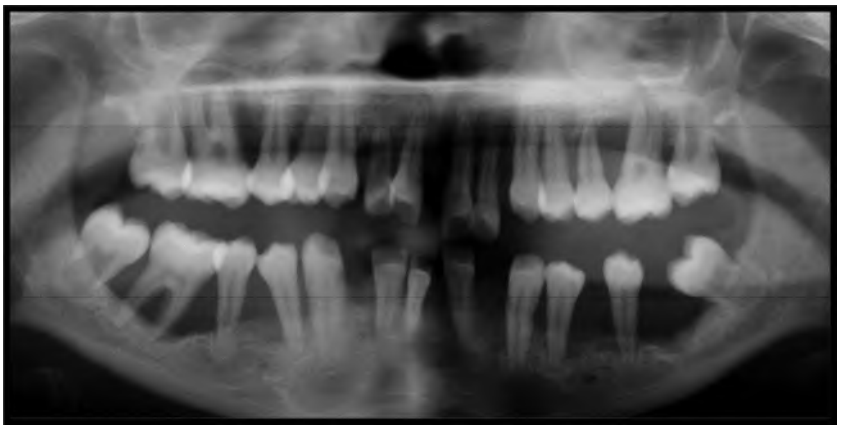

Figure 19-4 Severe periodontitis in leukocyte adhesion deficiency-1. Panoramic radiograph of a 13-year-old male with leukocyte adhesion deficiency-1. Severe (almost complete) bone loss is evident through the entire dentition.

Papillon–Lefèvre

Papillon–Lefèvre syndrome is a rare autosomal recessive genetic disorder, caused by mutations in the gene encoding lysosomal cysteine protease cathepsin C (*CTSC*). CTSC is necessary for post-translational modification and activation of serine proteases stored primarily in azurophilic granules, such as neutrophil elastase, cathepsin G (CTSG), proteinase 3 (PR3), and neutrophil serine protease 4 (NSP4). It is thought that patients have defective antimicrobial responses at mucosal surfaces due to this defect. These patients also present with severe periodontitis at an early age, but have limited infection susceptibility.

Localized Juvenile Periodontitis

Localized juvenile periodontitis (LJP) is a genetic defect impairing formylpeptide-induced chemotaxis of neutrophils (*FPR1*), which presents with specific predisposition to a severe but localized form of periodontitis in the teenage years.

Defects of Intrinsic and Innate Immunity

The innate immune system typically provides initial nonspecific immunity to pathogens, including initial recognition and responses, and is mediated primarily through phagocytes, APCs, and innate lymphocytes. *Mendelian susceptibility to mycobacterial disease* (MSMD) is related to defects in IL-12 and INFγ signaling, which is important for clearance of intracellular pathogens. Examples of genes involved are *IL12RB1*, *IL12B*, *INFGR1/2*, and *TYK2*. Susceptibly to viral infection is most often related to defects in NK cells and innate lymphocytes that protect the body from HSV, VZV, Epstein–Barr virus (EBV), and cytomegalovirus (CMV) infections and also play a role in tumor surveillance. Three subcategories in this section are related to viral susceptibility: epidermodysplasia verruciformis (HPV susceptibility), predisposition to severe viral infection (NK/T cell deficiencies, *STAT1/2*, *IFNAR2*), and herpes simplex encephalitis due to defects in signaling in resident central nervous system (CNS) innate cells.

Predisposition to fungal disease is associated with defective recognition of fungi (*CARD9* deficiency, leading to invasive fungal disease) or defective IL-17 responses (leading to mucocutaneous candidiasis).[21] Defects in microbial recognition through toll-like receptors (TLRs) and related signaling (IRAK1/4, MYD88) and TLR signaling pathway deficiencies predispose to bacterial infections.

In this category, diseases with prominent oral manifestations are as follows:

- *WHIM*, which stands for warts, hypogammaglobulinemia, recurrent infections, and myelokathexis (impaired egress of mature neutrophils from bone marrow), is caused by gain-of-function mutations in the chemokine receptor *CXCR4*. Constituent expression of CXCR4 impairs immune cell egress from the bone marrow and these patients present with pan-leukocytopenia. The signature pathogen in this disease is HPV. The dominant oral manifestation is severe periodontitis at an early age (teenage years), which is attributed to the neutropenia observed in these patients. Due to HPV susceptibility, these patients also are at increased risk for HPV-associated mucosal squamous cell carcinomas.
- *Mucocutaneus (oral) candidiasis*. Defective responses to the IL-17 cytokine have unequivocally been linked to oral fungal susceptibility.[21] Patients with mutations in the IL-17 receptor (*IL17RA, IL17RC*), the IL17 cytokine F (*IL17F*), IL-17 signaling (*TRAF3IP2*), as well as defects in the development of IL-17-secreting cells (*RORC*, *STAT3*) all present with severe, recurrent oral candidiasis. IL-17 responses have been shown to be critical for the induction of epithelial-mucosal antifungal immunity (Table 19-2, Figure 19-5).

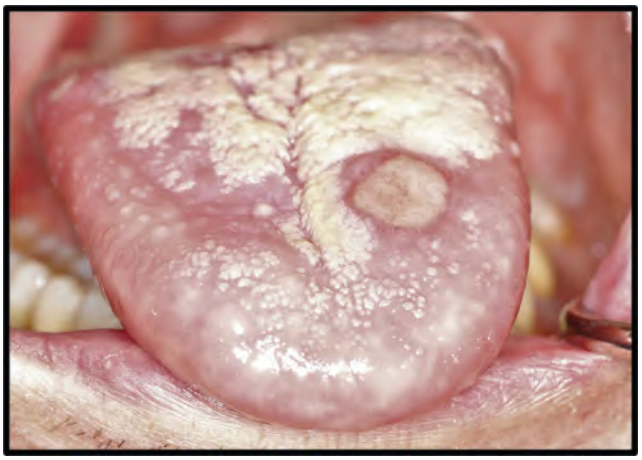

Figure 19-5 Severe oral candidiasis in a patient with IL-17 deficiency. A 23-year-old male patient with severe oral candidiasis despite antifungal treatment. A dense white coating is present on the tongue dorsum, which can be removed with a gauze upon examination.

Autoinflammatory Disorders

In the autoinflammatory disorders, overactivation of innate inflammatory pathways occurs in a nonspecific, antigen-independent manner and most commonly will cause recurrent fevers, skin rashes, and tissue damage. In this category of disorders, recurrent inflammation occurs without evidence of other disorders (e.g., cyclic neutropenia) or infections. Genetic testing is necessary to confirm the diagnosis. Subcategories in this group include the following:

- *Type I interferonopathies*. Defective regulation of type I interferon response is associated with severe inflammatory phenotypes and autoimmunity, presenting as atypical, severe, early-onset rheumatic diseases (e.g., CANDLE syndrome, *PSMB8*[a] mutation).[22]
- *Defects affecting the inflammasome*. The inflammasome is a multiprotein intracellular complex that detects microorganisms and cell damage–related mediators and acts to activate pro-inflammatory cytokines such as IL-1β and IL-18. Hyperactivation of the inflammasome leads to classically recognized inflammasome disorders such as familial Mediterranean fever (MEFV), familial cold autoinflammatory syndrome 1 and 2 (*NLRP3* and *NLRP12*), and neonatal onset multisystem inflammatory disease (NOMID, due to *NLRP3* mutations).
- *Non-inflammatory-related conditions*, including PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, acne, due to *PSTPIPI* mutations) and DIRA syndrome (deficiency of IL-1 receptor antagonist, due to *IL1RN* mutations).

A typical oral manifestation for many of the autoinflammatory syndromes is recurrent oral ulcers during periods of disease activity and inflammation (most prominent in periodic fever, aphthous stomatitis, pharyngitis, and adenitis [PFAPA] syndrome).[23]

Complement Deficiencies

The complement arm of the immune system protects the body from bacterial pathogens by opsonizing bacteria and leading to their phagocytosis and destruction. Additionally, complement proteins also play a role in clearance of apoptotic cell debris, which is necessary for the resolution of inflammation. Defective clearance of apoptotic cell debris is linked to persistent inflammation and autoimmunity. As such, patients with complement deficiencies can be predisposed both to bacterial infection and to autoimmunity. Interestingly, early classic complement component deficiencies (*C1q*, *C1r*, *C1s*, *C2*, *C4*, *C3*) present with systemic lupus erythematosus (SLE) and susceptibility to infections from encapsulated bacteria. Specific types of complement defects (*C1R*, *C1S*) are associated with severe periodontal disease. Terminal classic complement component deficiencies (*C5*, *C6*, *C7*, *C8*, *C9*) present with a unique susceptibility to recurrent *Neisseria* meningitis. Similar to terminal complement deficiency, alternative complement pathway defects due to properdin or factor D present with recurrent meningitis. Complement defects have not been clearly linked to oral phenotypes to date.

Phenocopies of Primary Immunodeficiencies

Phenocopies of PIDs include autoimmune lymphoproliferative diseases such as ALPS (mutations in *TNFRSF6*) and RAS-associated autoimmune leuko-proliferative disease (GOF mutations in *KRAS* and *NRAS*), associated with splenomegaly, lymphadenopathy, and cytopenia. Diseases in which autoantibodies target immune response mediators are also part of this category. Examples include APECED (also mentioned under diseases of immune deregulation) and thymoma (Good syndrome).

AUTOIMMUNE DISEASES

Autoimmune diseases represent a diverse family of conditions characterized by an immune-mediated response against self. Over 100 distinct autoimmune diseases have been described, showing a wide spectrum of manifestations from organ-specific autoimmunity (such as primary biliary cirrhosis) to organ-specific with systemic manifestations (such as Sjögren syndrome) to multiorgan systemic disease

(such as SLE). A common pathogenetic mechanism in all these disorders is the breakdown of immune tolerance. Following a break in tolerance, autoreactive T lymphocytes and/or autoantibodies trigger autoimmunity in one target organ or in multiple tissues. However, while a combination of genetic susceptibility and environmental triggering is thought to underlie the pathogenesis of all autoimmune disorders, triggering and pathogenesis of specific autoimmune diseases are generally incompletely understood.

Autoimmune diseases demonstrate considerable diversity regarding their clinical manifestations and molecular and pathophysiologic features. While some disorders lead to organ-specific damage, others exhibit widespread systemic autoimmunity. Similarly, while disease is mediated by autoantibodies with well-defined specific roles in some cases (such as pemphigus), others may be characterized by diverse autoantibodies with unclear roles and/or T cell–mediated immune damage.

The orofacial area, and in particular the oral mucosa and the salivary glands, is affected by multiple autoimmune diseases, either directly as a manifestation of their clinical phenotype, or indirectly due to possible comorbidities or adverse effects of the medications used for treatment. Identification of oral clinical manifestations can be key in the overall disease diagnosis and assessment. Additionally, dental or surgical management of autoimmune patients may be challenging due to the occasional immunocompromised status or their distinct clinical features. In this part of the chapter, selected autoimmune diseases and their clinicopathologic features and management are presented (Table 19-3), with an emphasis on identification of oral manifestations. However, other autoimmune disorders with oral manifestations (such as those affecting salivary glands and dermatologic diseases) are included in subsequent chapters.

Sjögren Syndrome

Sjögren syndrome is an autoimmune disorder in which immunocytes damage the salivary, lacrimal, and other exocrine glands and is thus termed an autoimmune exocrinopathy. Dry mouth and dry eyes are seen with lymphoid infiltrates in these and other exocrine glands and serum autoantibodies, as discussed in more detail in Chapter 9. Sjögren syndrome has two major clinical forms: primary Sjögren syndrome (SS-1), in which dry eyes and dry mouth are seen in the absence of a connective tissue disease, and secondary Sjögren syndrome (SS-2), which is more common, in which eyes and dry mouth are seen together with other autoimmune diseases, usually of connective tissue—most usually rheumatoid arthritis (RA), SLE, polymyositis, scleroderma, or mixed connective tissue disease. However, Sjögren syndrome shows a wide spectrum of clinical manifestations and new diagnostic criteria tend not to distinguish between the two clinical forms.

Systemic Lupus Erythematosus

SLE is considered a prototypic autoimmune disease characterized by a wide spectrum of clinical manifestations and an often unpredictable relapsing–remitting course. Patients can present with variable clinical features ranging from mild joint and skin disease to multiorgan life-threatening renal, hematologic, and CNS involvement. The etiology and pathogenesis of SLE remain largely unknown; however, it is recognized that genetic predisposition combined with environmental and possibly hormonal factors ultimately predisposes to disease. Immune dysregulation is thought to result from the breakdown in tolerance to self-antigens, leading to excessive inflammation, autoantibody production, and destruction of end organs. In fact, immunologic anomalies, particularly production of antinuclear antibodies (ANA) such as those against double-stranded (ds) DNA, are a hallmark of lupus. Diagnosis and management of lupus are particularly complex. Oral manifestations are a prominent feature that can aid in the diagnosis and should be taken into consideration during management of SLE. This section will review basic information on SLE pathogenesis, clinical manifestations, and diagnostics, with a focus on the oral features of the disease.

Epidemiology

SLE has an incidence of 23.2/100,000 person-years and a prevalence of 241/100,000 people in North America, based on a recent systematic review of epidemiologic studies. There is unequal distribution between sexes (females are affected 1.2–15 times more than males) and among different ethnic groups (people of African descent have the highest prevalence and Caucasians the lowest). The peak ages of prevalence are 45–69 for females and 40–89 for males.[24]

Genetic Susceptibility and Pathogenesis

SLE is considered a chronic inflammatory autoimmune disorder that is characterized by insufficient immune tolerance to nuclear antigens and pathologic production of nonspecific autoantibodies, eventually resulting in tissue damage. Even though its etiology remains unclear, complex pathogenetic mechanisms involving various distinct components of the immune system have been implicated. The role of genetic susceptibility in SLE is evident from the high heritability (43.9%) and the relative risk (5.87%) in first-degree relatives of patients with SLE. Although the disease can develop from a single-gene deficiency, such as of complement component 1q (*C1q*), three-prime repair exonuclease 1 (*TREX1*), or deoxyribonuclease 1-like 3 (*DNASE1L3*), in most cases it results from a combination of multiple gene variant effects.

Table 19-3 Summary of salient features for select autoimmune disorders with orofacial involvement.

Disease	Target Organ(s)	Main Autoantibodies	Histopathologic Findings (in the Orofacial Area)	Other Laboratory Findings	Orofacial Manifestations
Lupus erythematosus	SLE: Multiple organs	SLE: ANA (>95%) anti-ds-DNA (43–92%) anti-nucleosome (59–62%) anti-Sm (15–55%) anti-Ro (36–64%) anti-La (8–33%) anti-U1-RNP (23–49%) anti-phospholipids (30–40%)	Subepithelial and perivascular lymphocytic infiltrate with degeneration of the basal cell layer Direct immunofluorescence shows IgG, IgM, and complement deposition in the basement membrane SLE: Positive lupus band test	SLE: Anemia, leukopenia, thrombocytopenia, elevated ESR, hypocomplementemia	Ulcerative, atrophic/erythematous and/or white striated/radiating lesions of the oral mucosa (discoid lesions) Lupus cheilitis (rare malignant transformation) Butterfly rash or other erythematous lesions affecting the facial skin
Systemic sclerosis	Multiple organs, including skin	ANA (up to 96%) anti-Scl70 (up to 41%) ACA (up to 37%) anti-RNA polymerase III (up to 19%) anti-Th/To (up to 3%) anti-Pm/Scl (up to 13%)	Extensive dense collagen deposition in connective tissue	Various hematologic abnormalities (e.g., elevated ESR, hypergammaglobulinemia)	Mask-like face, reduced mouth opening (microstomia), telangiectasias, temporomandibular disorders, resorption of posterior mandible, diffuse widening of periodontal membrane, other comorbidities (periodontal disease, xerostomia)
Rheumatoid arthritis	Joints	Anti-CCPs (ACPAs) (up to 70%) RF (up to 70%) ANA (up to 60%)	Hyperplasia of the synovial cell lining Dense subacute inflammation of the synovial membrane Rheumatoid granulomas in skin lesions	Elevated ESR and CRP	TMD, TMJ radiographic abnormalities, periodontal disease, xerostomia (in cases of secondary Sjögren syndrome)
Dermatomyositis	Skeletal muscles and skin	ANA (up to 80%) Anti-MI2 anti-NXP2 anti-TIF1 anti-Jo1	Perifascicular atrophy Interface mucositis/dermatitis in mucocutaneous lesions	Elevated creatine kinase, aldolase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase	Dental and periodontal disease, TMD, telangiectasias, lichenoid lesions
Mixed connective tissue disease	Multiple organs	ANA (up to 100%) anti-U1 RNP (up to 100%) RF (up to 50%)	Overlapping with other connective tissue diseases	Anemia, leukopenia, thrombocytopenia	Trigeminal neuropathy and other overlapping manifestations
Granulomatosis with polyangiitis	Multiple organs (mainly upper and lower aerodigestive tract and kidneys)	ANCA including: PR3-ANCA (c-ANCA) (up to 95%) MPO-ANCA (p-ANCA)	Small-vessel necrotizing vasculitis with granulomatous features	Anemia, leukocytosis, eosinophilia, elevated ESR and CRP	Oral ulcerations, gingival involvement ("strawberry gingivitis"), destructive lesions (palatal perforation), salivary gland enlargement

ACA, anticentromere antibody; ACPA, antibodies to citrullinated proteins; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; ds, double stranded; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; RF, regulatory factor; SLE, systemic lupus erythematosus; Sm, Smith antigen; MPO, myeloperoxidase; PR3, proteinase 3; RNP, ribonucleoprotein; TMD, temporomandibular disorders; TMJ, temporomandibular joint.

Gene loci associated with common non-Mendelian SLE susceptibility have been described, mostly for intronic regulatory regions of genes involved in *immune pathways*. Examples of specific immune pathways involved in the genetics are (1) genetic loci associated with antigen presentation, such as the human leukocyte antigen (*HLA*) locus, which have shown a strong association with SLE development; (2) gene loci associated with mechanisms of apoptosis and clearance of apoptotic cell debris (such as *TREX1*, *DNASE1*, autophagy-related 5 (*ATG5*), and *RAD51B*), where it is thought that defects in apoptosis or clearance of cellular debris are related to release of self-proteins and nucleic acids, which are a common source of autoantigens in SLE; (3) gene loci involved in nucleic acid sensing and type I interferon (IFN) production, such as interferon-regulatory factor 5 (IRF5), IRF7, toll-like receptor 7 (TLR7), TLR8, and TLR9; and (4) other SLE-associated loci code for proteins involved in T- and B-cell function, such as ELF1, BANK1, BLK, and CD3Z.

These genetic loci reveal pathways deregulated in lupus. Excessive inflammation, deregulated IFN-I production, defective clearance of apoptotic debris, and T-cell/B-cell activation and autoantibody production with immune complex deposition are hallmarks of lupus. In fact, *immune complex deposition* underlies tissue destruction in lupus. Specific autoantibodies found to contribute to disease-related injury include anti–blood cell antibodies causing cytopenia, anti-dsDNA antibodies causing nephritis, and anti-phospholipid antibodies causing, through various pathologic mechanisms, fetal resorption.

Environmental factors triggering disease in susceptible individuals are poorly understood, yet viral and other microbiome triggering has been extensively hypothesized. Additionally, hormonal deregulations and other environmental triggers, such as ultraviolet radiation, tobacco consumption, and physiologic factors, have been investigated.

Clinical Features

SLE may be difficult to diagnose, especially in the early stages, when nonspecific signs and symptoms (constitutional symptoms), such as fatigue, headache, arthralgias, lymph node enlargement, fever, and significant weight loss, occur, causing diagnostic dilemmas with other autoimmune connective tissue diseases as well as neoplastic processes or infections. Besides constitutional systemic manifestations, SLE may be characterized by the involvement of various specific organs. *Renal disease*, which affects approximately 40–70% of patients, is considered one of the major causes of morbidity and mortality in SLE. The term lupus nephritis, which has been used to describe kidney involvement in lupus patients, ranges from mild clinical and histopathologic manifestations to severe renal failure, which is considered a prognostic factor and a determinant of the selected treatment.

The *musculoskeletal system* is also commonly affected (in up to 93% of SLE cases). Arthritis and arthralgias are a dominant feature of SLE. Arthritis, with demonstrable inflammation, occurs in 65–70% of patients and tends to be migratory, polyarticular, and symmetric. The arthritis is moderately painful, usually does not cause erosion, and is rarely deforming.

Cardiovascular manifestations are also common in SLE and typically include vasculitis and pericardial effusions. Additionally, rare occasions of myocarditis or endocardial involvement, such as Libman–Sachs endocarditis, have been described. Atherosclerosis, valvular heart disease, and defective coagulation mechanisms (related to antiphospholipid syndrome) can cause significant morbidity and demand specific medications.

Involvement of the *central or peripheral nervous system* in SLE also presents diverse features and may be associated with poor prognosis. Anxiety, mood disorders, psychosis, seizures, headaches, and myelin defects are examples of CNS manifestations in SLE, while various types of peripheral neuropathies have also been described.

Finally, pulmonary involvement (especially pleuritis, interstitial lung disease, pulmonary embolism), gastrointestinal disease (abdominal pain with nausea and vomiting, peritonitis, pancreatitis, enteritis, mesenteric vasculitis with intestinal infraction), genitourinary disorders (abortions associated with antiphospholipid syndrome), and ocular manifestations (retinal involvement with a "cotton-wool" appearance upon ophthalmoscopy, keratoconjunctivitis especially in patients with simultaneous Sjögren syndrome) can further describe the multisystemic phenotype of SLE.

Mucocutaneous Manifestations

Most lupus patients will develop cutaneous and mucosal lesions during their disease. There is tremendous variability in the type of skin involvement in SLE. The most common lesion is a facial eruption that characterizes acute cutaneous lupus erythema (also known as the "butterfly rash"), presenting as erythema in a malar distribution over the cheeks and nose (but sparing the nasolabial folds) that appears after sun exposure. Some patients may develop discoid lesions, which are more inflammatory, and tend to scar. Photosensitivity is also a common theme for skin lesions associated with SLE (Figure 19-6).

Oral Manifestations

The oral cavity is commonly affected during both systemic and cutaneous involvement in SLE. A wide spectrum of clinical manifestations may be observed that depend on the type of lupus and possible comorbidities.

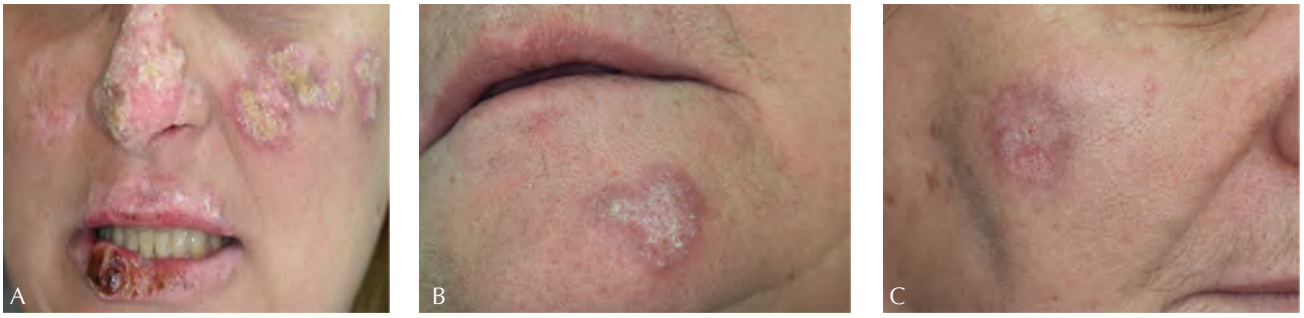

Figure 19-6 Extraoral cutaneous lesions in systemic lupus erythematosus (SLE). (A) Diffuse discoid lesions on the skin of a patient with SLE with development of squamous cell carcinomas on the vermillion border of the lower lip. Right lower lip presents with exophytic mass and ulcerations. (B–C) Discoid lesions on the facial skin of another patient with SLE.

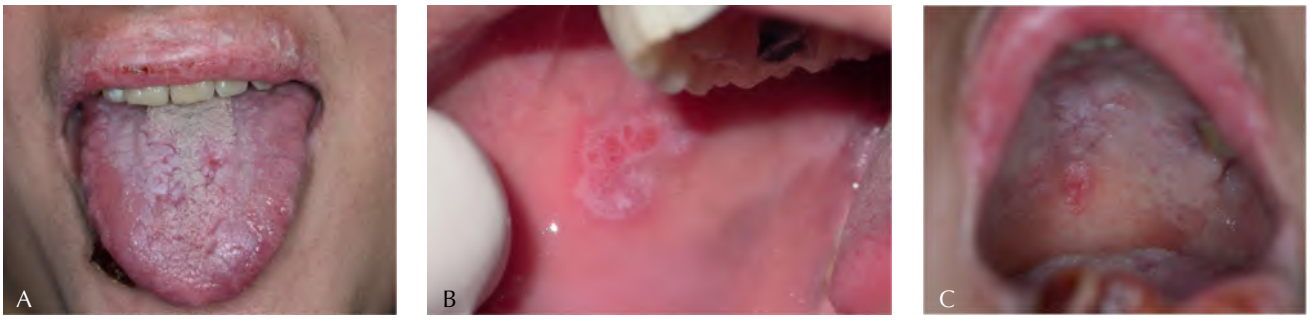

Figure 19-7 Intraoral lesions in systemic lupus erythematosus. (A) Nondescript widespread white coating on dorsal surface of tongue, with erythematous regions. (B) Central erythematous area surrounded by radiating white striations, mimicking lichen planus on buccal mucosa. (C) Nondescript white and red lesions on hard palate.

Typically, oral lesions in SLE occur in approximately 5–40% of patients, include nonspecific ulcerations and erythematous or discoid lesions, and predominantly affect the palatal mucosa, buccal mucosa, and gingiva (Figure 19-7). Due to their significant prevalence, oral ulcerations are included among the classification criteria of SLE. However, there are various disorders in the oral cavity manifesting as oral ulcerative lesions, hence this criterion should be supported by histopathologic examination and direct immunofluorescence. The vermillion border of the lower lip can be characteristically involved (lupus cheilitis). The temporomandibular joint (TMJ) can also be affected, with significant differences in reported symptoms and objective findings of SLE patients related to healthy controls. Finally, in addition to direct lupus-related lesions, some indirect manifestations of SLE may arise in the oral cavity and are discussed later in this chapter (See "General Considerations for Dental Management of Patients with Immune-Mediated Diseases").

The oral manifestations of the cutaneous forms of lupus erythematosus (CLE) closely mimic those of oral lichen planus, with characteristic central erythematous (erosive or atrophic) areas surrounded by white radiating striations (Figure 19-7), and may also be encountered in SLE patients (see Chapter 4). Even though this radiating pattern as well their asymmetric distribution are characteristic features that differentiate discoid lesions from lichen planus, diagnosis cannot be based solely on clinical features and necessitates clinicopathologic correlation. The most common sites of involvement are the lips (vermillion border and labial mucosa) and the buccal mucosa. Interestingly, a correlation between specific oral lesions (such as discoid plaques, cobblestone, or macules) and disease activity in CLE was recently reported; a similar association was seen between gingivitis in CLE, as well as gingival telangiectasias in SLE, and systemic inflammation. On rare occasions, squamous cell carcinoma may arise in discoid lesions affecting the lips[25] or even intraoral sites (Figure 19-6A), for which it is considered an oral, potentially malignant disorder based on the World Health Organization (WHO) classification.

Laboratory Findings

Pathologic values in complete blood count (CBC) are common and can be the initial sign leading to subsequent

diagnosis of SLE. Main manifestations include anemia (mainly related to chronic disease, iron deficiency, or hemolysis), leukopenia (lymphopenia and/or neutropenia), and thrombocytopenia (autoimmune or related to hypersplenism or hemolysis) and their extent correlates with disease activity. Erythrocyte sedimentation rate (ESR) is usually elevated along with normal C-reactive protein (CRP), which is a characteristic feature of SLE.

Regarding the serologic features of SLE, several autoantibodies have been studied as biomarkers for diagnosis of the disease. Certain markers are extremely sensitive but lack specificity; in particular, ANAs are positive in more than 95% of SLE patients and, despite their lack of specificity (being detected in several other autoimmune diseases and in healthy subjects), can be used as a reliable screening test. Other markers, despite being disease specific, are only detected in a subset of patients; for example, anti-double-stranded DNA (anti-dsDNA) and anti-Smith antigen (anti-Sm) antibodies are positive in approximately 50–70% and 30–40% of SLE patients, respectively. Additionally, their expression is correlated with specific clinical features and prognostic factors (e.g., antiphospholipid antibodies are associated with thrombocytopenia, thrombosis, atherosclerosis, and abortions, while antiphospholipid syndrome and anti-Sm are associated with higher mortality and morbidity). Another serologic finding is the decrease in complement markers (hypocomplementemia), especially CH50, C3, and C4.

Histopathologic Features of Mucocutaneous Lesions

Histopathology plays a crucial role in the diagnosis of SLE. Besides renal biopsy, which is included among the diagnostic criteria of SLE, mucocutaneous involvement should also be investigated in the majority of cases with histopathologic examination and immunofluorescence studies. Cutaneous and oral mucosal lesions, even though showing some minor differences, have been described as exhibiting similar features. A superficial (subepithelial or in proximity with the dermo-epidermal junction) lymphocytic infiltrate, associated with vacuolar degeneration of the basal cells of the epithelium (or epidermis) and thickening of the basement membrane, is usually observed. These features may cause diagnostic confusion with lichen planus; however, in lupus erythematosus the lymphocytic infiltrate may also display a deep perivascular location, edema in the connective tissue is more commonly present, while civatte bodies are rarely observed. Cutaneous lesions may present the characteristic follicular plugging, while, depending on the type of lesion, lupus erythematosus may exhibit an ulcerated, atrophic, or hyperplastic surface. Finally, rare types of CLE may present histopathologic findings that may cause confusion even with malignant neoplasms (lupus erythematosus panniculitis and subcutaneous panniculitis-like T-cell lymphoma).

Direct immunofluorescence may also offer important information leading to diagnosis in lupus patients with mucocutaneous involvement. Subepithelial (or dermo-epidermal) immunoglobulin and complement deposition (IgG, IgM, and C3) at the basement membrane zone can be found in most lupus erythematosus lesions. Occasionally, these findings may be observed even in clinically normal skin, especially in SLE patients, known as a positive lupus band test.

Diagnosis/Disease Classification

The wide spectrum of clinical manifestations, as well as laboratory findings, is suggestive of the diagnosis of lupus erythematosus. To date several criteria have been proposed that classify SLE and facilitate diagnosis, including clinical signs and symptoms from multiple organs as well as immunologic findings. The most recent classification criteria for SLE have been initiated by the European League Against Rheumatism and the American College of Rheumatology (Table 19-4).[26]

Management

Treating SLE is challenging and depends on the extent of manifestations, the type of target organ(s), and the severity of disease as well as possible morbidities. As a result, medications used to treat lupus may range from topical therapy for exclusive cutaneous lesions or nonsteroidal anti-inflammatory drugs for mild musculoskeletal involvement to systemic immunosuppressive therapy.[25] In addition, possible side effects of the selected medications should be prevented accordingly.

Corticosteroids remain the main choice during management of SLE, due to their effectiveness in limiting disease and flares. However, because of common complications after their long-term use (such as diabetes, infections, osteoporosis, hypertension, and avascular necrosis of bone), other immunosuppressants have been proposed. Alternative options include cyclophosphamide, mycophenolate mofetil, and azathioprine, which should also be used with caution due to their toxic effects. Less commonly used immunosuppressive drugs for SLE include tacrolimus, cyclosporine, and methotrexate. Hydroxychloroquine, an antimalarial used in a variety of autoimmune diseases, has demonstrated effectiveness in managing cutaneous lesions as well as constitutional manifestations. Finally, biologic agents affecting the B-cell component of the immune system, including belimumab, rituximab, ofatumumab, and atacicept, are recently used drugs that present efficacy in limiting disease activity. In addition to directly managing the manifestations of lupus, comorbidities should be prevented appropriately. To date there are no clear guidelines regarding management of oral complications of lupus erythematosus and treatment options presented in the literature are similar to the therapeutic protocol of cutaneous involvement. Topical or intralesional administration of corticosteroids seems to be the first treatment option.

Table 19-4 Classification criteria for Systemic Lupus Erythematosus (SLE).

Entry criterion	
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)	
If absent, do not classify as SLE	
If present, apply additive criteria	
↓	
Additive criteria	
Do not count a criterion if there is a more likely explanation than SLE	
Occurrence of a criterion on at least one occasion is sufficient	
SLE classification requires at least one clinical criterion and ≥10 points	
Criteria need not occur simultaneously	
Within each domain, only the highest-weighted criterion is counted toward the total score.§	
Clinical domains and criteria Weight	**Immunology domains and criteria Weight**
Constitutional	***Antiphospholipid antibodies***
Fever 2	Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant 2
Hematologic	***Complement proteins***
Leukopenia 3 Thrombocytopenia 4 Autoimmune hemolysis 4	Low C3 OR low C4 3 Low C3 AND low C4 4
Neuropsychiatric	***SLE-specific antibodies***
Delirium 2 Psychosis 3 Seizure 5	Anti-dsDNA antibody* OR Anti-Smith antibody 6
Mucocutaneous	
Nonscarring alopecia 2 Oral ulcers 2 Subacute cutaneous OR discoid lupus 4 Acute cutaneous lupus 6	
Serosal	
Pleural or pericardial effusion 5 Acute pericarditis 6	
Musculoskeletal	
Joint involvement 6	
Renal	
Proteinuria >0.5 g/24 h 4 Renal biopsy class II OR V lupus nephritis 8 Renal biopsy class III OR IV lupus nephritis 10	
Total score:	
↓	
Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled	

*In an assay with at least 90% specificity against relevant disease controls.

Reproduced with permission from Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol.* 2019;71:1400–1412.

§Additional criteria items within the same domain will not be counted.

Systemic Sclerosis (Scleroderma)

The word "scleroderma," originating from the Greek *scleros* and *derma* meaning hard skin, is considered an umbrella term characterizing a diverse group of disorders that exhibit excessive cutaneous fibrosis. Major disease subsets (also considered by many separate disease entities) include localized scleroderma (LSc), which is limited to skin involvement, and systemic sclerosis (SSc), a heterogenous disease, which affects a wide range of organs in addition to the skin, leading to significant morbidity.[28]

SSc presents with diverse manifestations and is subclassified into multiple subsets of disease. *Limited cutaneous SSc* refers to skin lesions in distal areas. In contrast, *diffuse cutaneous SSc* involves the proximal limbs or trunk, with a short history of Raynaud's phenomenon and frequent renal or cardiac involvement as well as lung fibrosis. *Sine scleroderma* is an entity that exhibits clinical and serologic evidence of SSc without skin sclerosis. *SSc overlap syndrome* refers to one of the aforementioned subsets in addition to manifestations from other autoimmune diseases.

Epidemiology

Both LSc and SSc are considered rare entities. More specifically, SSc exhibits a measured incidence that ranges between 4 and 43/million person-years, which is similar to that of LSc (3–30 cases/million person-years). In both entities, women are more commonly involved than men and a racial predisposition for Caucasian populations has been reported.

Pathogenesis

The pathogenesis of SSc is incompletely understood. Immune activation, vascular damage, and excessive synthesis of extracellular matrix are all well-appreciated features of the condition. Most hypotheses of the pathogenesis of SSc focus on the interplay between early immunologic events and vascular changes, which result in the generation of a population of activated fibroblasts generally considered to be the effector cell in the disease. There is no doubt that vascular and immunologic processes are central to the pathogenesis of scleroderma, although it is unclear what the initial events are and how different processes respectively trigger, amplify, and facilitate the development of the skin- and organ-based fibrosis with vasculopathy that is the hallmark of the disease.[28] The heterogeneity in the clinical features of patients with SSc is most likely a reflection of the variable contributions from each of these pathogenic factors. Incomplete understanding of the pathogenesis of the disease has rendered management very challenging, with the majority of trials of immunosuppressive agents showing limited promise.

Clinical Features

Cutaneous Manifestations

Skin thickening is the hallmark of cutaneous involvement in SSc. Skin involvement may be of acute onset in diffuse SSc or more slowly growing in limited SSc. The extremities and especially the fingers may be affected, causing a "puffy" appearance; progressively, the thin overlying skin becomes prone to ulceration and,in advanced stages, deformities may occur ("sclerodactyly") (Figure 19-8A). On rare occasions, calcifications of the skin may occur with the clinical presentation of multiple subcutaneous nodules. Additionally, hypo- or hyperpigmented areas as well as telangiectasias may be observed.

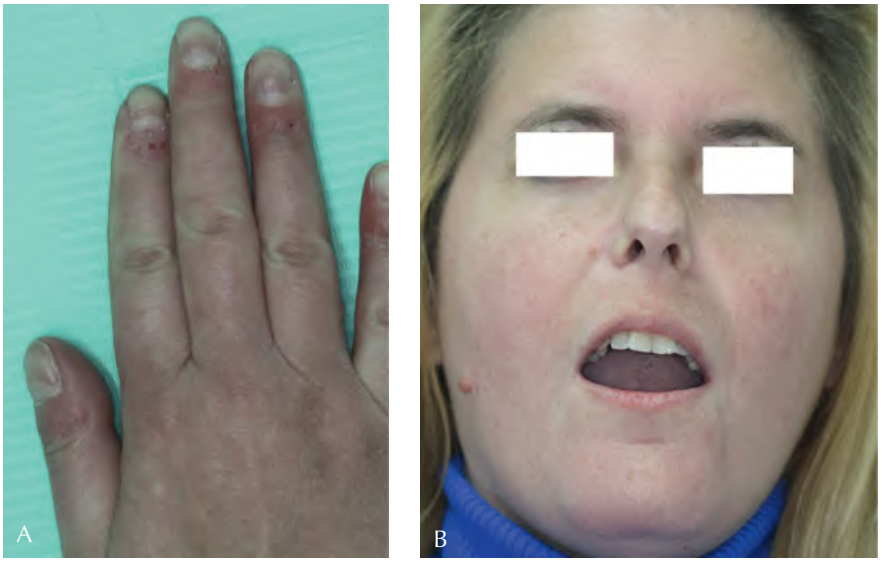

Figure 19-8 Extraoral manifestations in systemic sclerosis (SSc). (A) Finger involvement in SSc with thin, tense skin prone to ulceration. (B) Mask-like appearance of the face in a patient with SSc.

Skin lesions of SSc may occasionally be confused with those of LSc, especially of generalized morphea. In contrast, other subsets present distinct features, including dermal induration with a linear pattern involving the limbs or face (linear scleroderma) or circumscribed cutaneous plaques (circumscribed or plaque morphea), while even rarer manifestations may be present.

Other Manifestations

SSc is characterized by multiorgan involvement manifesting with various signs and symptoms and occasionally significant morbidities. Raynaud's phenomenon is the most common initial sign, developing simultaneously or prior to cutaneous involvement. Musculoskeletal involvement takes the form of generalized arthralgias and morning stiffness resembling RA. Myopathy is also common and is accompanied by elevated serum muscle enzymes. The upper or lower gastrointestinal tract may be affected with dysfunction in motility or gastroesophageal reflux, while, during late stages, fibrosis of the gastrointestinal tract may result in malabsorption. Pulmonary complications including interstitial lung disease and pulmonary hypertension are also common and associated with morbidity and mortality. Inflammatory processes may involve the heart, causing arrhythmias, hypertension, pericardial effusions, conduction defects, or "patchy fibrosis" of the myocardium. Finally, renal involvement is common and, before the initiation of angiotensin-converting enzyme inhibitors, was the most common cause of death in SSc patients. Renal crisis is most commonly encountered in patients with early onset of diffuse scleroderma, exhibits an acute course, and is associated with diverse manifestations, including malignant arterial hypertension, hyperreninemia, and progressive renal failure.

Oral Manifestations

The orofacial area may be involved in a similar pattern to other anatomic areas of SSc patients.[29] The lips become rigid, which, in addition to the generalized skin sclerosis, results in a mask-like appearance of the face (Figure 19-8B). Mouth opening is significantly decreased (microstomia) and the tongue becomes hard, leading to difficulties in speech and swallowing. Telangiectasias are also frequently present. If a biopsy of the affected mucosa is performed, diffuse deposition of dense collagen is seen in the connective tissue.

Temporomandibular disorders are also commonly encountered.[29] Mandibular movement may be limited secondary to muscular fibrosis. Additionally, myofascial pain, especially involving the masseter and posterior belly of the digastric muscle, feeling of locked jaw, and arthralgia are common symptoms in SSc patients.

The jaw bones exhibit clinical and radiographic findings in SSc patients. Mandibular resorption, either at the angle of the mandible, condyles, coronoid processes, or digastric region, is a result of masticatory muscle involvement (Figure 19-9). Additional radiographic signs include widespread widening of the periodontal membrane, especially around the posterior teeth (Figure 19-9), or soft tissue calcifications mimicking intraosseous lesions.

Other morbidities manifesting in the oral cavity of SSc patients include periodontal disease, xerostomia, and susceptibility to local infections. The high prevalence of periodontitis has been speculated to be related either to vasculopathy or to reduced mouth opening, along with limited manual dexterity that compromises dental hygiene in these patients. Xerostomia, related to fibrosis of the salivary glands, secondary Sjögren syndrome, or medications, may predispose to dental and periodontal disease as well as candidiasis.

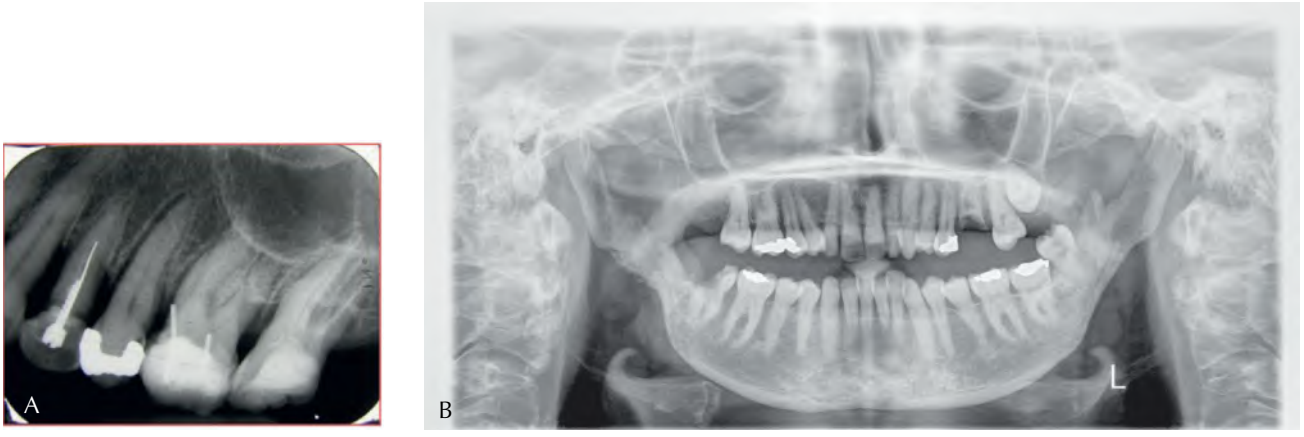

Figure 19-9 Radiographic findings in scleroderma. (A) Widening of periodontal ligament space on periapical radiograph. (B) Marked resorption of the angle, ramus, and coronoid process of the mandible, bilaterally. Courtesy of Professor Tsiklakis.

Laboratory Findings

The following routine laboratory tests are recommended in patients with suspected SSc:

- CBC and differential, which may reveal anemia due to malabsorption of iron or gastrointestinal blood loss.
- Serum creatinine level, which may indicate renal dysfunction.
- Creatine kinase (CK), which may be elevated in patients with myopathy or myositis.
- Urinalysis.

The following serologic tests may support the diagnosis if positive:

- Antinuclear antibody (ANA).
- Anti-topoisomerase I (anti-Scl-70) antibody.
- Anticentromere antibody (ACA).
- Anti-RNA polymerase III antibody.

Diagnosis

The most recent classification criteria for SSc were published in 2013 by the American College of Rheumatology in association with the European League Against Rheumatism. These criteria help clinicians classify patients as having SSc. Diagnosis is made upon exclusion of similar entities that could justify the clinical manifestations, including generalized morphea. Skin sclerosis of the fingers of both hands extending proximal to the metacarpophalangeal joints is by itself sufficient for classification as SSc, while other clinical or serologic features are helpful classification criteria.

Management

Treatment of SSc aims at limiting the inflammatory process that characterizes its clinical phenotype as well as managing the distinct clinical manifestations involving separate organs. The selected treatment is also based on the stage of disease and possible morbidities. Based on the most recent recommendations, immunosuppressants including methotrexate have been used for SSc treatment, especially for diffuse skin manifestations or lung disease. Additionally, hematopoietic stem-cell transplantation may be the treatment of choice in selected patients with progressive disease.

Even though oral complications of SSc may respond to systemic therapy, especially with early intervention, management of specific manifestations may be essential. Patients with limited mouth opening should undergo several stretching exercises that have been reported to be effective. Additionally, morbidities associated with disease (such as periodontitis or dry mouth and its sequelae) or adverse effects of treatment should be managed appropriately.

SSc exhibits a variable prognosis that depends on the extent and severity of organ involvement. Additionally, demographic parameters may be associated with a poorer prognosis (black race or male sex). Early treatment is considered essential to reduce mortality, since the progression of disease during the first three years is fast.

Rheumatoid Arthritis

RA is a chronic inflammatory autoimmune disease that is characterized by symmetric involvement of joints in a progressively destructive manner, which can cause significant disability if not properly treated. Besides musculoskeletal disease, other extraskeletal manifestations, as well as constitutional symptoms, may be observed.

Epidemiology

RA is considered among the most common autoimmune diseases, presenting a reported incidence of 0.5–1%. Even though not as evident as in SLE, slight differences between ethnic groups (Native Americans are more commonly involved) or topographic areas (northern hemisphere and urban areas present a higher incidence) may be observed. RA involves patients in their middle age with a female predominance (2:1 to 3:1).

Pathogenesis (Genetics and Environment)

The cause of RA remains unknown. As with other autoimmune diseases, a combination of host genetic and environmental factors is thought to underlie disease triggering. In RA immune cell infiltration of the synovial membranes of joints with T cells, B cells, monocytes, and neutrophils leads to inflammation of synovial membranes, "pannus" formation, and subsequent bone and cartilage erosion. Inflammatory mediators such as tumor necrosis factor (TNF) and IL-6 as well as Janus kinase (JAK)-STAT cytokine-mediated immune responses are clearly involved in disease activity, as blockade of relevant pathways has been effective for therapeutic intervention. One interesting aspect of the disease is that autoantibodies often develop 1–10 years prior to disease onset. Specifically, antibodies to citrullinated proteins (ACPA) develop 5–10 years before disease onset.

A genetic predisposition has clearly been defined in RA. Most significantly associated with RA are HLA class II antigens, such as *HLA-DRB1*01* and *HLA-DRB1*04*, containing a "shared" epitope—a stretch of five amino acids in the region responsible for antigen presentation to T lymphocytes. Also associated with RA are genetic loci relevant to T-cell function (*CTLA4*, *PTP22*), cytokine signaling (*TNF*, *IL2RA*, *IL2RB*), and B-cell activation (*CD4*), suggesting a role of these pathways in disease. In addition to genetic susceptibility, epigenetic modifications may be observed including modified DNA methylations, histone acetylation, as well as microRNA differential expression. Finally,

environmental triggers including smoking, alcohol consumption, socioeconomic level, and infectious agents, such as periodontal pathogens, have been associated with the development of RA.

Clinical Presentation

The most common and significant manifestation of RA is the development of symmetric polyarthritis with a migratory character and gradual increase of disease. The inflammatory process primarily involves the wrists and metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal articulations. Accompanying morning stiffness lasting from 30 minutes to several hours is also common. The fingers are affected in a fusiform pattern, mainly around the joints, in contrast to psoriatic arthritis where the whole digit is swollen ("sausage digit").

If RA is insufficiently treated, extraskeletal manifestations may develop. The occurrence of firm masses called rheumatoid nodules, especially in subcutaneous areas in proximity to bony prominences, is the most frequent finding. Severe complications may also develop, such as necrotizing vasculitis of the small and medium-sized arteries, interstitial lung disease, or cardiovascular disease, with the latter being the most common cause of mortality among RA patients.[32]

Intra- and Extraoral Manifestations

The TMJ is involved in almost every patient with RA according to the Helkimo index. Various clinical signs or symptoms of TMJ involvement, such as pain (frequently elicited by pressure on the joint), crepitation, reduced mouth opening, and impaired movement, have been described in RA patients. In advanced stages, progressive condylar destruction may cause malocclusion and anterior open bite, joint ankylosis, and facial asymmetry. Additionally, radiographic signs may be observed (on routine TMJ radiographs, CT or cone-beam CT (CBCT) scans, and other imaging modalities), including modifications in cortical integrity, erosions, diminished joint spaces, condylar asymmetry, flat condyles, and subcortical cysts (Figure 19-10).

Besides affecting the TMJ, RA may show several other manifestations in the orofacial area.[31] Cases of simultaneous (secondary) Sjögren syndrome are associated with hyposalivation, causing the subjective symptom of xerostomia and susceptibility to local infections (primary dental caries and candidiasis). The relationship of RA with dental and periodontal disease has been widely studied. Increased prevalence and severity of periodontal disease have been documented in RA patients, even in those newly diagnosed. Susceptibility to periodontal disease has been associated with various factors, including common disease mechanisms underlying both periodontitis and arthritis and impaired ability of RA patients to perform hygiene. Additionally, periodontitis has been hypothesized as a disease trigger for RA development. Finally, oral side effects of systemic medications used to treat RA have been reported.

Diagnosis

Diagnosis is primarily made by evaluation of the clinical and immunologic findings. Although to date there are no diagnostic criteria for RA, diagnosis may be facilitated by the classification criteria proposed by the American College of Rheumatology and European League Against Rheumatism (Table 19-5). If a patient presents with clinical features of synovitis, in the absence of an alternative diagnosis that can better explain the synovitis, four different parameters are assessed and, if the total score is greater than or equal to 6, definite classification as RA is accomplished.

Laboratory Findings

Typically, the main laboratory findings in patients with RA include acute-phase reactants and autoantibodies. CRP and ESR are the most significant markers used to detect inflammatory responses, with the former being more specific in measuring disease activity due to its association with inflammatory cytokines expressed in RA. The main autoantibodies used for diagnosis of RA are cyclic citrullinated peptides (anti-CCP) and rheumatoid factor. Both are specific markers, even though they are occasionally expressed in other diseases. Additionally, antibodies that may be detected in other autoimmune diseases, including ANA and anti-dsDNA, may also be positive in RA, despite the fact that biologic therapies may cause a reactive expression of these markers.

Management

A critical element in RA treatment is early diagnosis and treatment by a specialist. Due to significant progress in understanding of the disease, irreversible joint damage can be prevented today in 90% of patients. Initial-phase treatment for RA typically involves methotrexate (used as monotherapy or in combination with corticosteroids), which is considered an efficient treatment for RA and is associated with few and easily controllable adverse effects.[32] Symptomatology may also be improved by other drugs including nonsteroidal anti-inflammatory drugs (NSAIDs), which however do not inhibit disease development and should be used as supplementary therapy before a definite diagnosis of RA is established. Subsequent treatment typically involves disease-modifying antirheumatic drugs (DMARDs), such as TNF inhibitors, IL-6 inhibitors, and small-molecule inhibitors of JAKs involved in cytokine signaling.[30]

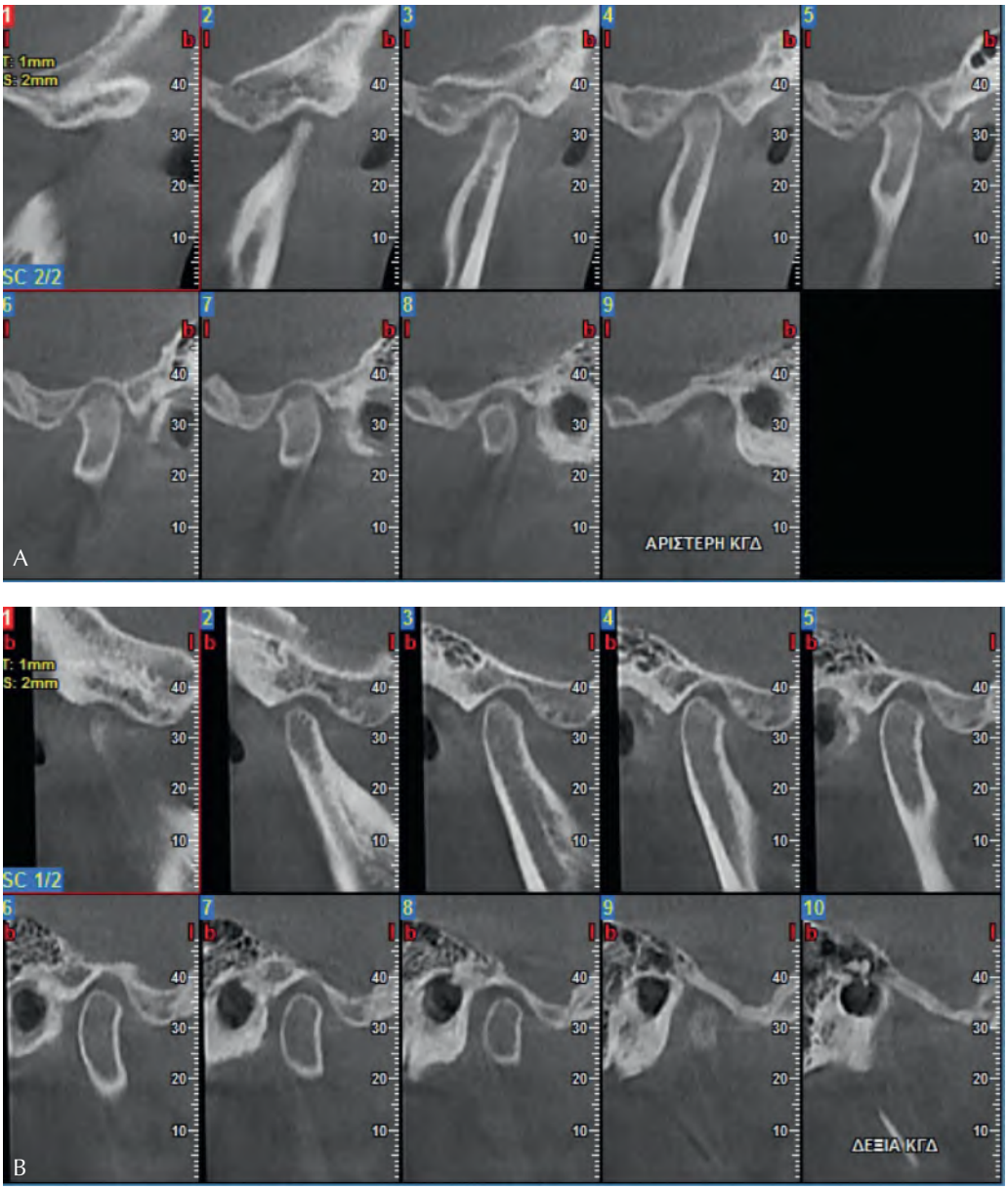

Figure 19-10 Temporomandibular joint (TMJ) imaging abnormalities in rheumatoid arthritis (RA). Cone-beam computed tomography of the TMJ of a patient with RA reveals (A) a flat condyle on the right side and (B) erosions of the condyle and diminished joint space on the left side. Courtesy of Professor Tsiklakis.

Oral manifestations of RA should also be treated accordingly. Even though oral manifestations may respond to the aforementioned systemic treatments, management of specific disorders is essential. When the TMJ is affected, treatment ranges from conservative (NSAIDs, physiotherapy, occlusal splints, as well as local injections of corticosteroids or anesthetics) to surgical reconstructive therapy in cases with significant defects. Finally, possible comorbidities (Sjögren syndrome, periodontal disease, or oral complications of systemic therapy) should be managed appropriately.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD), an entity that highlights the overlapping character between autoimmune inflammatory disorders, was first described almost five decades ago. More specifically, this term is used for cases presenting clinical manifestations in the spectrum of SLE, Sjögren syndrome, as well as inflammatory myopathies (IMs). Even though extensively described, its recognition as a separate entity is still a subject of controversy, with some authors believing that it represents an initial phase of another well-characterized connective tissue disease.

Table 19-5 Classification criteria for rheumatoid arthritis.

Rheumatoid arthritis score-based algorithm: a score of categories A–D ⩾6 out of 10 is required for definite classification as rheumatoid arthritis	Score
A. Joint involvement*	
1 large joint	0
2–10 large joints**	1
1–3 small joints (with or without large joints)	2
4–10 small joints *** (with or without large joints)	3
>10 joints (at least one small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
<6 weeks	0
≥6 weeks	1

*Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.
**Large joints refers to shoulders, elbows, hips, knees, and ankles.
***Small joints refers to the metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.
ACPA, antibodies to citrullinated proteins; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, regulatory factor.

Epidemiology

Few data can be retrieved from the literature regarding the epidemiologic features of MCTD; however, females seem to be more frequently involved compared to males and the disease could show an early onset. Overall, it is considered a rare disease with a measured prevalence ranging from 0.8 to 3.8 per 100,000 adults in Northern European populations.[33]

Pathogenesis

The cornerstone in the pathogenesis of MCTD is the presence of the anti-ribonucleoprotein (RNP) antibodies, albeit the exact biologic mechanisms are to date unspecified. A proposed hypothesis is that a genetic predisposition and especially the presence of distinct subsets of HLAs may play a key role. More specifically, several studies have linked MCTD with the presence of HLA DRB1*04, which seems to generate anti-U1-RNP expression.[33]

Clinical Features

Clinical manifestations identical to various connective tissue diseases are present, including Raynaud's phenomenon and "puffy" or swollen hands, myositis, arthritis, interstitial lung disease, pulmonary hypertension, cutaneous lesions and alopecia, esophageal dysmotility, neurologic symptoms, as well as renal disease. Insufficient data comparing adult patients and juveniles are available in the literature, although slight differences are described, such as the increased severity of lung disease in adults.

Orofacial involvements of MCTD have rarely been reported. Among them, trigeminal neuropathy is the most common manifestation. However, since this disease overlaps with other autoimmune diseases, signs or symptoms characterizing the phenotype, including xerostomia, lymphadenopathy, or lichenoid lesions, may be observed. Additionally, patients receiving high-dose immunosuppression could develop oral mucosal lesions as an adverse effect.

Laboratory Findings

Autoantibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1-snRNP) are considered specific markers for an MCTD diagnosis, even if their expression has been observed in other autoimmune diseases. ANAs are also expressed in almost every case. Other hematologic findings include anemia, leukopenia, and thrombocytopenia.

Diagnosis

MCTD has a complex nature and, as already mentioned, its characterization as a distinct entity is still under debate; hence, diagnosis is typically difficult. Additionally, alterations in diagnostic criteria of other autoimmune diseases render the classification of certain patients problematic. To date, various diagnostic (and/or classification) criteria have been proposed for MCTD, which, as in every other connective tissue disease, includes immunologic (anti-U1-RNP detection) as well as clinical parameters.

Management

No randomized trials have been conducted regarding treatment protocols in MCTD. Management mainly includes immunosuppressants, especially corticosteroids, as well as steroid-sparing medications, such as methotrexate, cyclosporine, and azathioprine. Further, specific manifestations (including Raynaud's phenomenon) should be treated accordingly (e.g., with calcium-channel blockers). MCTD presents a measured mortality rate of 8–36%, with common causes of death being related to pulmonary hypertension and interstitial lung disease.

Dermatomyositis and Other Inflammatory Myopathies

IMs are a complex group of diseases falling under the term "myositis," generally characterized by inflammatory processes involving the muscles in addition to extramuscular manifestations. Myositis may involve adults or juveniles and may present heterogeneous manifestations, justifying its subclassification into various separate entities. Dermatomyositis (DM) is one of the main disease subsets characterized by skin involvement accompanying the progressive muscle weakness. DM is also the most prevalent myopathy in young patients (juvenile DM), while occasionally amyopathic forms may develop, which are considered by some authors as separate disorders (amyopathic DM).[34] IMs presenting distinct demographic, clinical, or pathologic features are inclusion body myositis and immune-mediated necrotizing myositis. As observed in other autoimmune diseases, IMs may also exhibit accompanying features shared with other connective tissue diseases, for which the term overlap myositis is used. Myositis may be associated with malignant neoplasms (cancer-related myositis), as supported by the high incidence of cancer in DM patients. However, it has not been clarified whether muscle involvement is a paraneoplastic phenomenon or myopathy precedes cancer development. Other uncommon types of myopathy have also been described, while cases of muscle involvement that do not exhibit specific features observed in other myopathies fall under the term polymyositis (PM).

Epidemiology

IMs are considered rare, with estimated prevalence rates ranging from 9 to 33 cases per 100,000 individuals; women and African Americans are more frequently affected. Inclusion body myositis is the only exception affecting males more commonly than females. Even though the prevalence and incidence of IMs as a whole may be easily counted, calculating the epidemiologic features of specific subsets of disease may be problematic due to the modifications that occasionally occur in the classification of these entities.

Pathogenesis

IMs are generally characterized by immune and nonimmune events initiated in a context of genetic predisposition as well as environmental triggers. Inflammatory cells of the immune system accumulating in lesions of IMs include T cells (mostly $CD4^+$, $CD8^+$, and $CD28^{null}$ populations), B cells secreting autoantibodies, and cells of the macrophage-dendritic lineage. Additional mechanisms that do not implicate the immune system have been proposed, including hypoxia, endoplasmic reticulum (ER) stress, and autophagy, all of which are mutually connected. However, their heterogeneous clinicopathologic manifestations may reflect different underlying pathologic mechanisms. Muscle involvement in dermatomyositis is believed to be a result of autoimmune attack against endomysial capillaries, leading to ischemia and atrophy of the muscle fibers. On the contrary, PM displays endomysial $CD8^+$ T cells that identify an endogenous peptide, resulting in myofiber necrosis via secretion of perforin-1 and granzyme B.

Genetic as well as environmental factors have also been widely accepted to be related to disease development. The role of certain class 2 HLA alleles and especially HLA DRB1*0301 has been described and may be associated with specific autoantibody expression. Additionally, exogenous parameters including infections (e.g., of the respiratory tract) or ultraviolet radiation may trigger disease.

Clinical Features

Dermatomyositis is characterized by varying amounts of proximal muscle weakness with symmetric distribution and cutaneous involvement. Muscle involvement may range from mild to severe causing serious disabilities. The most pathognomonic clinical sign in DM is the presence of a papular violaceous rash affecting the metacarpophalangeal and interphalangeal joints, also known as Gottron's papules. A highly characteristic cutaneous manifestation is the so-called heliotrope rash (discoloration of the periorbital area), while other typical lesions include the Gottron sign (erythematous lesions of the elbows, knees, knuckles, or ankles), the V sign (erythema in the face, neck, and chest area), and the shawl sign (affecting the neck and shoulders).[34] Juveniles more commonly develop febrile illness as well as calcinosis of the skin. Besides other more uncommon cutaneous signs, DM may develop extramuscular and extracutaneous manifestations, especially cardiac involvement as well as interstitial lung disease. Noteworthy is that muscle involvement is almost identical between different types of IMs and difficult to differentiate solely on the basis of clinical manifestations. Diagnosis is usually made upon correlation of the clinical phenotype with the pathologic and laboratory findings.

Few data can be retrieved from the literature regarding oral manifestations of patients with IMs.[34] An increased number of decayed, missing, or filled teeth has been attributed to poor oral hygiene. Additionally, a decrease in masticatory forces and increased incidence of temporomandibular disorders (TMDs) has been reported. Mucosal involvement is also reported in patients with PM and DM, most frequently in the form of telangiectasia. Specific gingival lesions have been described in patients with juvenile DM, described as having a "bushy loop" appearance. However, histopathologic examination was not performed in these cases to exclude other well-known entities with a similar clinical appearance. Lichenoid lesions have also been reported to affect patients with DM. Nevertheless, there is insufficient data on whether these manifestations could belong to the

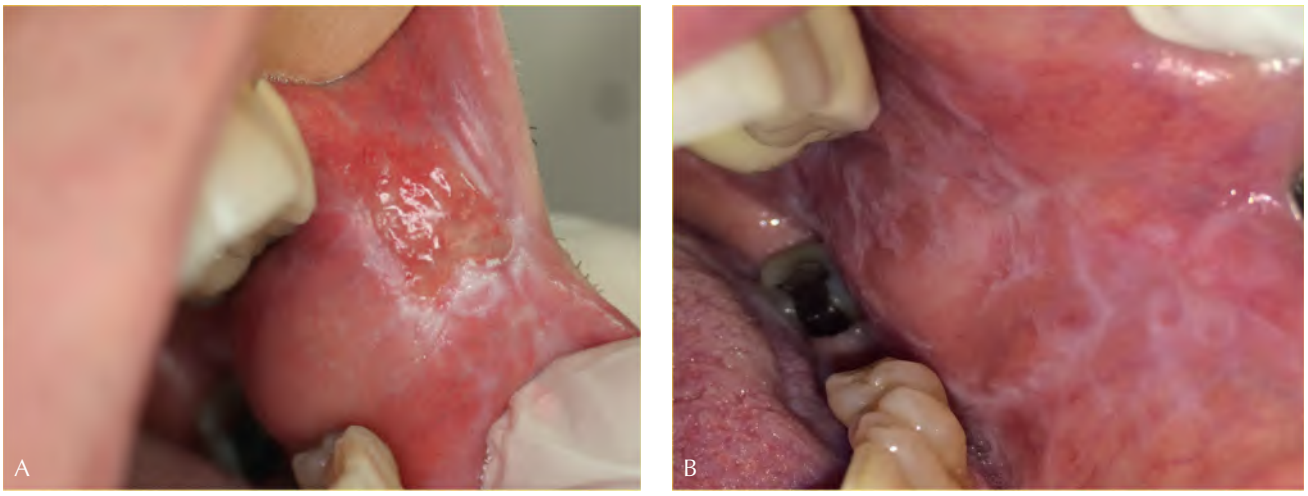

Figure 19-11 Intraoral (buccal mucosal) lesions in a patient with dermatomyositis. The appearance of lesions can change over time from (A) ulcerative to (B) striated.

spectrum of DM, represent lichen planus that coexists/interacts with DM, or are merely coincidental (Figure 19-11). As already mentioned, malignant neoplasms may be associated with DM and oral cancer cases have been reported in patients with DM, even though an exact causal relationship cannot be established. Fibrosis of the salivary glands is a common finding, while calcinosis of the soft tissues in juveniles can affect the head and neck region and be radiographically detectable.

Pathologic Features

Histopathologic examination of muscular tissue in patients with IMs may be helpful in establishing the diagnosis and categorizing patients, as different microscopic features may be observed in separate subsets of disease. Perifascicular atrophy is observed upon biopsy in addition to endomysial, perimysial, or perivascular inflammation and occasional necrotic muscle fibers.

Biopsy of cutaneous or mucosal lesions may be helpful for diagnosis in patients with DM. In acute phases, microscopic features may be similar to those in lupus erythematosus and include a hyperkeratotic and commonly atrophic epithelium/epidermis with hydropic degeneration of the basal cell area and perivascular inflammation along with interface dermatitis/mucositis. These histopathologic features may be characterized as exhibiting lichenoid features, highlighting the loss of sufficient data on whether previously reported intraoral lesions are manifestations of lichen planus or DM. Other cutaneous signs of DM may present distinct histopathologic features (e.g., Gottron papules show hyperacanthosis and papillomatosis). Direct immunofluorescence could facilitate diagnosis in equivocal cases exhibiting a granular deposition of immunoglobulins and complement in the dermo-epidermal junction.

Laboratory and Other Findings

The main laboratory feature in IMs is the presence of elevated muscle enzymes, especially CK, which also helps determine disease activity in individual patients. Electromyographic examination is a routine test that facilitates diagnosis, showing features of myopathy. Autoantibodies play an important role in the diagnostic process, as their detection is associated with discrete subsets (e.g., DM associated with anti-MI2 as well as anti-NXP2 antibodies, while anti-Jo1 antibodies are found in overlap myositis) and specific manifestations (e.g., anti-TIF1 in DM is strongly associated with cancer involvement).

Diagnosis

Diagnosis of IMs is made upon correlation of clinical, laboratory, and histopathologic manifestations. More specifically, in 2003 a classification was introduced and approved by the Myositis Study Group and the 119th European Neuromuscular Centre workshop, facilitating the classification of IMs except inclusion body myositis. Patients meeting these criteria may further be subclassified into different subsets based on their specific manifestations.

Management

Treating IMs may be a challenge due to their low prevalence rates as well as heterogeneous manifestations and subtypes, which render the establishment of specific protocols impossible for the time being. First-line treatment of these patients mainly includes corticosteroids in addition to reinforcement of physical exercise, followed by steroid-sparing immunosuppressive agents (including azathioprine and methotrexate). Intravenous immunoglobulins and biologic agents may be used in severe cases, while in patients exhibiting dysphagia invasive management or injection of botulinum toxin is

proposed. Plasmapheresis may also be performed in patients with interstitial lung disease.

Oral manifestations of DM should also be managed accordingly.[34] Dental, periodontal conditions, and TMD require appropriate treatment, while appointments should be short for patients with muscle weakness of the neck. Since mucosal involvement in DM has not been fully clarified, there are no specific guidelines regarding the management of lesions arising in these patients and biopsy and histopathologic examination should be performed. Follow-up of these patients is essential to control dental and periodontal health as well as to identify early signs of cancer.

IMs exhibit variable prognosis that depends on the onset of treatment and severity of organ involvement. Patients with cancer development, esophageal involvement, cardiovascular disease, or pulmonary dysfunction have a poor prognosis, while the main causes of death include respiratory or cardiac complications, infections, and cancer.

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is an autoimmune disease classified under the broad category of ANCA-associated vasculitis (AAV) due to the pathogenetic association with antineutrophil cytoplasmic antibodies (ANCAs).[35] The hallmark of the disease is the presence of small-vessel necrotizing vasculitis with granulomatous features, resulting in multisystemic manifestations with significant morbidity and mortality. Although generally considered a distinct entity, recent reports suggest a more unifying classification of AAV due to the significant overlapping features of GPA with microscopic polyangiitis (MPA), as well as their similar pathogenetic characteristics. Other studies emphasize the genetic differences between these two entities (with GPA being more commonly associated with proteinase 3 ANCA (PR3-ANCA]) and support a classification of AAV into PR3-ANCA-associated vasculitis and myeloperoxidase (MPO) ANCA-associated vasculitis, depending on their underlying genetic abnormalities.

Epidemiology

GPA is considered a rare disease with a prevalence between 2 and 13 per 100,000 individuals and an inpatient prevalence of approximately 30 patients per 100,000 admissions. Older patients with a mean age of more than 60 years are typically affected, Caucasians are more susceptible and equal distribution between the two sexes is observed.

Pathogenesis

The exact etiology of GPA development has not yet been fully elucidated. As observed in other autoimmune diseases, environmental and genetic factors have been implicated as responsible for immune response deregulation. Exposure to external triggers, such as dust or silica, is included among the most frequent exogenous factors associated with GPA. Additionally, infectious agents, such as *Staphylococcus aureus* of the upper aerodigestive tract, have been suggested to play a role in triggering the disease. Drugs may also cause AAV-like phenomena with distinct features (i.e., resolution after discontinuation of the agent), while they may also trigger disease in already genetically predisposed GPA patients. Responsible agents for drug-induced AAV include antibiotics, antithyroid medications, and anti-TNF agents. A genetic predisposition has been highlighted by some GPA cases reported in siblings, as well as from recent findings in genome-wide association studies of AVA. More specifically, vasculitis with anti-PR3 ANCA (which most commonly exhibits phenotypic features of GPA) was associated with the gene encoding for proteinase 3, *HLA-DP*, as well as the gene encoding for α1-antitrypsin. In contrast, cases of vasculitis with antimyeloperoxidase ANCA (most commonly MPA) exhibited association with the *HLA-DQ* gene. Regarding the immune mechanisms participating in AVA pathogenesis, the role of neutrophils in facilitating loss of tolerance to the antigens recognized by ANCA has been underlined. Patients with GPA exhibit high frequency of long-lived plasma cells secreting ANCA. After interacting with ANCA, neutrophils and monocytes release cytokines, proteases, and ROS, while neutrophil extracellular trap products (NET-derived products) are secreted, resulting in activation of dendritic cells and eventually compromising Treg function.[36]

Clinical Features

A wide spectrum of manifestations has been described in GPA with varying degrees of organ involvement. While the upper aerodigestive tract is the predominant site of involvement in limited disease, generalized forms have been associated with major organ dysfunction as well as deteriorating general health. Additionally, nonspecific constitutional signs and symptoms including fever, fatigue, and weight loss are commonly encountered (in approximately half of cases) in generalized GPA. The ear, nose, and throat (ENT) region is considered the most commonly involved, especially in limited disease. Signs may include rhinorrhea with hemorrhagic crusts, deformities of the nose (scooped-out or depressed appearance), perforation of the nasal septum, sinusitis, chronic otitis media, and tracheal or subglottic stenosis. Nasal–sinus involvement is very characteristic of GPA and may be the only sign, while nasal obstruction with olfactory dysfunction is commonly the first manifestation. Other target organs are commonly affected. More specifically, the lungs are frequently involved, with alveolar hemorrhage as well as parenchymatous nodules being the most significant

pulmonary lesions in GPA. Pauci-immune necrotizing glomerulonephritis is a characteristic renal sign that is associated with microhematuria and proteinuria; noticeably, the severity of renal dysfunction is associated with prognosis in these patients. The nervous system may also be affected, usually with peripheral neuropathy (mononeuritis multiplex or sensorimotor neuropathy), while CNS involvement (pachymeningitis) is considered rare. Necrotizing nodular episcleritis is considered the most common ocular sign in GPA, while corneal ulcerations, scleritis, and retinal vasculitis may also be observed. Less common but characteristic signs of disease include the involvement of the eye socket with a granulomatous retro-orbital pseudotumor or dacryoadenitis. Cardiac manifestations may be a result of the necrotizing vascular changes characterizing the disease, with variable levels of severity. Finally, the gastrointestinal tract is commonly affected by ulcerative lesions, often resulting in perforation.

Mucocutaneous manifestations may be present and include oral manifestations. Purpura, leuco-cytoclastic vasculitis, cutaneous ulcerations, subcutaneous nodules, and pyoderma gangrenosum are common cutaneous manifestations, albeit to a variable extent. Oral mucosal involvement also exhibits heterogeneous manifestations that may vary depending on the clinical course of the disease.[37] Acute and rapidly progressing lesions are observed in widespread disease, including oral ulcerations with occasional necrotic features, while more chronic lesions with gradual deterioration and destruction of hard and soft tissues are observed in localized disease. Perforation of the palate may be observed, while involvement of the gingiva may exhibit a characteristic vegetating or granular appearance, called "strawberry gingivitis," which may occasionally be the first manifestation of the disease (Figure 19-12). The salivary glands may be involved in GPA showing enlargement, with the parotid being the most commonly affected major salivary gland, sometimes preceding involvement of other organs.

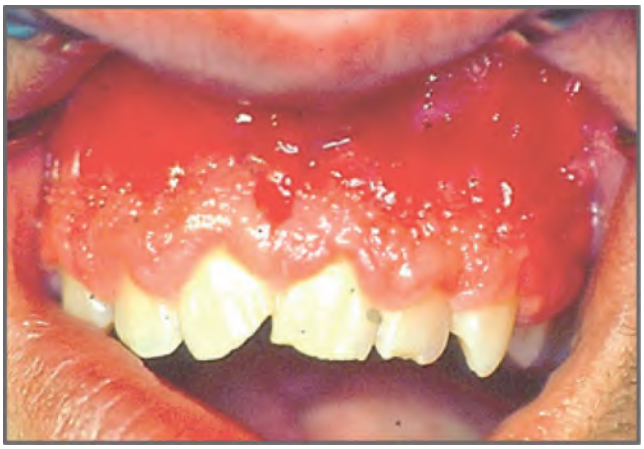

Figure 19-12 Diffuse gingival involvement in granulomatosis with polyangiitis (GPA), assuming a characteristic "strawberry gingivitis" appearance. Courtesy of Professor Kolokotronis.

Pathologic Findings

Biopsy is essential for the diagnosis of GPA. In some organs, including the kidney, the histopathologic features are considered prognostic factors. The microscopic characteristics in mucocutaneous GPA lesions include necrotizing vasculitis and granulomatous inflammation, with occasional palisading features (epithelioid histiocytes and multinucleated giant cells surrounding a central area of necrosis). Occasionally, however, nonspecific findings may be encountered, including acute or chronic inflammation, scattered multinucleated giant cells, increased vascularity, and pseudo-epitheliomatous hyperplasia, especially in biopsies retrieved from the gingiva of GPA patients. Nevertheless, even these features could suggest the diagnosis, which may be further substantiated after correlation with the clinical characteristics of the lesion as well as the possible involvement of other organs.

Laboratory Findings

Laboratory work-up is essential for GPA patients, facilitating diagnosis and occasionally determining prognosis. Anemia, leukocytosis, and eosinophilia may be observed in GPA. ESR and CRP may also be elevated, especially in active disease, while involvement of specific organs may be associated with respective laboratory findings (e.g., urine proteinuria in kidney involvement). The most important serologic marker for GPA is ANCA, although it is not necessary for diagnosis, which is primarily based on clinicopathologic correlation. Both indirect immunofluorescence, which may identify cytoplasmic c-ANCA (most common in GPA) or perinuclear p-ANCA, and enzyme immunosorbent assays (ELISA), which measure PR3-ANCA and MPO-ANCA titers, have been traditionally used with significant sensitivity and specificity. However, a recently published position paper proposes that high-quality immunoassays and not indirect immunofluorescence are sufficient to primarily screen patients with suspected AVA.

Diagnosis

Diagnosis of GPA is based on the clinical as well as histopathologic features, while ANCA serology may be indicative. Although no diagnostic criteria exist, classification criteria may simplify the diagnostic procedure. These criteria were proposed by the American College of Rheumatology in 1990 and include oral, nasal, pulmonary, and renal manifestations, in addition to histopathologic evidence of granulomatous inflammation.

Management

The major aim of treatment for patients with GPA is to achieve remission and survival by minimizing recurrences and fatal outcomes. The currently used recommendations were recently initiated by the European League Against Rheumatism in conjunction with the European Renal Association/European Dialysis and Transplant Association. They include guidelines about the first phase of treatment, consisting of immunosuppressive therapy (including cyclophosphamide and rituximab) in addition to glucocorticoids, and the second phase (remission maintenance). The initial therapeutic approach is usually individualized and depends upon the severity of disease and patient's general health. Although the aforementioned therapeutic approaches have minimized morbidity and mortality, GPA may be associated with relapses and life-threatening complications. Limited ENT involvement and granulomatous inflammation upon biopsy have been associated with recurrences, while the severity of renal involvement is a major prognostic factor. The most common causes of death are infections and kidney failure.

GENERAL CONSIDERATIONS FOR DENTAL MANAGEMENT OF PATIENTS WITH IMMUNE-MEDIATED DISEASES

Dental treatment and surgical procedures in the orofacial area in patients with immune-mediated diseases should be performed after consideration of multiple parameters and in close and continuous collaboration with the caring medical team. These disorders constitute a special category that should be managed with caution due to a variety of general and disease-specific complications that are related to the disease itself or the medications used to treat it.

Susceptibility to Infections

Dental and oral mucosal infections may pose an increased risk for systemic infection in immunocompromised patients. Most cases of oral microbiota leading to systemic infections in immunocompromised hosts are related to invasion in the presence of an existing dental infection (but not typically in the presence of oral health). In the presence of ongoing odontogenic infections, microbial translocation from the oral cavity has been considered a risk factor for distal infections, particularly during invasive dental procedures. Odontogenic infections have been associated most commonly with infectious endocarditis, but also with infections in the CNS and less commonly with distal skeletal infections. Cases of infections in the CNS have been reported in immunocompromised patients, and in a few cases the organism has been traced from the primary odontogenic infection. Septicemia from oral infections has also been reported in immunocompromised patients in multiple cases with the organism *Leptotricia buccalis*.

Patients with primary immunodeficiencies[38] may be at an increased risk for oral infections (as described in the earlier sections) as well as for dissemination of microbiota from dental infections from the mouth into the systemic circulation. To date, there are no specific guidelines for dental management and/or for use of antibiotic prophylaxis in patients with primary immunodeficiencies. Common recommendations include aggressive prevention to avoid and treat early oral and dental infections in such patients, close monitoring, and coordination of treatment with the medical team. Due to the severity of immunodeficiency in such patients, often dental treatment will be advised to be performed within the hospital setting.

Patients with autoimmune diseases are also often considered immunocompromised, either because of the disease itself or secondary to the use of immunosuppressive medications. Leukopenia is also a possible manifestation of autoimmune diseases or the medications used to treat them and is associated with susceptibility to infections; hence, procedures associated with bacteremia should be performed with caution. However, a recent study including patients with different levels of neutropenia concluded that extractions are safe and with few associated complications. Even though there are insufficient data about the use of antibiotics in these patients, perioperative treatment is generally proposed, especially in patients with moderate to severe neutropenia (<1000/μL). There is also no consensus regarding the use of antibiotics in patients under corticosteroid treatment. As a result, the main consideration is the potential modification of the dose of corticosteroids to prevent an adrenal crisis, which is discussed later in this chapter.

Besides exhibiting a higher risk of infection after dental procedures, patients with autoimmune diseases may develop specific infections with oral manifestations. Herpes zoster or HPV infection is considered common in patients with SLE and could manifest in the oral cavity. Oral candidiasis may also be frequently encountered in autoimmune disease patients as a side effect of corticosteroid or other immunosuppressive treatment or a consequence of reduced salivary flow, and should be managed accordingly.

Additionally, SLE and other autoimmune disorders lead to valvular disease, requiring prosthesis and increasing the risk for bacterial endocarditis following surgical procedures. Such patients will require antibiotic prophylaxis prior to surgical procedures, based on the most recent guidelines about patients with valvular disease from the American Heart Association and the American College of Cardiology. Prosthetic joints used to manage certain autoimmune diseases and especially RA exhibit a higher risk of infection,

even though this risk has not been associated with dental procedures. Patients with prosthetic joints do not require antibiotic prophylaxis prior to dental procedures to avoid infection of the prosthetic joints.

Risk of Bleeding

Coagulation is commonly impaired in autoimmune diseases for multiple reasons, including thrombocytopenia associated with the disease (e.g., in SLE), use of certain myelotoxic drugs, or treatment with anticoagulants or antiplatelet regimens (in patients with risk for thrombosis). Such patients may be at increased risk of bleeding subsequent to surgical interventions. Recent studies suggest that extractions in patients with thrombocytopenia are usually safe and complications are easily managed with local measures. However, patients exhibiting a platelet count under 50,000/μL require platelet transfusion, so cases with severe thrombocytopenia should be managed in a hospital environment. In patients with anticoagulant therapy, INR should be measured and if its value is between 2.0 and 3.5, minor interventions are allowed, while for more invasive procedures, replacement of the regimen with low molecular weight heparin should be considered. Insufficient data exist regarding the management of patients receiving novel direct anticoagulants. Discontinuation of antiplatelet therapy should be considered prior to intervention. Communication between the patient's dental and medical practitioners is necessary, especially for complex cases.

Adrenal Suppression

Corticosteroids are included among the most common medications used to treat autoimmune connective tissue diseases due to their significant efficacy in limiting disease activity. However, their side effects, including adrenal suppression, should be taken into consideration during dental treatment. To date, few cases of adrenal suppression following dental procedures have been reported. Adrenal suppression is considered to correlate with the dosage and duration of corticosteroid treatment.

Currently, confusing data exist in the literature regarding management of patients under corticosteroids. While some authors propose perioperative steroid cover for these patients, others support giving supplementary steroids only in cases treated under general anesthesia. As a result of the absence of specific guidelines, every case should be individualized, and treatment planned with the caring physician.

Cardiovascular Disease

As already described, several autoimmune diseases display a multisystemic clinical appearance, occasionally involving the cardiovascular system. More specifically, patients with SLE or SSc may exhibit hypertension, while SSc cases may also present with arrhythmias. Common atherosclerosis in SLE may also be associated with ischemic episodes and angina. The dental practitioner must always assess the general condition of these patients before starting any minor or invasive procedure and establish a communication with the patient's physician. Antianxiety techniques and pain control play a key role in the prevention of medical emergencies, appropriate management of which, should they happen, requires proper medical supplies and experience on behalf of the dentist.

Liver and/or Kidney Disease

Renal involvement is common in patients with autoimmune diseases (e.g., lupus nephritis), while nephrotoxicity or hepatotoxicity is included among the side effects of certain medications for connective tissue diseases. Renal and liver function should be monitored in these patients, as the doses of common medications prescribed by the dentist may be modified depending on the extent of disease and the type of drugs used. Additionally, dental procedures should be performed under appropriate conditions in patients under hemodialysis (treatment should be performed the day after dialysis).

Hyposalivation and Xerostomia

The salivary glands are a common site of involvement by several autoimmune diseases as a part of their phenotypic characteristics (e.g., fibrotic changes in SSc), a feature of secondary SS (e.g., in SLE or RA), or an adverse effect of certain medications for rheumatic diseases (e.g., drugs treating cardiovascular or musculoskeletal manifestations). Salivary gland involvement results in hyposalivation and the subjective feeling of xerostomia. Management of xerostomia and its etiologic factors is discussed in other chapters.

Dental and Periodontal Disease

Periodontal disease is more prevalent in patients with various autoimmune diseases. Appropriate periodontal treatment with frequent follow-up visits should be performed in these patients, in addition to control of the possible aggravating factors. Toothbrushes with customized handles and of special size are useful for patients displaying impaired manual dexterity (e.g., in patients with SSc or RA) or in cases of reduced mouth opening (e.g., in patients with SSc).

Oral Mucosal Involvement as an Adverse Effect of Immunosuppressive Therapy

Specific reactions to certain medications may affect the oral cavity with heterogeneous clinical manifestations.

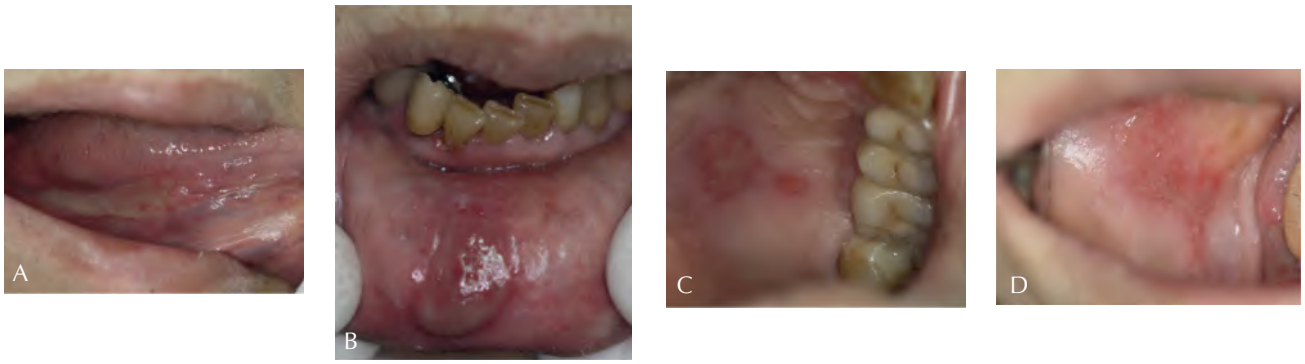

Figure 19-13 Oral aphthous-like lesions associated with methotrexate treatment in a patient with rheumatoid arthritis: (A) tongue; (B) lip; (C) palate; (D) buccal mucosa.

Anemia, neutropenia, and thrombocytopenia induced by certain myelotoxic drugs (or by certain diseases, including SLE) may cause corresponding oral mucosal lesions in the oral cavity (such as atrophy, neutropenic ulcers, and petechiae, respectively). Systemic drug administration (e.g., methotrexate) may also cause occasional adverse mucosal reactions, which may vary from mucosal ulcers or erythema to lichenoid lesions (Figure 19-13). Other oral lesions related to medications for rheumatic diseases include pigmentation (e.g., related to hydroxychloroquine) or diffuse gingival enlargement (e.g., due to cyclosporine). The clinician should be aware and suspicious of these conditions, especially if their occurrence shows a chronological relationship with the administration of the offending drug.

ALLERGIC AND HYPERSENSITIVITY REACTIONS

The modern dentist uses a wide variety of drugs to treat patients, including antibiotics, hypnotics, and anesthetics. All practitioners who use these medications must know how to manage adverse reactions triggered by these agents.[39] A dental practitioner also uses a wide range of materials such as impression materials, adhesives, latex, and restorative and endodontic materials that contain potential allergens. These include preservatives, coloring agents, fixatives, binding agents, flavorings, and latex.

Hypersensitivity Reactions

Immunologic reactions may be of several different types: type 1 IgE-mediated (anaphylactic), type 2 antibody-mediated, type 3 (immune complex–mediated), and type 4 (cell-mediated or delayed hypersensitivity). Type 1 reactions are acute (e.g., penicillin, latex, or peanut allergy) and require immediate recognition and action. Type 2 reactions are not usually found in response to dental materials or drugs, but are found in autoimmune conditions affecting the oral cavity, such as pemphigus. Such conditions are discussed in Chapter 3, "Ulcerative, Vesicular, and Bullous Lesions." Type 3 reactions can be seen in response to dental materials, but more commonly in response to viral infections such as recurrent herpes labialis, giving rise to erythema multiforme or Stevens Johnson syndrome (clinical manifestations are discussed in Chapter 3). Delayed hypersensitivity (cell-mediated or contact sensitivity) reactions to dental materials are very common and are usually seen in the oral cavity where an amalgam or gold restoration is in direct contact with the buccal or lingual mucosa. Stomatitis associated with allergy is discussed in Chapter 3. In this section, acute allergic reactions and their management are discussed.

Acute allergic reactions are caused by an immediate-type hypersensitivity reaction mediated by IgE and are the most serious of allergies.[40] Reactions can occur rapidly, and full-scale anaphylactic reactions may occur and be associated with local as well as systemic swelling. Type 1 reactions require the presence of mast cells with attached IgE. A patient previously exposed to a drug or other antigen has antibody (primarily IgE) fixed to mast cells. When the antigen (in the form of a drug, food, or airborne substance) is reintroduced into the body, it will react with and cross-link the cell-bound antibody. This causes an increase in intracellular calcium and the release of preformed mediators including histamine, proteases, and newly synthetized lipid-derived mediators such as leukotrienes and prostaglandins. Cytokines are also released, which attract eosinophils and augment the inflammatory response. These substances cause vasodilation and increased capillary permeability, ultimately leading to fluid and leukocyte accumulation in the tissues and edema formation. Constriction of bronchial smooth muscle results when IgE is bound in the pulmonary region. The anaphylactic reaction may be localized,

producing urticaria and angioedema, or may result in a generalized reaction, causing anaphylactic shock.

Localized Anaphylaxis

A localized anaphylactic reaction involving superficial blood vessels results in urticaria (hives). Urticaria begins with pruritus (itching) in the area where histamine and other active substances are released. Wheals (welts) then appear on the skin as an area of localized edema on an erythematous base. These lesions can occur anywhere on the skin or mucous membranes. There seems to be little doubt that the oral mucosa is well endowed with mast cells and that type 1 reactions can occur in the oral cavity. Urticaria of the lips and the oral mucosa occurs most frequently after food ingestion by an allergic individual. Common food allergens include chocolate, nuts, shellfish, and tomatoes. In the oral allergy syndrome (see later), it is thought that patients become sensitized by inhalation of allergens such as birch, and then react orally to cross-reactive foods, including apples. Drugs such as penicillin and aspirin may cause urticaria, and cold, heat, or even pressure may cause the reaction in susceptible individuals. Impression compounds, coloring agents, and preservatives, as well as ingredients of mouthwashes, may all cause local swelling or even anaphylaxis.

Angioedema is characterized by rapid development of edematous swelling, particularly of the head and neck, sometimes accompanied by urticarial rashes. It occurs when blood vessels deep in the subcutaneous tissues are affected, producing a large diffuse area of subcutaneous swelling under normal overlying skin. This reaction may be caused by contact with a known allergen, but a significant number of cases are idiopathic. Many patients have short-term disfiguring facial swelling, but if the edema involves the neck and extends to the larynx, it can lead to fatal respiratory failure.

Angioedema most commonly occurs on the lips (Figure 19-14) and tongue and around the eyes. It is temporary and not serious, unless the posterior portion of the tongue or larynx compromises respiration. The patient who is in respiratory distress should be treated immediately with 0.5 mL of epinephrine (1:1000) subcutaneously, or better intramuscularly. This can be repeated every 10 minutes until recovery starts. The patient should be given oxygen, placed in a recumbent position with the lower extremities elevated unless there is a danger of shortness of breath or vomiting, given fluids intravenously, and transported to hospital immediately. Patients may need intubation to maintain the airway. When the immediate danger has passed, 50 mg diphenhydramine hydrochloride (Benadryl®, Pfizer, Parsippany, NJ, USA) should be given four times a day until the swelling diminishes.

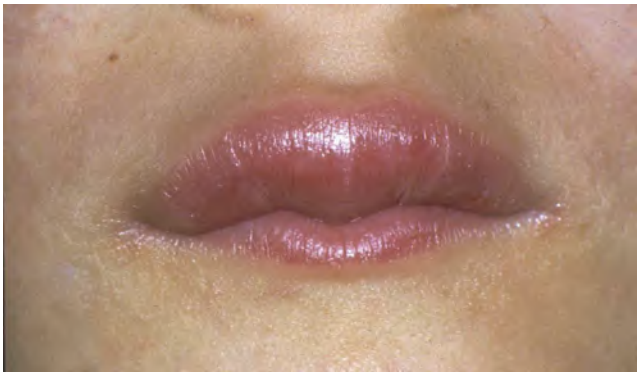

Figure 19-14 Immediate type 1 swelling of the lips after ingestion of peanuts in a patient with peanut allergy.

Hereditary angioedema (HAE) is another life-threatening condition that is not associated with allergens. It is a genetic disease with an autosomal dominant pattern of inheritance. The underlying defect is a failure to produce adequate levels of C1 esterase inhibitor (C1 inh), which normally acts as an inhibitor of the first component of complement and kallikrein. This inhibitor controls the degree of complement activation. Activation of kinin-like substances causes a sudden increase in capillary permeability. C4 is consumed and plasma levels fall, but C3 levels remain normal. An acquired form of angioedema in which antibody develops against C1 inh has also been described. Dental procedures can trigger attacks of HAE. These attacks do not respond well to epinephrine, and diagnosed patients are usually treated with the androgen danazol that increases C1 inh plasma levels. Fresh-frozen plasma may be given to patients before dental procedures until recombinant C1 inh is available for clinical use.

Generalized Anaphylaxis

Generalized anaphylaxis is an allergic emergency. The mechanism of generalized anaphylaxis is the reaction of IgE antibodies to an allergen, causing the release of histamine, bradykinin, and slow-reacting substance of anaphylaxis (SRS-A) from mast cells and later eosinophils. These chemical mediators cause the contraction of smooth muscles of the respiratory and intestinal tracts, as well as increased vascular permeability. Within dentistry, penicillin is a frequently encountered cause, but muscle relaxants, cephalosporins, sulfonamides, vancomycin, radiographic contrast media, and vaccines may also cause anaphylaxis.[41]

The following factors increase the patient's risk for anaphylaxis: history of allergy to other drugs or food, history of asthma, family history of allergy (atopy), and parenteral administration of the drug. Anaphylactic reactions may occur within seconds of drug administration or 30–40 minutes later, complicating the diagnosis. Symptoms of generalized anaphylaxis should be known so that diagnosis and

prompt treatment may be initiated. It is important to be able to differentiate anaphylaxis from syncope or a hypoglycemic event. The generalized anaphylactic reaction may involve the skin, the cardiovascular system, the gastrointestinal tract, and the respiratory system. The first signs often occur on the skin and are similar to those seen in localized anaphylaxis (e.g., facial flushing, pruritis, paresthesia, or peripheral coldness). Pulmonary symptoms include dyspnea, wheezing, and asthma. Gastrointestinal tract disease, such as abdominal pain and vomiting, often follows skin symptoms. Symptoms of hypotension (loss of consciousness, pallor, and a cold clammy skin) appear as the result of the loss of intravascular fluid. The pulse becomes rapid, weak, and faint. If untreated, this leads to shock. Patients with generalized anaphylactic reactions may die from respiratory failure, hypotensive shock, or laryngeal edema.

Management

The most important therapy for generalized anaphylaxis is the administration of epinephrine.[42] Clinicians should have a vial of aqueous epinephrine (at a 1:1000 dilution) and a sterile syringe easily accessible. For adults, 0.5 mL of epinephrine should be administered intramuscularly or subcutaneously; smaller doses from 0.1 to 0.3 mL should be used for children, depending on their size. If the allergen was administered in an extremity, a tourniquet should be placed above the injection site to minimize further absorption into the blood. The absorption can be further reduced by injecting 0.3 mL epinephrine (1:1000) directly into the injection site. The tourniquet should be removed every 10 minutes.

Epinephrine will usually reverse all severe signs of generalized anaphylaxis. If improvement is not observed in 10 minutes, readminister epinephrine. If the patient continues to deteriorate, several steps can be taken, depending on whether the patient is experiencing bronchospasm or edema. For bronchospasm, slowly inject 250 mg aminophylline intravenously, over a period of 10 minutes. Too rapid an administration can lead to fatal cardiac arrhythmias. Do not give aminophylline if hypotensive shock is a part of the clinical picture. Inhalation sympathomimetics may also be used to treat bronchospasm, and oxygen should be given to prevent or manage hypoxia. For the patient with laryngeal edema, establish an airway. This may necessitate endotracheal intubation; very rarely, a cricothyroidotomy may be necessary. Patients who have had an anaphylactic attack should carry self-injectable epinephrine.

Latex Allergy

Latex allergy associated with undesirable cutaneous and mucosal reactions has been noticed with increasing frequency over the last few years, possibly related to the greater use of protective gloves. While less than 1% of the general population is sensitized to latex, the US Occupational Safety and Health Administration estimates that over 8% of healthcare workers may be sensitized. Dental staff and students appear to be at high risk for latex sensitization and the overall prevalence of skin sensitization in dentists in a number of studies was about 10%, higher in those reporting asthmatic symptoms.[43] Much of the sensitization appears to have been by inhalation of the glove powder and the rate of sensitization is now falling, since gloves are mainly powder free.

The symptoms of latex allergy are usually those of type 1 hypersensitivity, but contact dermatitis to rubber chemicals is also well described. Sensitized individuals produce specific IgE antibody to at least 10 potent latex allergens, Hev b 1–Hev b 10, each of which differs in its structure, size, and net charge, but testing for them is not yet routine. Cross-reacting antigens are found in bananas, kiwi fruit, avocados, and chestnuts. The important concept that latex allergy can induce clinical symptoms to specific foods (food allergy) is reinforced by the demonstration of amino acid sequence homology between latex antigens and proteins in kiwi fruit, avocados, tomatoes, and potatoes. Cross-reacting IgE antibodies to 33kd and 37kd antigens shared between bananas and latex have been described.

Testing

Recently a skin prick test reagent that contains most of the known clinically significant allergens for diagnosis of type 1 latex allergy has been standardized. The protein content of the gloves correlates with immunoreactivity and the ratio of the IgE to IgG response correlated positively with the severity of symptoms. In most studies, a history of atopy was a significant factor in latex allergy. There seems to be a reasonable correlation between in vitro; IgE testing and in vivo; skin prick tests.

Management

Patients with latex allergy may also show high levels of positive responses to certain foods, so a good medical history is imperative.[43] Urticaria, rhinitis, and eyelid edema can be immediate manifestations of latex allergy. Severe systemic reactions (such as asthma and anaphylaxis) may result in permanent disability or even death. In the healthcare setting, the two major strategies for management are the safe care of the latex allergic patient and the prevention and treatment of occupational latex allergy in employees. In managing a patient with latex sensitivity, the distinction between an immediate hypersensitivity reaction to latex and allergic contact dermatitis due to other irritants must

be established. At initial evaluation, latex allergy status should be established by the history and documented clearly on the chart. Any history of an immediate hypersensitivity reaction to latex necessitates a latex-free environment for that person, including "hypoallergenic" latex gloves. Latex-containing products (such as blood pressure cuffs and disposable tourniquets) should not be worn *or used in the vicinity of* persons who are allergic to latex. Premedication with antihistamines, steroids, and histamine H2 blocking agents is sometimes carried out in operating rooms, but anaphylactic reactions have occurred despite such pretreatment.

Workers who are irritated by gloves should change the type of gloves worn or the type of soap used for scrubbing. In addition, the use of cotton liners and emollients may effectively prevent sensitivity reactions. In cases of true latex allergy, the avoidance of all latex products is the only measure that can avert a serious allergic reaction. All persons with latex hypersensitivity should carry an epinephrine autoinjection kit and wear MedicAlert identification. Acute systemic reactions to latex should be treated in the same manner as other anaphylactic reactions (see earlier; i.e., airway and circulation assessment, administration of oxygen, and administration of epinephrine and steroids as needed). In the course of resuscitation, all latex contact must be avoided.

Oral Allergy Syndrome

Swelling of the lips, tongue and palate, and throat, along with oral pruritis and irritation, sometimes associated with other allergic clinical features including rhino-conjunctivitis, urticaria, and even anaphylaxis, has been termed the oral allergy syndrome.[44] It seems to be precipitated by fresh foods, including apples, in people who have been sensitized to cross-reacting allergens in pollens, particularly birch.

Immune Complex Diseases: Serum Sickness and Erythema Multiforme

Serum sickness is named for its frequent occurrence after the administration of foreign serum, which was given for the treatment of infectious diseases before the advent of antibiotics. It is a type 3 immune complex–mediated disease. The reaction is now uncommon, but still occurs as a result of the susceptible patient being given tetanus antitoxin, rabies antiserum, or drugs that combine with body proteins to form allergens.

The pathogenesis of serum sickness differs from that of anaphylaxis. Antibodies (usually IgG) form immunocomplexes in blood vessels with administered antigens. The complexes fix complement, which damages vessels and attracts leukocytes to the area, amplifying direct tissue injury. Serum sickness and vasculitis usually begin 7–10 days after the administration of the allergen, but this period can vary from 3 days to as long as 1 month. Unlike other allergic diseases, serum sickness may occur during the initial administration of the drug.

Major symptoms consist of fever, swelling, lymphadenopathy, joint and muscle pains, and rash. Less common manifestations include peripheral neuritis, kidney disease, and myocardial ischemia. Serum sickness is usually self-limiting, with spontaneous recovery in 1–3 weeks. Treatment is symptomatic; aspirin is given for arthralgia, and antihistamines are given for the skin rash. Severe cases should be treated with a short course of systemic corticosteroids, which significantly shortens the course of the disease. Although serum sickness is rare, the dentist who is prescribing penicillin should be aware of the possibility of its occurring days or weeks after use of the drug. It is thought that penicillin binds to host proteins to form a recognizable antigen and, as antibodies form, they meet across vessel walls and give a localized vasculitis.

Oral erythema multiforme is thought to be an immune complex disease where 7–10 days after a herpes simplex infection, IgG antibodies are formed and bind to remaining residual tissue-located herpes antigen, giving rise to localized inflammation and ulceration. Similar oral appearances can sometimes occur after systemic therapy with antihypertensive drugs.

Delayed Hypersensitivity: Oral Lichenoid Reactions

Cell-mediated damaging immune reactions can occur in the oral cavity. Lichen planus is thought to be a cell-mediated autoimmune reaction against basal epithelial cells. Similarly, oral lichenoid reactions (OLRs) reflect cellular immunity to antigens found in dental restorations (Chapter 3). These are usually associated with contact sensitivity to amalgam fillings, but similar OLRs can be found with gold, composite, or glass ionomer materials. They are important to recognize, since there is increasing evidence of the malignant potential of such lesions. The lesions usually present as chronic, unilateral, mixed red and white lesions in direct proximity to a restoration, and histologically appear very similar to lichen planus with a predominantly lymphocytic infiltrate. The combination of history, clinical appearance, and histology usually leads to the diagnosis. Damaging immune-mediated reactions, including cell-mediated, can also occur to many other dental materials, including dentifrices, toothpastes, and mouthwashes.[45]

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20

Transplantation Medicine

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INTRODUCTION

Transplantation is the treatment of choice for the restoration of function in end-stage organ disease. Innovative surgical techniques have played a major role in enhancing the success of organ transplants, leading to improved graft and patient survival. Advances in the biology of organ preservation have led to improved cold storage of the solid organs, improving the overall quality of the transplanted organs and diminishing the damage incurred by warm ischemia, allowing optimization of the medical conditions of the donor and the recipient. Furthermore, insights into the biology of immune responses to transplanted tissues have aided in the development of immunosuppressive techniques to prevent the rejection of the organ transplant while minimizing the morbidities associated with chronic immunosuppression. The main limitation to even greater use of transplantation as a treatment modality for end-stage organ damage remains the shortage of organ donors.

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

Attempts at organ and bone marrow transplantation date back to the 1800s. Dr. Joseph Murray performed the first successful human renal transplantation between identical twin brothers in 1954. This procedure was well tolerated, as there was no rejection by the genetically identical recipient. The first successful allogeneic (not genetically identical) transplantation was a kidney transplant between fraternal twins performed in 1959, in which the recipient was "conditioned" (immunosuppressed to prevent rejection) by total body irradiation. In 1962, a successful cadaveric donor renal transplantation was achieved, and in 1966, a pancreas transplantation was successfully performed. In the following year, the first human liver transplantation was performed, resulting in a 13-month survival. In the same year, a heart was transplanted. In 1968, a genetically related bone marrow transplantation (today referred to as a hematopoietic stem cell transplantation [HSCT]) was performed, and in 1973, a genetically unrelated HSCT was performed. Lung transplantation has also been performed both as a single procedure and in combination with a heart transplantation. The first heart–lung transplantation in the United States was done in 1981, and the first ever single-lung transplantation was performed in Canada in 1983. Other organs that have been successfully transplanted include the small bowel, skin, various limbs, face, and components of the human eye.

In past decades, significant advances—including tissue typing and the development of immunosuppressive medications and medication regimens—have increased the success of transplantation. Overall, long-term patient survival has also significantly increased over the past 30 years, in both solid organ and HSCT recipients. Most transplant clinicians consider the discovery of the immunosuppressive agent cyclosporine (CSA) to be the most significant advance in transplantation medicine. This medication was approved for use in 1983. Both solid organ and non–solid organ transplantations are becoming more routine throughout the world. In November 2013, over 120,000 patients in the United States alone were waiting for a solid organ transplant. In 2012, 28,052 solid organs were transplanted, approximately the same number as was seen in 2005, and in 2019, 39,719 transplants were performed (Table 20-1).[1]

As the process of solid organ transplantation expands, there is a continued need to increase the supply of organs suitable for transplantation. The limitation of available donor organs will hopefully become less of an issue with increased awareness of organ donation and perhaps with collaborative sharing initiatives, alternative organ procurement methods, including xenografts or stem cell–derived tissue, or printed organs.

The likelihood of a dentist having to treat a transplanted patient is increasing, as many of these transplant recipients resume a normal life after transplantation and many achieve long-term survival beyond 10 years. This chapter reviews different aspects of transplant medicine pertinent for the oral health professional.

CLASSIFICATION

Most transplant clinical classification systems employ both the type of tissue transplanted and the genetic relationship of the tissue to the recipient. It is extremely important for the dental clinician to know exactly what type of transplantation was performed, as both the management and the prognosis are intimately related. This will become evident later in this chapter.

Some authorities broadly divide transplantations into solid organ/tissue transplant or HSCT. Virtually all solid organs/tissues have been transplanted, including heart, lung, kidney, liver, stomach, intestine, pancreas, skin, tendons, nerves, veins, and eye components, as well as composite tissue transplants, including the face and the limbs. HSCT is another type of transplantation frequently used to treat various hematologic and some nonhematologic malignancies, as well as other disorders. HSCT uses either an autologous "self" donor graft or a "nonself" donor (allogeneic graft).

Table 20-1 Waiting lists and transplanted solid organs (2019) in the united states.

Organ	Awaiting Transplants	Transplants Performed	Total Transplants Performed to Date
All*	112,402	39,719	804,607
Liver	12,698	8,896	174,582
Kidney	94,552	23,401	473,811
Lung	1,275	2,714	41,529
Heart	3,669	3,552	76,493

*Note that these numbers do not equal those cited in the text, since other organs, including the small intestine and pancreas, are not included in this table. All transplants up to end of 2019.

Source: Based on Organ Procurement and Transplantation Network (OPTN). https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#. Accessed March 24, 2020.

Classification of transplants can also be based broadly on the genetic relationship of the recipient to the donor. For the purpose of this chapter, the transplanted cell, tissue, or organ is referred to as the graft. A transplant to and from one's self (autograft) is known as an autologous transplant. A transplantation from an identical twin (identical genetic makeup) is known as an isograft, with the process of this type of transplantation known as isogeneic or syngeneic transplantation. Most transplants are from donors that are not genetically identical to the recipient (allografts). These types of transplants are known as allogeneic transplants. Finally, transplants from donors of one species to recipients of another species (xenografts) are known as xenogeneic transplants.

Due to the scarcity of isografts and the obvious limitations to autografts, allogeneic transplants are most commonly used today. The success of allogeneic transplantation relies on more or less sophisticated mechanisms for identifying and matching specific genetic markers between the donor and the recipient depending on the organ, as well as suppressing the recipient's immune system to prevent transplant rejection. These are concepts that serve as the basic foundation in transplantation medicine. In the future, these concepts may be extended and improved to allow transplantation across species. Tissue xenografts, which have been treated to reduce their immunogenicity, have been used as a successful treatment modality in some applications (i.e., porcine heart valves), but whole-organ xenografts have been unsuccessful. Research regarding genetically altered xenografts is ongoing. When the important immunologic barriers to xenogeneic transplantation are eliminated, the use of animal donors may possibly alleviate the relative paucity of available organs. Of course, significant ethical questions, as well as transplant longevity and transmissible infectious diseases from animals, are issues that must be addressed before these types of transplants become commonplace. Bioengineered tissues that have been fabricated in vitro and transplanted back into the patient have also been successful, including a trachea and a bladder.

TRANSPLANTATION IMMUNOLOGY

Transplantation immunology encompasses most aspects of the human immune response to alloantigens expressed by the recipient as well as the donor organ/tissue. When donor and recipient genetic disparities exist, the recipient mounts a specific immune response to the alloantigens expressed by the donor grafted organ/tissue. In addition, donor T cells contained within the transplanted graft or organ can recognize foreign tissue in the host and mount a "graft-versus-host" reaction. Transplantation medicine would be grossly unsuccessful if this concept were not appropriately appreciated and manipulated.

T lymphocytes are the primary, though not the only, cells that mediate graft rejection as well as graft-versus-host disease (GVHD). T cells can become activated shortly after transplant by recognizing foreign major and minor human leukocyte antigen (HLA) molecules. The major histocompatibility complex (MHC), a genetic region found on the short arm of chromosome number 6 of all mammalian cells, codes for HLA molecules that allow immune cells to identify self from nonself. Although there are many other gene products, from more than 30 histocompatibility gene loci, which can stimulate graft rejection, it is the HLA system that produces the strongest immunologic response.

MHC genes are inherited from each parent; every child has components of both the mother's and the father's HLAs on their cell surfaces. The MHC/HLA system is broadly divided into regions. MHC class I and class II regions are those significantly involved in rejection and GVHD (see later in the chapter). MHC class I regions include HLA-A, -B, -C, -E, -F, and -G. (The present role of the -E, -F, and -G regions in transplantation is not well understood.) MHC class II regions include HLA-DR, -DQ, -DP, -DO, and -DN. MHC class II genes have two chains, allowing for four different gene products for each locus.

The MHC has extensive polymorphism, allowing remarkable diversity among genes of the HLA system. There are over 180 different class I alleles in the HLA-B region alone and over 220 class II alleles in just one loci of the HLA-DR region that have been recognized in humans. Deoxyribonucleic acid (DNA)-based typing (see below) has led to a more specific and detailed classification of the transplantation genes, such that the HLA alleles are related to their DNA sequences.

HLA class I antigens are expressed on most nucleated cells and on red blood cells, whereas class II antigens are expressed only on certain cells known as antigen-presenting cells (APCs). APCs include macrophages, B cells, dendritic cells, and some endothelial cells. The expression of these MHC gene products (antigens) on a cell's surface is regulated by various cytokines such as interferon (IFN) and tumor necrosis factor (TNF).

In the setting of solid organ transplantation, the transplanted foreign MHC molecules activate the immune response by stimulating the recipient's T cells to respond to foreign antigens. The interaction of the MHC of the donor cells with the recipient's T-cell receptor initiates the immune reaction that can lead to rejection. T cells can be activated either by the donor's or the recipient's APCs, resulting in the expression and production of lymphokines and cytokines that promote activation of cytotoxic T cells, activation of B cells, and activation of natural killer cell activity, as well as promote enhanced expression of MHC and increased macrophage activity. This, in turn, causes further

immune reactions that result in direct tissue damage and damage to the vascular endothelium of the graft, which may ultimately result in graft rejection.

Despite the treatment of recipients with immunosuppressive drugs, the potential for immunologic rejection is not entirely eliminated. Rejection may be characterized as acute, a process evolving rapidly over days to weeks. Acute rejection can occur at any time, from hours after transplant to years later. This acute process is related to the primary activation of T cells and usually can be reversed by modifying or intensifying the immunosuppressive regimen.

Chronic rejection of the allograft is also a significant problem leading to organ failure. This type of rejection is slow and insidious and in most cases cannot be reversed by conventional immunosuppressive drugs. It likely occurs by continued, albeit muted, cell-mediated toxicity that results in vascular endothelial damage of the transplanted organ (as well as other actions, which have not been fully elucidated), leading ultimately to graft failure.

Another type of rejection is known as hyperacute rejection; this occurs within minutes to hours after a transplantation procedure. This pattern of rejection occurs in patients who have undergone previous transplantations, patients who have had multiple pregnancies, and patients who have had multiple blood transfusions. It is caused by the presence of preformed antidonor antibodies in the recipient that activate complement cascade, resulting in severe damage to the parenchymal constituents of the graft, which often cannot be reversed.

Transplant immunology is even more complicated in the setting of allogeneic HSCT. Without proper immune suppression, residual host lymphocytes can mediate graft rejection, leaving a patient aplastic. However, unlike solid organ transplant, a hematopoietic stem cell graft has large numbers of mature lymphocytes capable of reacting against nonself antigens in the host in inducing GVHD. Donor leukocytes tend to react against the skin, liver, and gastrointestinal tract. Occasional involvement of the lungs can be seen as well. GVHD varies from nonexistent in approximately 50% of patients to severe and life-threatening. GVHD remains one of the major limitations to successful HSCT. Intensive therapies designed to minimize GVHD have resulted in higher rates of relapse from loss of the potential "graft-versus-tumor" (GVT) effect and from higher rates of infection. Ultimately, therapies that may limit GVHD and retain the important GVT activity of the donor graft will be needed to improve the outcomes of HSCT, and several strategies are in clinical testing.

It should also be noted that in unusual cases after solid organ transplant, mature donor lymphocytes transplanted with the organ can engraft and likewise cause GVHD. This is particularly complicated and similar to "transfusion-associated GVHD" (TA-GVHD), which can lead to marrow aplasia without the support of a donor stem cell graft. Similar to TA-GVHD, the prognosis is often poor, and treatment requires early recognition and intensive intervention with immune suppression.

CLINICAL INDICATIONS

The clinical indications for transplantation vary, but the disease outcome can be fatal without the transplant. The more common indications for transplantation are listed in Table 20-2.

Other indications can be added to this list when quality of life can be improved by transplantation. For example, autologous HSCT may ameliorate the effects of systemic lupus erythematosus or other autoimmune disorders. HSCT has been performed as a treatment for the management of various metabolic disorders and solid tumors, germ cell tumors, and neuroblastoma.[2]

In recent years there has been a steady increase in vascularized composite allograft transplantations. These include facial, craniofacial, hand, limb, and genitourinary transplantations. Such transplantations prompt new ethical questions.[3]

MEDICAL MANAGEMENT

Medical management of the transplant candidate focuses on successfully preventing rejection. In solid organ transplantation, when the donor and recipient tissue are genetically identical (autologous or syngeneic), the outcome of the transplantation relies upon the surgical success of the procedure. For autologous HSCT, success is largely dependent on the high-dose chemotherapy or radiation used to eradicate residual malignant cells prior to HSCT. When tissue from genetically different sources is transplanted, a sophisticated means of preventing rejection must be instituted to ensure graft survival, and in the setting of allogeneic stem cell transplant, methods must be used to prevent both graft rejection and severe GVHD. Transplantation surgeons and oncologists have improved the surgical procedures for various transplantations. Medical management to achieve longer-term successful grafts and longer-term overall patient survival has been quite successful, yet it still is fraught with longer-term complications. The success of an allogeneic transplantation relies on the ability to identify and match certain genetic markers between the donor and the recipient while suppressing the recipient's immune system in order to prevent rejection.

Table 20-2 Major indications for transplantation*.

Type of Transplant	Indications
Kidney**	End-stage renal disease
	Diabetic nephropathy
	Glomerulonephritis
	Pyelonephritis
	Congenital abnormalities
	Nephrotic syndrome
Liver	Fatty liver disease (both alcohol and nonalcoholic fatty liver)
	Viral cirrhosis
	Autoimmune chronic liver disease
	Biliary atresia (children)
Pancreas	Severe diabetes
	Severe hypoglycemic unawareness
	Hypertensive nephrosclerosis
Isolated pancreatic islets	Severe hypoglycemic unawareness
Intestinal	Short bowel syndrome
	Functional bowel problems
Heart	Hypertrophic cardiomyopathy
	Dilated myopathy
	Valvular heart disease
	Severe coronary artery disease
	Congestive heart failure
	Congenital heart defect
Heart and lung	Multiorgan end-stage disease
	Congenital abnormalities
	Amyloidosis
Lung	Primary pulmonary hypertension
	Chronic obstructive pulmonary disorder/emphysema
	Pulmonary fibrosis
	Cystic fibrosis
Hematopoietic cell transplantation (autologous)**	Acute myelogenous leukemia
	Multiple myeloma and amyloidosis
	Lymphoma (Hodgkin and non-Hodgkin)
	Some solid tumors (germ cell, ovarian)
	Systemic lupus erythematosus/autoimmune disorders
	Ewing sarcoma
	Neuroblastoma
	Wilms tumor
	Osteosarcoma
	Medulloblastoma
	Juvenile rheumatoid arthritis

(*Continued*)

Table 20-2 (Continued)

Type of Transplant	Indications
Hematopoietic cell transplantation (allogeneic)**	Acute myelogenous leukemia
	Acute lymphoblastic leukemia
	Chronic myelogenous leukemia
	Multiple myeloma
	Aplastic anemia
	Primary immune deficiencies
	Hemoglobinopathies (sickle cell anemia, thalassemia)
	Myelodysplastic syndrome
	Multiple sclerosis
	Fanconi anemia
	Dyskeratosis congenital
	Blackfan–Diamond anemia
	Wiskott–Aldrich syndrome
	Lymphoproliferative disorder
	Chronic granulomatous disease
	Mucopolysaccharidoses (MPS-I and MPS-VI)
	Some metabolic diseases
	Osteopetrosis
	Globoid cell leukodystrophy (Krabbe)
	Metachromatic leukodystrophy
	Cerebral X-linked adrenoleukodystrophy
Face and/or craniofacial	Composite midface defects/mutilation
Limb	Upper-extremity disabilities
	Lower-extremity disabilities
Genitourinary transplantations	Absolute uterine-factor infertility (uterus)
	Genital loss (penile)

* Partial listing only. Additional specification on the Organ Procurement and Transplant Network webpage.[1]
** Per the specifications of the Guidelines from the American Society for Blood and Marrow Transplantation.[2]

BLOOD AND TISSUE TYPING

Standard ABO and Rh blood typing is performed to prevent hyperacute rejection of the transplant based on isoagglutinin incompatibility. ABO matching is mandatory for solid organ transplant and directly impacts short-term graft survival. ABO matching does not appear to impact graft survival after allogeneic HSCT; the impact on patient outcomes such as relapse is controversial, but is likely to be small and of unclear significance that may depend on graft source and disease.

Cross-matching (crossing recipient serum with donor lymphocytes) is usually done to prevent hyperacute rejection in allogeneic solid organ transplants. This is a basic serologic test that is regarded as necessary, particularly in those allogeneic transplant recipients who have previously experienced massive immune challenges such as a prior transplantation, multiple pregnancies, or multiple blood transfusions, and have developed preformed anti-HLA antibodies. The existence of preformed alloantibodies is detected by single HLA antigen bead technology. Since transplantation of solid organs (heart, lung, liver) often requires some expediency, time-consuming complex cross-matching or tissue typing cannot be performed. Instead, absence of antibodies to a panel of cells (defined in advance and known as panel-reactive antibodies) is usually adequate for heart and lung transplantation. Interestingly, MHC compatibility in liver transplantation seems negligible in achieving better outcomes. This is fortunate, because the timing of liver transplantation often precludes HLA typing.

The most critical matching criterion for allogeneic HSCT is tissue typing to determine and match HLA. HLA molecules

are found on donor and recipient cells, and in the setting of HSCT are critical for determining engraftment and complications such as GVHD. HLA typing is much less critical in renal transplantations and for graft survival in liver or heart transplantations. Tissue typing can be performed by serologic assays, but more commonly, most typing is performed using rapid DNA-based testing methods. Polymorphisms in HLA antigens are common, and it is now practical and routine to test not just for HLA antigens but for HLA alleles. In the setting of allogeneic HSCT, it is clear that allele level matching improves outcomes. Matching at class I HLA-A, -B, -C, and class II (HLA-DR) is critical in all cases. The role of matching at the HLA class II molecule DQ is less clear and a single DQ mismatch does not seem to impact the outcome after HSCT.

IMMUNOSUPPRESSION

Immunosuppressive regimens vary among transplant centers and according to organ type (intestines, liver, etc.). Since tissues in allogeneic transplants are not genetically identical, medications used to control the immune response are essential for graft survival. All allogeneic transplantations initially require immunosuppression to prevent acute and hyperacute and/or acute cellular rejection. Furthermore, most allogeneic solid organ transplant recipients require lifelong maintenance immunosuppression and may require even more intensive immunosuppression should they develop rejection. Long-term immunosuppression is usually not required in allogeneic HSCT, and autologous HSCT generally requires no immunosuppression at all.

Most immunosuppressive medications are nonspecific and cannot prevent a specific component of the immune response. More sophisticated and directed agents are currently in development that will allow for graft tolerance while allowing the immune reaction to infection or other detrimental antigens to remain intact.

One of the most significant advances in transplantation has been made in pharmacotherapeutic immunosuppression. As mechanisms of graft rejection are better understood, agents become more specific in their mode of immune modulation.

Immunosuppression in solid organ transplant can be divided into induction (used at the time of implantation of the graft or soon after) and maintenance (to prevent rejection long term) (Figure 20-1). The most frequently used contemporary medication classes are discussed in this chapter (see Table 20-3), with a brief review of some key formulations.

Calcineurin Inhibitors

Calcineurin activates a nuclear component of T cells that is thought to initiate gene transcription for the formation of interleukin (IL)-2. The development of calcineurin inhibitors (known as CNI), specifically cyclosporine A (CSA) in 1981, was a watershed moment in solid organ transplantation and immediately lead to drastically lower rates of rejection.

Cyclosporine

CSA is a cyclic polypeptide macrolide medication derived from a metabolite of the fungus *Tolypocladium inflatum*. It specifically and reversibly inhibits immunocompetent lymphocytes in the G0 and G1 phase of the cell cycle by binding with the intracellular protein cyclophilin, and inhibiting calcineurin, which is presumed to inhibit IL-2 by preventing gene expression. CSA also reduces the expression of IL-2 receptors. This medication has some effect on humoral immunity but not on phagocytic function, neutrophil migration, macrophage migration, or direct bone marrow

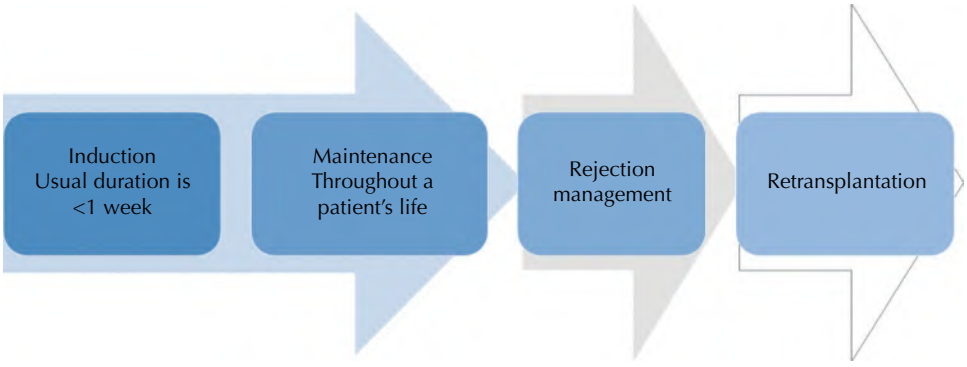

Figure 20-1 Phases of immunosuppression in solid organ transplantation. During the induction phase, the goal is to prevent early rejection. During the maintenance phase, the goals are to prevent acute/chronic rejection, to maximize immunosuppression, and to minimize toxicity. If rejection develops, the treatment goals are to increase immunosuppression, filter/remove/block offending immune components, and enable residual organ function. In some patients, retransplantation is needed in order to overcome the rejection.

Table 20-3 Major immunosuppressive agents*.

Drug	Type	Indications	Major Side Effects†	Implications in the Dental Office†
Cyclosporine	Calcineurin inhibitor	Maintenance IS	Nephrotoxicity Neurotoxicity Elevation of blood pressure Cosmetic side effects PTLD	Immunosuppression related‡ Drug–drug interaction (P-450 CYP3A)§ Vital signs monitoring Gingival overgrowth Risk of neoplasm
Tacrolimus	Calcineurin inhibitor	Maintenance IS	Nephrotoxicity Neurotoxicity Post-transplantation diabetes mellitus Elevation of blood pressure PTDM	Immunosuppression related‡ Drug–drug interaction (P-450 CYP3A)§ Vital signs monitoring Risk of neoplasm
Sirolimus	mTOR inhibitor Antiproliferative	Maintenance IS Potential treatment for chronic rejection Used in CNI-sparing IS	Delayed wound healing Hyperlipidemia Hypertriglyceremia Proteinuria Bone marrow suppression Interstitial pneumonitis	Immunosuppression related‡ Drug–drug interaction (P-450 CYP3A)§ Vital signs monitoring Risk of neoplasm
Everolimus	mTOR Inhibitor Antiproliferative	Maintenance IS Potential treatment for chronic rejection Used in CNI-sparing IS	Delayed wound healing Hyperlipidemia Hypertriglyceremia Proteinuria Bone marrow suppression	Risk for osteonecrosis of the jaws Risk of neoplasm
Azathioprine	Antimetabolite	Adjuvant to maintenance IS	Bone marrow suppression Hepatotoxicity	Immunosuppression related‡ Risk of neoplasm
Mycophenolate mofetil	Antimetabolite	Adjuvant to maintenance IS	Immunosuppressant‡ Leukopenia	Immunosuppression related‡ Absorption is altered by antibiotics, antacids, and bile acid binders Risk of neoplasm
ATG/ALG	Polyclonal antibody	Induction IS Treatment of very severe rejection	Leukopenia PTLD Pulmonary edema Renal dysfunction	Immunosuppression related‡ Risk of neoplasm
Basiliximab	Monoclonal antibody	Induction IS	Pulmonary edema Renal dysfunction	Immunosuppression related‡ Risk of neoplasm

Corticosteroids	Nonspecific immunosuppressant	Induction IS Maintenance IS Treatment of acute rejection	(see Box 20-1)	Immunosuppression related‡ Peptic ulcer related (avoid NSAIDs) Vital signs monitoring Poor wound healing Risk of neoplasm Steroid supplement may be needed with stressful procedures As applicable for diabetes, if develops Possible history of bisphosphonates

ASA, acetylsalicylic acid; ATG/ALG, antithymocyte globulin/antilymphocyte globulin; CNI, calcineurin inhibitor; CV, cardiovascular; IS, immunosuppression; mTOR, mammalian target of rapamycin; NSAIDs, nonsteroidal anti-inflammatory drugs; PTDM, post-transplantation diabetes mellitus; PTLD, post-transplantation lymphoproliferative disorder.

* Major mechanisms of action are outlined in the text.

† Partial listing only.

‡ Use of an immunosuppressant results in an increased risk of infection.

§ Dental/oral pharmacotherapeutics that are metabolized by the liver's cytochrome P-450 CYP3A system alter this drug's serum levels. This group of medications includes, but is not limited to, erythromycin, clarithromycin, azole antifungals, benzodiazepines, carbamazepine, colchicine, prednisolone, and metronidazole.

suppression. Absorption of this drug is variable, and blood levels must be drawn 2 hours after dosing to ensure that the drug is in the therapeutic range.

Tacrolimus

Tacrolimus (FK-506; Prograf) is a macrolide immunosuppressant produced by *Streptomyces*. Similar to CSA, it suppresses cell-mediated reactions by suppressing T-cell activation. Tacrolimus inhibits calcineurin by interacting with an intracellular protein known as the FK-binding protein. Consequently, T cells are not activated, and cell-mediated cytotoxicity is impeded. There may be a lower incidence of rejection with the use of tacrolimus compared with the use of CSA in liver, kidney, and lung transplantations. Overall graft and patient survival rates in kidney transplantations do not seem to differ significantly with the use of this medication, although the safety profiles do differ and seem to favor tacrolimus.[4]

Inhibitors of Mammalian Target of Rapamycin

Sirolimus (rapamycin; Rapamune) and everolimus (Afinitor) are other macrolide immunosuppressive agents. Sirolimus is produced by *Streptomyces hygroscopicus*. These mammalian target of rapamycin (mTOR) inhibitors are used for prophylaxis against acute rejection of solid organ transplants and may be appropriate for use in chronic rejection. They inhibit the activation of a particular cellular kinase (target of rapamycin [TOR]), which then interferes with the intracellular signaling pathways of the IL-2 receptor, thereby preventing lymphocyte activation. Everolimus is more selective for mTORC1 and may have less impact on glucose homeostasis. Both sirolimus and everolimus lead to inhibition of T-cell response to IL-2 and other cytokines. The overall effect is interference of T-cell activation during the cells' G1 to S phase. Sirolimus and everolimus are used in conjunction with CNIs. Their antiproliferative effects lead to potential inhibitory effects on neoplasia and fibrosis as well, but can impair wound healing.[4] They can also be associated with significant toxicity. Sirolimus has been shown to reduce acute rejection when azathioprine (AZA) is used.

Inhibitors of Purine and Pyrimidine Synthesis

Azathioprine

AZA is an antimetabolite that inhibits ribonucleic acid and DNA synthesis by interfering with the purine synthesis that results in decreased T- and B-cell proliferation. It does not interfere with lymphokine production, but has significant anti-inflammatory properties. AZA can be bone marrow suppressive, leading to pancytopenia, and it can also cause hepatotoxicity, usually mild but potentially severe. Therapeutic response is delayed, normally taking 3 months but occasionally requiring up to 6 months in some patients.[5] In addition, polymorphisms in the *TPMT* gene that codes for an enzyme involved in AZA metabolism are associated with severe bone marrow toxicity, including aplastic anemia. For these reasons, AZA has lost favor with the advent of mycophenolate mofetil (MMF).

Mycophenolate Mofetil

MMF, an ester of mycophenolic acid, is an antimetabolite used for prophylaxis against graft rejection, and may have some action in reversing ongoing acute rejection. It inhibits inflammation by interfering with purine synthesis. Both T cells and B cells, which are dependent on this synthesis for their proliferation, are prevented from reproducing. Additionally, MMF interferes with intercellular adhesion of lymphocytes to endothelial cells. It does not inhibit IL-1 or IL-2. MMF is used as an adjunct to CNI-based immunosuppression and is commonly used in all solid organ transplants.

Corticosteroids

Corticosteroids are consistently used in all allogeneic transplantations for prophylaxis against graft rejection and for reversal of acute rejection. The mechanism of action of this medication is nonspecific, as it affects the immune system in many complex ways. Steroids have anti-inflammatory effects and are able to suppress activated macrophages. They also interfere with antigen presentation and reduce the expression of MHC antigens on cells. Steroids reverse the effect of IFN-γ and alter the expression of adhesion molecules on vascular endothelium. These medications also have significant effects on IL-1 activity and block the IL-2 gene and its production.

Antibody-Based Immunosuppression

Antithymocyte and Antilymphocyte Globulin

Polyclonal antilymphocyte sera, antilymphocyte globulin (ALG), and antithymocyte globulin (ATG) are part of the same medication class. These agents are produced by immunizing animals with human lymphoid cells; the animals produce antibodies, which then reduce the number of circulating T cells after infusion into transplanted recipients. Individually, these agents affect lymphocyte immunosuppression by reacting with common T-cell surface markers and then coating (opsonizing) the lymphocyte—marking it as foreign for phagocytosis. Polyclonal antibodies are used as conditioning agents prior to transplantation as well as for reversal of steroid-resistant rejection.

Basiliximab

Basiliximab (Simulect) is made of synthetic monoclonal antibodies used in some centers for induction immunosuppression. These monoclonal antibodies bind the CD25 receptor (IL-2 receptor) on the surface of activated T cells (IL-2 receptor antagonists), preventing the expansion of CD4 and CD8 lymphocytes. They may be effective in conjunction with MMF and corticosteroids to eliminate the need for CNI use in the early post-transplantation period. Anti-CD25 agents have also been reported to be efficacious in treatment of corticosteroid-resistant GVHD.

Alemtuzumab

Alemtuzumab (previously known as Campath-1; currently, Lemtrada) is a monoclonal antibody that binds to and depletes CD52, which is expressed on the surface of mature lymphocytes. It is used for the treatment of chronic lymphocytic leukemia, and in some conditioning regimens for bone marrow, kidney, and islet transplantation.

Conditioning in Hematopoietic Stem Cell Transplantation

Unlike solid organ transplant, HSCT requires "conditioning" of the patient with cytotoxic chemotherapy. Traditional conditioning regimens were designed to take advantage of the dose–response activity against cancer cells. High doses of chemotherapy or radiation are used to eradicate residual tumor prior to infusion of the hematopoietic stem cell product. Typical myeloablative agents include cyclophosphamide in combination with busulfan, etoposide, fludarabine, or often total body irradiation (TBI). A complication of the conditioning regimen is myeloablation, requiring the need to transplant additional donor hematopoietic stem cells. The conditioning therapy must also be sufficiently immunosuppressive to prevent graft rejection, or patients would be left aplastic and die from complications of cytopenias and infections. It has been recognized for years, however, that the success of transplantation is also related to the immunologic activity of the donor graft, independent of the conditioning therapy. Donor T cells have the ability to react against and kill residual tumor cells and induce a GVT effect. This observation led to the development of reduced-intensity conditioning (RIC) regimens designed primarily for immunosuppression to allow donor cell engraftment, and to take advantage of the GVT activity without the organ toxicity often associated with very high doses of chemotherapy and radiation. Typical regimens for RIC HSCT include similar drugs and TBI as used in myeloablative transplant, but, as the name implies, often at reduced doses. While treatment-related morbidity and mortality are less with these regimens, this is often offset by higher relapse rates. RIC HSCT results in significantly less organ toxicity, including mucositis.

Other Immune-Modulating Agents

Rituximab (Rituxan and Biogen) is a chimeric monoclonal antibody that binds to CD20 antigen of B cells. It depletes the level of mature B cells by various mechanisms such as mediation of antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and B-cell apoptosis.[6]

Bortezomib (Velcade) is a proteasome inhibitor. Proteasome inhibition can downregulate NF-κB activity; decrease cell proliferation/differentiation; induce apoptosis via cell cycle arrest, endoplasmic reticulum stress, and caspase induction due to the accumulation of unfolded or misfolded proteins; and downregulate antigen presentation, cell–cell interaction, and cell migration.[7] Bortezomib is approved in the United States for multiple myeloma and mantle cell lymphoma; however, based on its mechanism of action, it is used extensively for the management of rejection in transplantation.

Eculizumab (Soliris) is a humanized monoclonal antibody directed against the complement C5a component. It is currently being used in renal transplantation and HSCT.

Newer Immunosuppressive Strategies

A scientific breakthrough concept is the chimeric antigen receptor (CAR) T-cell therapy. The CAR is directed at a disease-specific antigen. During this process, the patient's leukocytes are collected via leukapheresis. These T cells are processed ex vivo using retrovirus or lentivirus to transduce expression of vector containing a gene coding the CAR construct. The CAR construct is a protein that has an extracellular domain that can identify the abnormal cell, and at least two intracellular domains. The intracellular domains have two roles: direct activation of the T cell and co-stimulation of the T-cell activation (CD28 or 4-1BB domains). Then the engineered CAR T cells are grown in culture to produce an appropriate quantity. Finally, the CAR T cells are infused into the patient, typically following a lymphodepleting conditioning regimen, such as fludarabine and cyclophosphamide. These CAR T cells identify the disease-specific abnormal cells and destroy them.

Two types of engineered T cells are approved by the US Food and Drug Administration: axicabtagene ciloleucel and tisagenlecleucel. The early indications were refractory lymphoid malignancies, especially diffuse large B-cell lymphoma (DLBCL) and acute lymphoblastic leukemia (ALL), which often express CD-19. Therefore, the CAR T cells are targeted at the CD-19. This technology is being expanded in other diseases. Promising results were reported in the

treatment of multiple myeloma, with CAR T-cell therapy targeting the B-cell maturation antigen.[8] This CAR T-cell therapy is also being explored with certain efficacy in clinical trials in solid malignancies such as glioblastoma, neuroblastoma, non-small-cell lung cancer, osteosarcomas, and Ewing sarcoma.[9,10] Therefore, the number of patients undergoing transplants of this type is expected to increase.

Although CAR T cells achieved complete remission in a large portion of the patients with relapse-free survival of up to 12 months, it is associated with severe toxicities, including cytokine release syndrome and neurotoxicity. Current research is aimed at improving the response rate and duration of remission and decreasing toxicity.[11]

Similar immunosuppressive therapies are used in patients undergoing HSCT. Immunosuppression in this setting is used not only to prevent graft rejection, but also to prevent GVHD. Approaches used for GVHD prevention and management include pharmacologic agents that inhibit T-cell function, antibody therapy directed against T cells, selection of stem cell grafts in ways that eliminate T cells prior to transplant, various approaches to inhibit T-cell trafficking to sites where GVHD can be initiated, enhancement of suppressive mechanisms that can limit T-cell activity (such as infusion of regulatory T cells and mesenchymal stem cells), and the use of other novel compounds that may modulate T-cell function and activity. More recently, tyrosine kinase inhibitors (TKIs) were attempted for steroid-resistant chronic GVHD (cGVHD). The first agent was imatinib (Gleevec) for sclerodermatous cGVHD, and more recently ibrutinib (Imbruvica) for second-line treatment for cGVHD.[12] Ibrutinib inhibits the Bruton tyrosine kinase, as well as the interleukin-2–inducible kinase (ITK), which initiates a cascade that ends with T-cell activation, cytokine release, and rapid proliferation.[13] The T-cell activation by ibrutinib inclines toward Th2, which is linked to cGVHD. The most promising therapies for cGVHD in early-phase trials include Janus kinase (JAK) inhibitors (ruxolitinib and bacritinib), immune checkpoint inhibitors (abatacept), monoclonal antibodies against integrin (natalizumab), proteasome inhibitors (ixazomib and carfilzomib), cytokines (IL-2 and IL- 22), CCR5 receptor antagonists (maraviroc), and cytokine modulators (alpha-1 antitrypsin).[14] This is a rapidly changing landscape and has been reviewed in detail.

ANTIMICROBIAL MEDICATION

In addition to immunosuppressive medication regimens, antimicrobial medication regimens are important in preventing infection in the transplant recipient. These regimens vary from center to center and from program to program. Transplant patients are typically profoundly immunosuppressed for months. Many factors affect the pace of immune reconstitution, but it is common to use prophylactic antibiotics for bacterial, protozoan, fungal, and viral infections. Antimicrobial medication coverage has proven to be effective in the prevention of common transplant-associated infections (Table 20-4).

The Centers for Disease Control and Prevention (CDC) have published updated guidelines for preventing opportunistic infections among HSCT recipients based upon the quality of the evidence supporting the recommendation.

Table 20-4 Most common pathogens requiring prophylaxis post liver transplantation.

Pathogen	Prophylaxis	Duration of Prophylaxis*
Cytomegalovirus (CMV)	Ganciclovir Valganciclovir	6 months
Pneumocystis jiroveci	TMP–SMX† Atovaquone Dapsone Aerosolized pentamidine Dapsone plus pyrimethamine	3–12 months
Candida Albicans	Fluconazole Itraconazole Echinocandins	3–6 months
Herpes simplex virus	Ganciclovir Valacyclovir Acyclovir§	3–6 months

* Varies according to transplant center.
† Trimethoprim–sulfamethoxazole.
§ Choice in patients that do not require concomitant CMV prophylaxis.

Prophylaxis is, however, very different from the empiric treatment required in febrile neutropenia.

COMPLICATIONS

Complications with transplantation are still common and require close evaluation and management. General complications can be broadly characterized into those caused by rejection, side effects from medication, and those induced by immunosuppression. Additionally, there are some organ-specific complications observed in certain types of transplantation.

Rejection

As previously mentioned, rejection of the transplanted organ remains a significant obstacle to long-term transplant graft and patient survival. Rejection is characterized by time course and mechanism of injury. Rejection leads to end-organ damage and can lead to allograft failure, often associated with reappearance of complications of organ failure. Clinically, rejection may manifest in many ways, including abnormal liver function such as bilirubin, albumin, and International Normalized Ratio (INR; liver failure); a decreased metabolism of medications (rejection of liver/kidney); or even complete organ failure and death (rejection of liver/lung/heart). In cases of end-organ disease (except those of kidney failure), retransplantation may be the only way to prevent death.

Rejection is continually screened for throughout the post-transplantation period. Most chronic rejections are insidious and are detected by laboratory analysis and by organ biopsy. Graft biopsy provides a reliable means to assess rejection. An alternative approach to monitoring rejection in a transplanted heart is the use of pacemakers to record changes in ventricular evoked response (VER). Subtle changes in VER have been correlated with rejection of heart transplants.

Complications of Immunosuppression Medication

Medications used to produce immunosuppression and prevent graft rejection have significant systemic side effects, which pose serious complications to the transplant recipient. Some of the major side effects are listed here (Table 20-3); however, complete drug information can be obtained through an appropriate medication reference source.

CSA, a mainstay in immunosuppression, is nephrotoxic and may alter renal function. It is also associated with hypertension and lowering of seizure threshold, as well as rare cases of hepatotoxicity. It also has cosmetic side effects such as gingival hyperplasia and hirsutism that can be quite concerning to patients. CSA is metabolized via the P-450 CYP3A system of the liver; therefore, it has many drug interactions, including interactions with drugs frequently used in dentistry, such as lidocaine and oxycodone.

Tacrolimus has been associated with hypertension and nephrotoxicity. In addition, it is neurotoxic and rare hepatotoxicity has been described.[4] There are many other side effects associated with the use of this medication, one of which is the development of insulin-dependent post-transplantation diabetes mellitus (PTDM). The incidence of PTDM appears to be higher with tacrolimus use than with CSA use in liver transplantation. Tacrolimus is metabolized by the P-450 CYP3A system in the liver. It is 99% protein bound and requires titration. Tacrolimus also has significant interactions with medications used in dentistry, such as ibuprofen and metronidazole.

Sirolimus causes or exacerbates proteinuria and may cause abnormal liver enzymes. It can cause stomatitis and oral ulceration and lead to interstitial pneumonitis in rare cases.[4] Sirolimus is also associated with a high incidence of hyperlipidemia owing to elevated triglyceride and cholesterol levels. Being a substrate for P-450 CYP3A, sirolimus interferes too with the metabolism of other medications.

AZA may cause bone marrow suppression, resulting in pancytopenia, which leaves the patient not only susceptible to opportunistic infections, but also at significant risk for bleeding. It also causes skin rash and pancreatitis in some patients.[4]

MMF has significant drug interactions that are particularly important to the dentist. One interaction commonly cited occurs as a result of antibiotic regimens that can alter gastrointestinal flora, leading to dramatic changes in MMF drug levels. For example, if a patient is taking a broad-spectrum antibiotic for a dentoalveolar infection, the possibility and probability of an abnormal MMF level do exist. Other medications, such as antacids (containing magnesium or aluminum) and bile acid binders, may also interfere with the absorption of MMF. MMF is usually well tolerated, without significant hepatotoxicity (although higher doses are associated with gastrointestinal symptoms of nausea, vomiting, and diarrhea) or nephrotoxicity, but hematologic alterations (mostly leukopenia) can be a side effect. It is also teratogenic.

Monoclonal and polyclonal antibodies can be associated with a severe reaction known as cytokine release syndrome. Cytokines (including TNF-α) are rapidly released, resulting in significant medical issues, including fever, chills, nephrotoxicity, vomiting, pulmonary edema, and, in a few instances, arterial thrombosis.

Both monoclonal and polyclonal antibodies have been associated with significant side effects (in addition to significant cytokine release), including a high risk of viral/fungal infection and an increased incidence of post-transplantation lymphoproliferative disorder (PTLD).

Corticosteroids, another mainstay used in transplantation immunosuppression, can have multiple detrimental side effects (Box 20-1).

Cytotoxic agents such as cyclophosphamide, busulfan, and TBI cause bone marrow suppression, resulting in pancytopenia.

Complications of Immune Modulation

Immunosuppression used to prevent rejection of a transplanted organ also can pose serious complications to the recipient, including life-threatening infections and cancer.

Infections after HSCT are a significant problem. The type of transplant and the time that has transpired since the transplantation often predict the specific infection. For example, patients who have had an HSCT usually have broad immunologic defects, either due to their underlying disease or more likely from a combination of immunosuppressive drugs and delayed immune reconstitution. This impacts all components of the immune system. These patients are at a significantly higher risk of infection than are those patients transplanted with solid organs. Additionally, transplants of certain organs are associated with a greater likelihood of a particular infection.

Box 20-1 Corticosteroid Adverse Effects

- Induces diabetes
- Induces muscle weakness
- Induces osteoporosis
- Alters fat metabolism and distribution
- Induces hyperlipidemia
- Induces electrolyte imbalances
- Induces central nervous system effects, including psychologic changes
- Induces ocular changes—cataracts, glaucoma
- Aggravates high blood pressure
- Aggravates congestive heart failure
- Aggravates peptic ulcer disease
- Aggravates underlying infectious processes (e.g., tuberculosis)
- Suppresses the hypothalamic–pituitary–adrenal axis, resulting in adrenal atrophy
- Suppresses the stress response

Timing following the transplantation may correspond with a specific infective process. Bacterial infections are usually seen in the early postoperative period (immediately after transplantation) in solid organ transplantations. The type of bacteria varies with each specific organ and may include both gram-positive and gram-negative bacterial species. Drug-resistant bacterial infections have been documented, such as staphylococcal infections associated with skin wounds, upper and lower respiratory infections (pneumonia), and tuberculosis. Infective endocarditis has also been seen in transplant recipients. In this population, endocarditis is often related to *Staphylococcus* infection or aspergillosis.

Systemic viral infections are a common problem in immunosuppressed patients. CMV and herpes simplex viruses (HSVs) are often the etiologic viral agents involved. Other viral agents, including adenovirus, respiratory syncytial virus (RSV), varicella-zoster virus (VZV), Epstein–Barr virus (EBV), and human parvovirus B19, are also common causes of disease in a transplant population. Viral infections may be related to time following transplantation. HSV infections usually occur at 2–6 weeks after organ transplantation, whereas CMV infections generally occur at 1–6 months after transplantation, and VZV infections typically occur between 2 and 10 months post transplantation.

Patients who are immunosuppressed are susceptible to local and systemic fungal infections that vary from those of *Candida* species to deep fungal infections caused by *Aspergillus*, *Cryptococcus neoformans*, *Fusarium*, and *Trichosporon*. Invasive fungal infections are usually seen later in the transplantation process. Systemic fungal infections are often difficult to treat in the immunosuppressed patient and require systemic antifungal agents. Some have considered the role for macrophage colony-stimulating factor, a cytokine used to stimulate macrophages and monocytes, in the treatment of patients with fungal infections.

Parasitic infections caused by *Toxoplasma gondii* and others can be seen in immunosuppressed transplant recipients, but are uncommon in the context of solid organ transplantation.

In addition to, and perhaps directly related to, infectious complications, immunosuppression renders the patient at higher risk for the development of secondary cancers. The immune system provides surveillance against antigens that may act as initiators or promoters of cancer. When the immune response is muted, so, too, is this surveillance system. Cancers most commonly associated with immunosuppression are squamous cell carcinomas of the skin, lymphomas (mostly B-cell lymphomas including PTLD), and Kaposi's sarcoma. Human herpesvirus 8 has been

implicated in Kaposi's sarcoma and EBV in PTLDs. The most important factors in the development of PTLD are the level of immunosuppression and the EBV serology status. Additionally, there seems to be a clinico-pathologic difference between those transplant recipients who are diagnosed with PTLD early (within the first year of transplantation, which are EBV + PTLD) versus those diagnosed after the first year.

Specific Complications of Transplantation

Solid Organ Transplantation

A significant medical complication seen in patients receiving solid organ transplants is accelerated advanced cardiovascular disease (CVD), including coronary artery disease (CAD). The cause of this rapid CVD is unknown, but some researchers postulate it could be either infectious (CMV), medication induced, or potentially both. In this population, CVD is likely multifactorial. For instance, many investigators have explored the etiologic role of immunosuppression in the development of CVD. Hypertension is a common side effect of CNIs. Steroids and CNIs are diabetogenic, CSA and sirolimus cause hyperlipidemia. All these medical complications are part of the metabolic syndrome and recognized as risk factors for CVD.

In many transplantation facilities, hypertension is treated by calcium-channel blockers (CCBs). Some clinicians note that this group of medications may raise serum levels of CSA, thus decreasing the cost of immunosuppression. Caution must be exercised with any drug affecting CSA metabolism; for this reason, most clinicians prefer to prescribe medications that do not alter CSA levels. Non-dihydropyridine CCBs are often first line, but can have adverse oral effects, such as gingival overgrowth (see below).

PTDM is another significant condition frequently seen post transplant. Experimental and clinical observations both suggest that this phenomenon is related in some part to immunosuppressive agents. PTDM may cause both macro- and microvascular changes, which affect both graft and patient survival.

Neuropsychiatric complications, such as anxiety, seizures, and neuropathies, can also be noted in transplant recipients.

More specifically in lung transplant, the second most common long-term cause of morbidity and mortality (infection being the first) after transplantation is bronchiolitis obliterans. This disorder is caused by inflammation and constriction in bronchioles. It may be related to chronic rejection and infection and perhaps altered microvasculature.

Heart transplantation can also be associated with particular complications. As previously mentioned, post-transplantation CAD is common in all transplants, including heart transplants. Additionally, early after transplantation the heart is denervated, such that symptoms of angina may be absent and the heart may have diminished vagal response. There is, however, evidence of sympathetic and possibly parasympathetic nerve regeneration later in the post-transplantation period, suggesting that angina and heart-rate changes from stress are regained. Care of patients with cardiac transplants must recognize these cardiac abnormalities. Mitral and tricuspid regurgitation has also been observed after heart transplantation (see Chapter 14 on Cardiovascular Disease).

Hematopoietic Stem Cell Transplantation

Perhaps the most significant complications are those observed after an allogeneic HSCT. Allogeneic transplantation often involves both administration of intensive chemotherapy and/or radiation, as well as the administration of immunosuppressive therapy. The major complications of allogeneic HSCT include (1) end-organ damage from pretransplantation conditioning therapy; (2) GVHD; (3) infections.

Major complications occur after HSCT that are directly related to the conditioning regimen. Unlike solid organ grafting, HSCT requires intensive chemotherapy and/or radiation to "condition" the recipient to accept the graft. The conditioning regimen must provide deep immunosuppression to prevent rejection and typically has cytotoxic effects to kill any residual malignant cells. Direct organ toxicity can occur with all types of HSCT, but appears higher after myeloablative conditioning than after nonmyeloablative or reduced-intensity conditioning. One major complication is sinusoidal obstructive syndrome (SOS), previously known as veno-occlusive disease of the liver. SOS is felt to be initiated by endothelial injury that leads to nonthrombotic sinusoidal occlusion, with an increase in sinusoidal pressures. This leads to cholestasis and ultimately can result in portal hypertension. It is associated with renal abnormalities and increased capillary permeability. SOS can ultimately lead to multisystem organ failure, encephalopathy, and even death. Clinical manifestations of SOS include jaundice, hepatomegaly, and fluid retention. Treatment for this process is supportive, and severe SOS is associated with high mortality rates. Another major complication is pulmonary toxicity, manifested as interstitial pneumonitis or alveolar hemorrhage. Pulmonary complication of both solid organ transplantation and HSCT has been reviewed in detail. The use of RIC for allogeneic transplantation appears to minimize direct organ toxicity and nonrelapsed mortality.

Perhaps the most frequently cited complication uniquely associated with HSCT is GVHD, which is a complex immunologic phenomenon that occurs when immunocompetent cells from the donor are given to an immunodeficient host. The host possesses antigens foreign to the transplanted graft that stimulate an immune response by the newly engrafted immune cells. GVHD affects the entire gastrointestinal system, including the mouth, as well as the skin and the liver. Other organs that may be involved in GVHD are the eyes, vagina, joints, lungs, and musculoskeletal tissues. This reaction can be lethal and requires therapy with intensive immunosuppression. Mucosal ulceration seen in GVHD may serve as an entry port for other infectious pathogens. This graft-versus-host reaction can attack the host's hematologic cancer cells as well, leading to an antitumor effect that may be protective against relapse.

LONG-TERM PROGNOSIS POST TRANSPLANT

Transplantation outcomes have improved over the past several decades. Outcomes of solid organ transplants are summarized in Table 20-5. Clinical outcomes of solid organ transplantation are reported as graft survival and patient survival.

The number of patients on waiting lists for solid organ transplants continues to increase. The deaths of patients awaiting kidney transplants increased in 2019 to 3,759 while the death rates for patients awaiting heart and liver transplants in 2019 was 224 and 1,200, respectively. Since 2015, there has been a consistent reduction in number of deaths of heart transplant candidates (from 406 in 2015 to 224 in 2019). This may be due to adoption of new medical innovations such as ventricular assistance device.

Current estimates of HSCTs performed annually are greater than 50,000 worldwide. The annual rate of growth of this procedure has been estimated to between 40% and 50%. Improved HSCT-related healthcare has resulted in less morbidity and lower mortality rates. Historically, HSCTs for hematologic malignancies were undertaken as salvage therapy for refractory cancers, but outcomes are actually better for patients who are treated with HSCT soon after diagnosis or in remission, rather than after multiple relapses of hematologic disease. Outcomes have improved in both autologous and allogeneic HSCTs. There are various reasons that the success of HSCT has improved. In the setting of autologous HSCT, changes in conditioning regimens, hematopoietic growth factors, and the use of peripheral blood stem cells rather than bone marrow stem cells have been credited in part with improving mortality by shortening the duration of neutropenia (and incidence of severe infections) after intensive chemotherapy or radiation. In addition, better supportive care, antibiotic use, and blood product support have all improved outcomes for autologous HSCT. For allogeneic HSCT, CSA was introduced in the 1980s as an immunosuppressive agent limiting the severity of GVHD, making allogeneic donor HSCT practical. Decrease in severe GVHD has improved outcomes in allogeneic HSCT. Additionally, CMV accounted for high rates of mortality seen in patients treated with an allogeneic HSCT. Viral transmission can be limited by using screened "CMV-free" blood products for CMV-negative patients or using leukocyte-reduced blood products for transfusions. CMV-positive patients are treated with a

Table 20-5 Patient survival rates for transplants performed 2008–2015.

	Type of Transplant			
Type of Survival	**Renal (Living Donor)**	**Renal (Cadaveric Donor)**	**Liver (Cadaveric Donor)**	**Lung (Cadaveric Donor)**
1-year graft survival (%)	97.5	93.2	89.1	86.7
5-year graft survival (%)	85.6	74.4	71.9	52.5
1-year patient survival (%)	98.8	96.3	91.2	87.4
5-year patient survival (%)	92.1	83.3	75.0	55.0

Source: Based on Organ Procurement and Transplantation Network (OPTN). https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#. Accessed March 24, 2020.

prophylactic or, more recently, "preemptive" strategy using new high-sensitivity assays for CMV reactivation. These procedures have decreased the mortality associated with CMV interstitial pneumonitis. Post-transplantation cell growth factors have also been cited as improving outcomes in allogeneic HSCT patients. In allogeneic HSCT, advances have led to a decrease in overall mortality. The introduction of nonmyeloablative HSCT with RIC regimens allows for faster recovery of blood lineages and fewer complications post transplant. There are many patients who have survived HSCT for 5 years or more, and the future holds even greater promise as various transplantation techniques become further refined.

Outcomes of recipients who have received both bone marrow and solid organ transplantation have also been reviewed. There are many clinical and immunologic considerations that are highlighted by reviewing this unique patient population. Further research regarding the concept of immunologic tolerance/chimerism in patients who have had both a solid organ and an HSCT transplant may provide clues for future studies or for consideration of routine treatment regimens, including HSCT with the transplanted solid organ. Close monitoring of these patients will allow a better understanding of the concept of chimerism and tolerance.

ORAL HEALTH SEQUELAE IN TRANSPLANTATION

Oral complications post transplantation may affect the patient at any time. Some may subside and others may become chronic and be detrimental to patient quality of life. The following section will extend on each oral complication (Box 20-2).

Infections

Following transplantation, patients are more susceptible to bacterial, viral, and fungal infections, to include the oral cavity. Signs of oral infection may be muted by a decreased inflammatory response, or occasionally signs of infection may be exaggerated. Oral infection is often related to the level of immunosuppression and the patient's ability to mount an immune response. Oral infections must be diagnosed and aggressively treated, as these localized infections can spread quickly. Furthermore, systemic infections can present as changes in the oral tissues and it is important to remember that in severely immunocompromised patients, infections could be caused by opportunistic microbes that are not usually associated with oral infection. Laboratory tests such as culture, polymerase chain reaction (PCR), and sensitivity testing are prudent to target the therapy to the source of the infection.

Box 20-2 Oral Complications in Transplant Patients

1) Infections - viral, fungal, deep fungal, bacterial
2) Dental caries
3) Periodontal and gingival complications
4) Oral ulcerations due to medications
5) Dysgeusia and dysphagia
6) Malignancy - lymphoma, Kaposi sarcoma, basal cell carcinoma
7) Graft-versus-host disease
8) Soft tissue overgrowth (nongingival)
9) Oral mucositis
10) Salivary gland dysfunction
11) Developmental tooth defects and dentofacial growth alterations
12) Neurologic complications
13) Vitamin deficiency–related oral lesions

Viral infections occur frequently in immunosuppressed patients. Recurrent HSV is the most common viral pathogen cultured from oral infections in HSCT patients. Recurrent HSV infections can be labial or intraoral (Figures 20-2, 20-3, and 20-4). Whereas in immunocompetent individuals HSV typically presents on keratinized mucosa, in immunocompromised patients the nonkeratinized mucosa may also be affected. Recrudescence intraoral herpes may be chronic and difficult to diagnose based solely on clinical appearance, and is associated with decreased mortality at 2 years post HSCT.[15]

VZV, EBV, and CMV have been implicated in oral disease, although they are much less common than HSV. VZV may affect the oral or extraoral tissues, and its unilateral presentation is often diagnostic. Oral CMV has a nonspecific

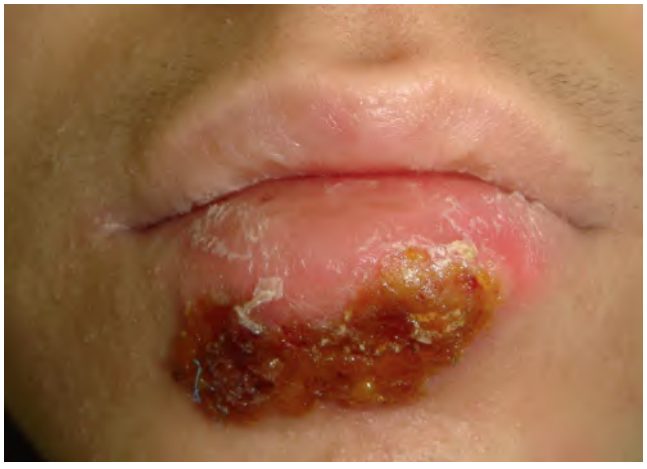

Figure 20-2 Recurrent herpes labialis in an immunocompromised patient.

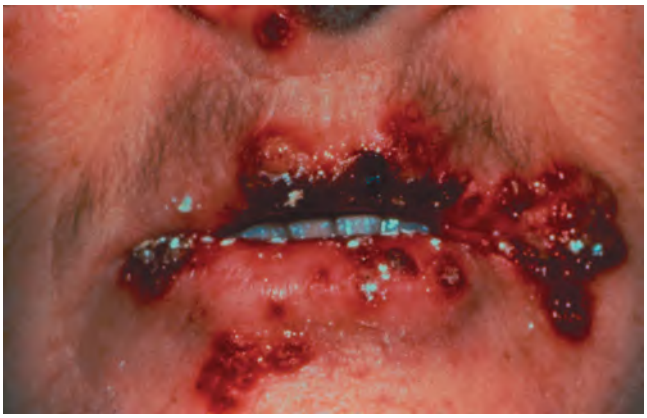

Figure 20-3 Recurrent herpes labialis in an immunocompromised patient.

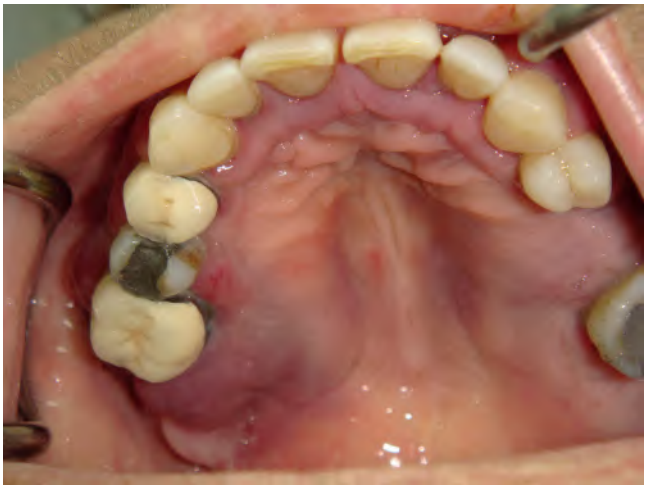

Figure 20-4 Kaposi sarcoma in a patient post hematopoietic stem cell transplantation.

presentation and it is critical to test for this potentially fatal virus. It is unclear whether human herpesvirus 6 infection is associated with oral lesions, although it has been detected in the saliva.[16]

Oral hairy leukoplakia related to EBV has been reported in transplant recipients not infected with the human immunodeficiency virus (HIV). Whereas in the past this pathology was typically observed in HIV patients, and to a lesser extent in patients post solid transplant, it has been reported in immunocompetent individuals.

Before transplantation, viral serologic tests are performed, and patients are immunized according to the recommended protocols.[17–19] Antiviral prophylaxis is often used and strategies for preemptive treatments are recommended. Treatment of viral infections requires administration of the appropriate antiviral agent. Occasionally, HSV is not responsive to acyclovir, valacyclovir, or famciclovir, therefore requiring foscarnet or cidofovir. If the disease has disseminated, the antiviral treatment will be delivered IV in an inpatient

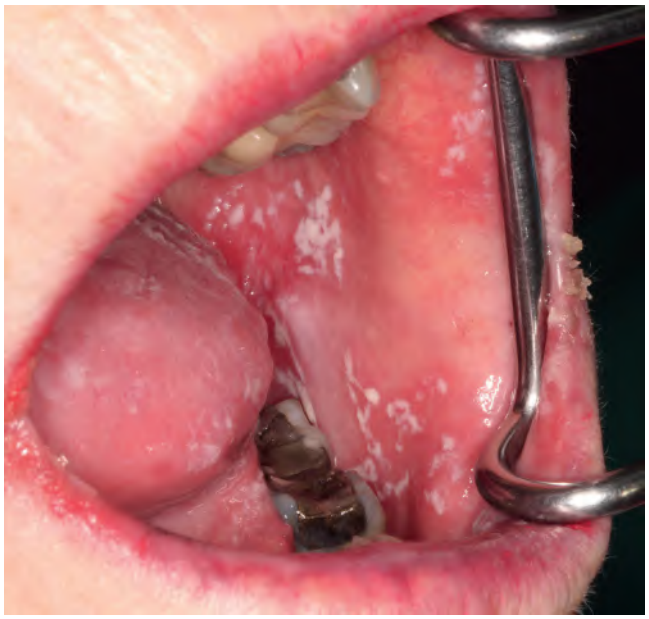

Figure 20-5 Pseudomembranous candidiasis in a transplant recipient.

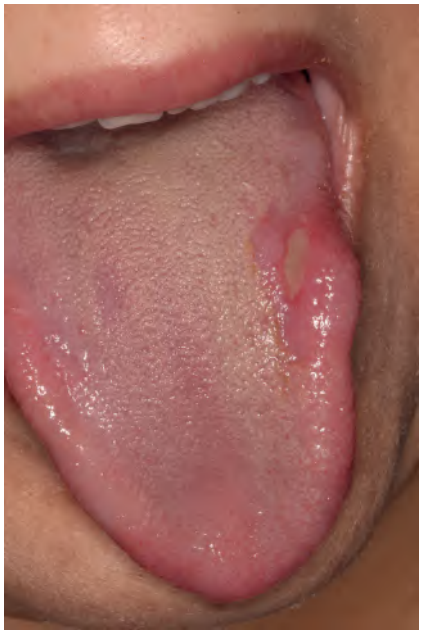

Figure 20-6 An everolimus induced oral ulcer in a patient post cardiac transplant.

setting. For CMV the first line of treatment is ganciclovir, valganciclovir or letermovir. New antiviral agents and strategies are being developed such as brincidofovir (CMX001), as well as virus-specific T-cell infusions.

Immunosuppressed patients are more susceptible to fungal infections such as *candidiasis*, as well as deep fungal infections such as aspergillosis, cryptococcosis, mucormycosis, and blastomycosis (Figures 20-5 and 20-6). There are various oral

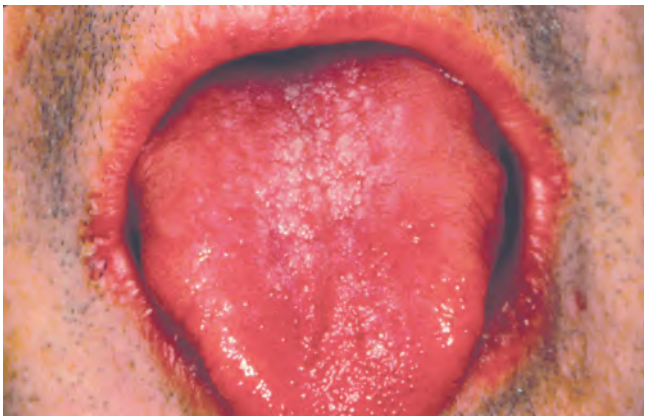

Figure 20-7 Atrophic candidiasis.

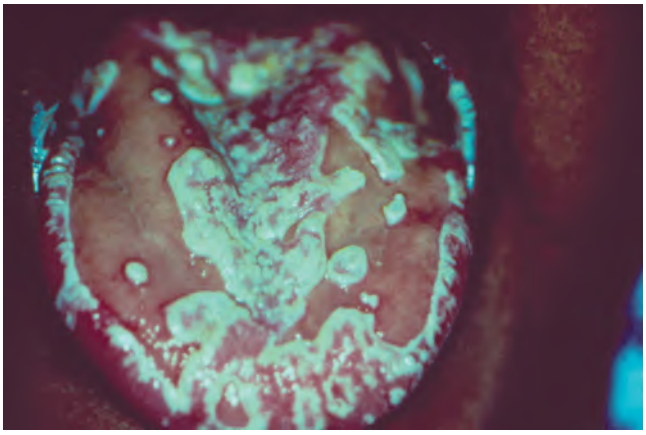

Figure 20-8 Hyperplastic candidiasis in a kidney transplant recipient. This infection did not respond to fluconazole.

presentations to these infections. Candidiasis can occur in the classic, pseudomembranous form, or it can be atrophic or even hyperplastic (Figures 20-5, 20-7, and 20-8). Occasionally candidiasis is not responsive to standard antifungals and may need treatment with IV antifungal agents.

Deep fungal infections involving the upper respiratory tract/sinuses may present as necrotic plaques on the palate of recipients of HSCT (Figure 20-6). Rarely, deep fungal infections may present in other sites in the oral cavity. These fungal infections are very difficult to treat and often require IV antifungal agents and surgical debridement. In severely neutropenic patients, these infections may be fatal, with the patient ultimately succumbing to a disseminated deep fungal infection.

Bacterial infections frequently affect the oral mucosa in patients undergoing HSCT. The main causative bacterial species are gram-negative bacilli (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) and gram-positive cocci (*Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pyogenes*), typically presenting as a painful ulceration. The clinical signs may be deceiving, as immunosuppression masks the full scale of the local inflammation.[20,21] Treatment is based on antibiotics and basic oral care. In HSCT, the protocol usually includes a combination of two or three types of antibiotics. Culture and antibiotic sensitivity are critically important if the empiric choice of antibiotic(s) is ineffective.

Dental Caries

An increased incidence of caries in the post-transplantation period has been reported. Children who have undergone HSCT for ALL have a higher incidence of caries and a higher decayed, missing, and filled teeth (DMFT) index. An age and gender, case-control matched study reported a significant increase in the prevalence of caries and periodontal disease in patients post liver transplantation compared to controls. Other studies describe a relative decrease of salivary immunoglobulin A (IgA) levels and increased salivary pH in children post liver transplantation, and altered dental development post HSCT. A retrospective study in a cohort of patients who developed chronic GVHD after allogeneic transplantation showed that more than 50% developed extensive cervical caries 2 years after transplantation. These studies highlight the importance of dental caries as a late complication of GVHD post transplantation.

Periodontal and Gingival Complications

Periodontal health in the transplant population is often compromised. Medical necessities including the long-term use of steroids and immunosuppressants contribute to the high rate of periodontal problems.[22,23] Side effects of transplant-related medications have been associated with periodontal disorders, particularly gingival overgrowth. The medication-induced gingival overgrowth seen in the transplant recipient in Figure 20-9 appears to be related to the immunosuppressive agent CSA. Furthermore, CSA-associated

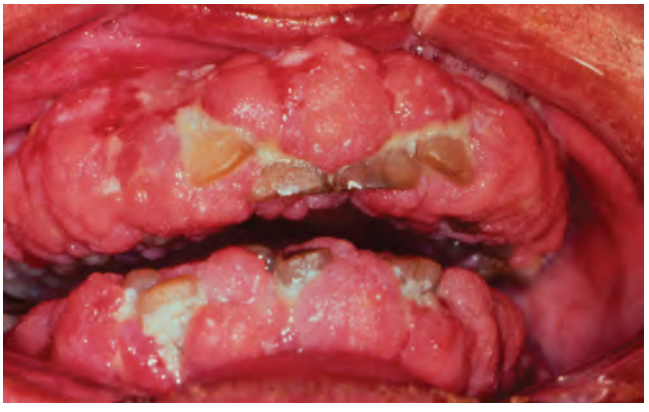

Figure 20-9 Gingival overgrowth in a kidney transplant recipient taking cyclosporine and nifedipine who also had poor oral hygiene.

gingival overgrowth may be amplified by the coadministration of nifedipine, a calcium-channel blocker often used to treat hypertension in this patient population. Nifedipine is frequently the drug of choice because it does not alter plasma levels of CSA. Administration of tacrolimus instead of CSA has significantly reduced the incidence and severity of gingival hyperplasia.[24]

A biopsy/histopathologic analysis should be performed on the overgrown gingival tissue if malignancy is suspected. Impeccable oral hygiene can prevent gingival overgrowth. Partial reversal of CSA-induced overgrowth has been reported upon discontinuation of the medication. Although treatment of severe gingival overgrowth usually requires a gingivectomy, nonsurgical periodontal treatment (scaling, root planing, oral hygiene instructions) reduces bleeding on probing, plaque index, probing depth, and the hypertrophy index in some transplant patients.

Oral Ulcerations Due to Medications

With the introduction of novel immunosuppressant agents, new oral complications have been identified. Targeted therapy agents are reportedly associated with several types of oral lesions. Among the classes of targeted therapy prescribed in transplant patients, the following cause oral complications: mTOR inhibitors (everolimus, temsirolimus, and sirolimus), multikinase angiogenesis inhibitors (sorafenib, sunitinib, cabozantinib, pazopanib), human epidermal growth factor receptor inhibitors (dacomitinib, afatinib), and TKIs (imatinib).[25] Another group of drugs increasingly utilized in transplant medicine is the immune checkpoint inhibitors for post-transplant malignancies, including the PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab).[26] Additional agents belonging to the targeted therapy or immune checkpoint inhibitors have reportedly induced oral lesions.

The most commonly reported oral complication of targeted therapy is mucositis or stomatitis. However, this description often includes many types of oral lesions presenting as erythema or ulceration. The more specific description includes aphthous-like ulcers appearing either as a single small elliptic ulcer ("minor"), a polygonal ulcer larger than 10 mm ("major"), or simultaneous numerous ulcers. The agents causing the aphthous-like ulcers are sirolimus, everolimus, temsirolimus, and to a lesser extent sunitinib. These lesions may be severe, causing pain, limiting oral intake, and leading to discontinuation of the drug. The treatment is frequently dose adjustment and topical steroids.

Another unique oral mucosal lesion associated with targeted therapy is lichenoid changes in the form of white striations with erythema or ulceration, which was reported in association with sunitinib, nivolumab, and imatinib.[25,26]

Interestingly, some of these agents have been reported to induce geographic tongue (bevacizumab, sorafenib, and sunitinib), grayish-bluish hyperpigmentation of the palate (imatinib), and reactional hyperkeratotic plaques (dabrafenib, sorafenib).[25–28]

Dysgeusia and Dysphagia

Taste changes are common post HSCT, and have also been documented post solid organ transplant. These changes can appear in the days following the HSCT conditioning regimen and usually resolve within 2.5 months,[29] but may linger for years.[30] In pediatric patients these changes reportedly resolve in about 6 months.[31] Immediate hypogeusia was reported in 66% of patients during the neutropenic phase, and the bitter taste commonly described seems to be related to the cytotoxics, and not to the presence of oral mucositis or to reduced salivary flow.[32] Late taste change may be related to cGVHD.[33]

After liver and kidney transplants, dysgeusia was reported in 11%–24% of patients.[23,34]

Taste changes after solid organ transplant are usually associated with polypharmacy and the medications administered during the course of immunosuppression.[26] Targeted therapy and immunotherapy are also associated with altered taste.[26,30] Additionally, vitamin deficiency and poor nutrition may contribute to taste loss.

Malignancy

Oral lesions in transplant recipients may be neoplasms, since these patients are at a higher risk of developing lymphoma, which is on the spectrum of PTLDs. PTLD develops in the presence of immunosuppression; it may manifest as a benign localized lesion, as a flu-like disease, or as a full-blown lymphoma. Often EBV is identified in malignant PTLD and in these cases the treatment includes acyclovir and a reduction of immunosuppression. However, not all lymphomas regress following this protocol. Oral manifestations of PTLD include a persistent localized ulcer or a mass.[35]

Patients post HSCT are considered high risk for squamous cell carcinoma of the oral mucosa.[36] This risk is associated with cGVHD, azathioprine in the conditioning regimen, or radiation at a young age.[37] Accordingly, the National Institutes of Health (NIH) consensus paper recommends thorough evaluation of oral tissues twice a year.

Post-transplant oral Kaposi sarcoma (OKS) is not as frequent as AIDS-associated OKS and overall is considered rare. OKS in the mouth and oropharynx accounted for about 2% of all post-transplant Kaposi sarcomas.[38] The median time to its development is 23.3 months.[39] When OKS develops, it most often affects the hard and soft palate, gingiva, and dorsal

tongue. When large OKS may be associated with pain and bleeding, and may become secondarily infected. The adjacent teeth may become mobile, and the OKS may interfere with oral function. Treatment for Kaposi sarcoma post transplant is by reduction of immunosuppression, conversion to mTOR inhibitors, chemotherapy, or a combination of these.[40]

Graft-versus-Host Disease

GVHD is usually considered a unique complication of HSCT, but has also been reported post colon transplant, face transplant, and blood transfusion.[41] In the oral cavity, cGVHD can manifest with a lichenoid appearance, erythema, or ulceration (Figure 20-10). These lesions are usually associated with pain and sensitivity to foods that are tolerated in non-cGVHD patients. The ulcerations may serve as a port of entry for pathogens. The gingivae are often atrophic and there may be desquamative gingivitis. cGVHD can affect the salivary glands, resulting in dry mouth or multiple mucoceles, which contribute to difficulty swallowing, oral candidiasis, and rampant caries. Additionally, cGVHD may affect the connective tissue and result in limited mouth opening and tongue movement. Taken together, these changes restrict oral intake and have a negative impact on the patient's quality of life. The latest version of the scoring systems for oral cGVHD was developed by the NIH and published in 2014 (Figure 20-11).[42] It refers to most of these oral manifestations and helps to communicate between clinicians, as well as to evaluate the response to treatment.

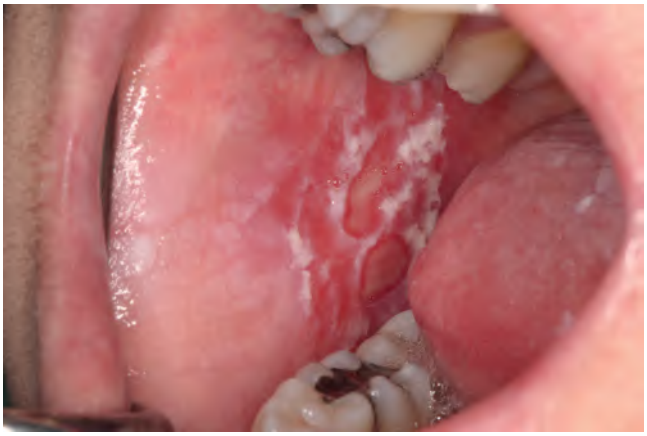

Figure 20-10 Graft-versus-host disease in a hematopoietic cell transplantation recipient.

Treatment goals are to relieve symptoms, control the activity level of the disease, and surveil for oral cancer. Oral cGVHD is challenging to treat and may require a change to the immunosuppressive regimen, and the implementation of systemic or topical mucosal therapy. When oral cGVHD is the only resistant site to systemic steroids, or when it is the sole site of the cGVHD, topical steroids are usually employed.[43] Topical tacrolimus, phototherapy, CO_2 laser, or topical CSA may be beneficial. Intra-lesional steroid injections may be applied in persistent isolated lesions. It is important to manage complications of oral cGVHD, such as caries and oral candidiasis.

Benign Soft Tissue Overgrowth (Nongingival)

Patients post HSCT may develop benign oral lesions such as pyogenic granuloma and verruciform xanthoma.[44,45] The evidence of these rare lesions is based on case reports. Nevertheless, it seems that chronic inflammation associated with cGVHD releases lipids that are phagocytosed by histiocytes, which is the first step in the development of a xanthoma, or induces capillary proliferation, which is the hallmark of pyogenic granuloma. Rarely, CSA may induce soft tissue overgrowth, unrelated to the gingivae, and these lesions have been seen in the buccal mucosa, alveolar mucosa, and elsewhere in the oral cavity (Figure 20-12).

There is an anecdotal report of tertiary hyperparathyroidism affecting the mandible.[46] Although the patient had a kidney transplant, the parathyroid glands functioned abnormally while the patient was in kidney failure, and parathyroid gland function did not return to normal, causing multiple brown tumors to develop in the mandible.

Oral Mucositis

Oral mucositis (OM) is defined as an inflammation of the mucosa accompanied by a burning or tingling sensation. It is

Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25–50%)	2	Lichen-like changes (>50%)	3
Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
							Total score for all mucosal changes	

Figure 20-11 2014 National Institutes of Health assessment tool for oral chronic graft-versus-host disease.

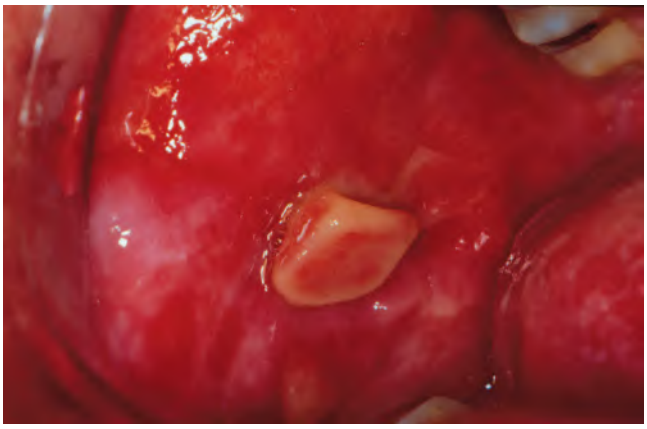

Figure 20-12 Nongingival soft tissue growth.

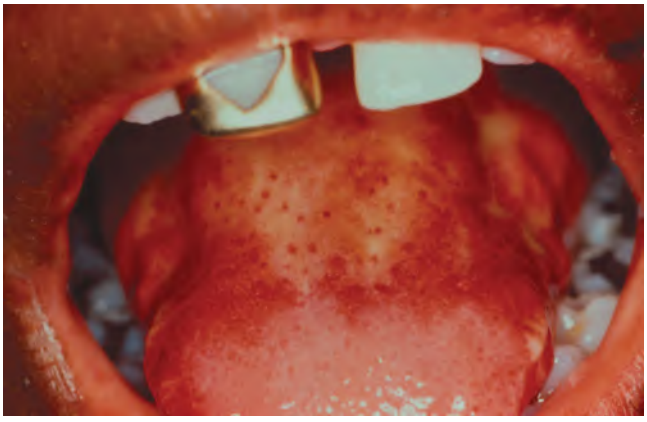

Figure 20-13 Mucositis shortly after induction chemotherapy for acute myelogenous leukemia.

characterized by atrophy of the squamous epithelium, vascular damage, inflammatory infiltration, and ulceration (Figure 20-13). It is common in patients who have had chemotherapy, radiotherapy to the head and neck, or HSCT. Mucositis is a diagnosis of exclusion, made by elimination of other etiologies, such as infection, topical drug chemical irritation, local trauma, or hypersensitivity reaction to a drug. OM in patients undergoing HSCT is associated with worse outcomes in terms of increased risk of significant infection, additional days of fever, total parenteral nutrition, injectable narcotic therapy, hospitalization, and an increase in 100-day mortality risk.[47]

The pathogenesis of mucositis involves simultaneous multistep molecular reactions that are outlined as a five-phase model: induction, upregulation and message generation, signaling and amplification, ulceration, and healing.[48] The understanding of the pathogenesis of mucositis has advanced over the years and the role of the microbiome in the development of mucositis has been noted.[49] There are numerous scales evaluating and measuring OM. The most commonly used are the World Health Organization (WHO) scale and the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale. The Oral Mucositis Assessment Scale (OMAS) has been validated and is often used in research. In addition, measurements of oral pain are used routinely following HSCT.

There are several goals in the management of OM, specifically prevention, treatment, and pain relief. A plethora of interventions for OM have been studied, including photobiomodulation; anti-inflammatory agents; vitamins, minerals, and nutritional supplements; growth factors and cytokines; antimicrobials; mucosal coating agents; anesthetics; analgesics; cryotherapy; natural and miscellaneous agents; and protocols categorized as basic oral care.[50] The Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) developed evidence-based guidelines for the management of mucositis.[51–58] The 2019 MASCC/ISOO guidelines are presented in Table 20-6.

A detailed description of the oral complications associated with oncologic treatment and their management can be found in Chapter 9.

Salivary Gland Dysfunction

Salivary gland dysfunction is common in patients after HSCT and may be related to the toxic effects of the conditioning regimens. Additionally, cGVHD may cause salivary dysfunction. The pathogenesis of salivary gland cGVHD is similar to the process reported in Sjögren's syndrome (Figure 20-14).

Xerostomia affects up to 48% and up to 30% of liver and kidney transplant recipients, respectively.[23,59] The risk of xerostomia correlates with the number of medications taken by the patient. The targeted therapy and immunotherapy agents sunitinib, everolimus, sorafenib, pazopanib, cabozantinib, bevacizumab, and imatinib reportedly cause xerostomia.[60,61]

Developmental Abnormalities

Developmental tooth defects affect up to 55% of survivors of childhood cancer.[62] Younger age at treatment and intensive chemotherapy increase the risk of long-term dental abnormalities among those treated with HSCT.[63] In particular, children conditioned with TBI and high-dose chemotherapy before HSCT are at high risk for dental developmental abnormalities.[63] The most common dental anomaly is microdontia, followed by tooth agenesis (20.4%), V-shaped roots (14.8%), and taurodontism (Figure 20-15). Dentofacial growth alterations have been reported in children post

Table 20-6 The MASCC/ISOO clinical practice guidelines for the management of oral mucositis.

Section	Intervention		LoE	Category	Guideline statement	Comment*
BOC	Multiagent combination	1	III	Suggestion	• The panel suggests that implementation of **multiagent combination** oral care protocols is beneficial for the prevention of OM during CT	New in 2019
		2	III	Suggestion	• The panel suggests that implementation of **multiagent combination** oral care protocols is beneficial for the prevention of OM during H&N RT	New in 2019
		3	III	Suggestion	• The panel suggests that implementation of **multiagent combination** oral care protocols is beneficial for the prevention of OM during HSCT	New in 2019
	Professional oral care	4	III	NGP/ expert opinion	• No guideline was possible regarding the use of **professional oral care** for the prevention of OM for patients with hematologic, solid, or H&N cancers due to limited and inconsistent data • An expert opinion complements this guideline. Although there was insufficient evidence to support the use of professional oral care for OM prevention, the panel is of the opinion that dental evaluation and treatment as indicated prior to cancer therapy is desirable to reduce risk for local and systemic infections from odontogenic sources	New in 2019
	Patient education	5	III	NGP/ expert opinion	• No guideline was possible regarding the use of **patient education** for the prevention of OM in hematologic cancer patients during HSCT or CT due to limited and inconsistent data • An expert opinion complements this guideline. The panel is of the opinion that educating patients about the benefits of BOC strategies is still appropriate as this may improve self-management and adherence to the recommended oral care protocol during cancer treatment	New in 2019
	Saline or sodium bicarbonate	6	III	NGP/ expert opinion	• No guideline was possible regarding the use **of saline or sodium bicarbonate** rinses in the prevention or treatment of OM in patients undergoing cancer therapy due to limited data • An expert opinion complements this guideline. Despite the limited data available for both saline and sodium bicarbonate, the panel recognizes that these are inert bland rinses that increase oral clearance which may be helpful for maintaining oral hygiene and improving patient comfort	New in 2019
	CHX	7	III	Suggestion against	• The panel suggests that **CHX** not be used in the prevention of OM in patients undergoing H&N RT	Confirmed in 2019

(*Continued*)

Table 20-6 (Continued)

Section	Intervention		LoE	Category	Guideline statement	Comment*
Anti-inflammatory agents	Benzydamine	8	I	Recommendation	• The panel recommends **benzydamine** mouthwash for the prevention of OM in patients with H&N cancer receiving a moderate dose RT (<50 Gy)	Confirmed in 2019
		9	II	Suggestion	• The panel suggests the use of **benzydamine** mouthwash for the prevention of OM in patients with H&N cancer receiving RT-CT	New in 2019
PBM (laser/light therapy)	PBM	10	I	Recommendation	• The panel recommends the use of intra-oral **PBM** therapy using low level laser therapy for the prevention of OM in adult patients receiving HSCT conditioned with high-dose CT, with or without total body irradiation using one of the selected protocols;** it is recommended that the specific PTPs of the selected protocol will be followed for optimal therapy	New in 2019
		11	II	Recommendation	• The panel recommends the use of intra-oral **PBM** therapy using low level laser therapy for prevention of OM in adults receiving RT to the H&N (without CT);** the specific PTPs of the selected protocol should be followed for optimal therapy • Safety considerations unique to patients with oral cancer should be considered	New in 2019
		12	I	Recommendation	• The panel recommends the use of intra-oral **PBM** therapy using low level laser therapy for the prevention of OM in adults receiving RT-CT for H&N cancer (LoE I);** the specific PTPs of the selected protocol should be followed for optimal therapy • Safety considerations unique to patients with oral cancer should be considered	New in 2019
Cryotherapy	Cryotherapy	13	II	Recommendation	• The panel recommends using oral **cryotherapy** to prevent oral mucositis in patients undergoing autologous HSCT when the conditioning includes high-dose melphalan	Confirmed in 2019
		14	II	Recommendation	• The panel recommends using 30 minutes of oral **cryotherapy** to prevent oral mucositis in patients receiving bolus 5-FU CT during the infusion of the CT	Confirmed in 2019
Antimicrobials, coating agents, anesthetics, analgesics	Morphine rinse	15	III	Suggestion	• Topical **morphine** 0.2% mouthwash is suggested for the treatment of OM-associated pain in H&N cancer patients treated with RT-CT	Confirmed in 2019
	Sucralfate	16	II	Recommendation against	• **Sucralfate** (combined topical and systemic) is not recommended for the prevention of OM-associated pain in H&N cancer patients treated with RT	Confirmed in 2019
		17	II	Recommendation against	• **Sucralfate** (combined topical and systemic) is not recommended for the treatment of OM-associated pain in H&N cancer patients treated with RT	Confirmed in 2019
		18	II	Recommendation against	• **Sucralfate** (combined topical and systemic) is not recommended for the treatment of OM-associated pain in solid cancer patients treated with CT	Confirmed in 2019

Growth factors & cytokines	KGF-1	19	I	Recommendation	• The use of **KGF-1** intravenously is recommended for prevention of OM in patients with hematological cancer undergoing autologous HSCT with a conditioning regimen that includes high dose chemotherapy and TBI	Confirmed in 2019
	GM-CSF	20	II	Suggestion against	• The evidence suggests that topical **GM-CSF** should not be used for the prevention of OM in patients undergoing HSCT	
Natural & miscellaneous	Glutamine	21	I	Recommendation against	• The panel recommends against the use of **glutamine** (parenteral) for the prevention of OM in patients undergoing HSCT	Confirmed in 2019
		22	II	Suggestion	• The panel suggests **glutamine** (per os) for the prevention of OM in patients with H&N cancer receiving RT-CT • The suggestion is with caution due to the higher mortality rate seen in HSCT patients treated with parenteral glutamine	New in 2019
	Honey	23	II	Suggestion	• **Honey** is suggested for the prevention of OM in H&N cancer patients treated with either RT or RT-CT	New in 2019
	Chewing gum	24	III	Suggestion against	• **Chewing gum** is not suggested for the prevention of OM in pediatric patients with hematological or solid cancer treated with CT	New in 2019
Antimicrobials, coating agents, anesthetics, analgesics	Patient-controlled analgesia with morphine	1	**II**	Recommendation	• The panel recommends that **patient-controlled analgesia with morphine** be used to treat pain due to oral mucositis in patients undergoing HSCT	Rolled over to 2019
	PTA or BCoG	2	**III**	Recommendation against	• The panel recommends that **PTA** and **BCoG** antimicrobial lozenges and PTA paste not be used to prevent OM in patients receiving RT for H&N cancer	Rolled over to 2019
	Iseganan	3	**II**	Recommendation against	• The panel recommends that **iseganan** antimicrobial mouthwash not be used to prevent OM in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT	Rolled over to 2019
		4	**II**	Recommendation against	• The panel recommends that **iseganan** antimicrobial mouthwash not be used to prevent OM in patients receiving RT or RT-CT for H&N cancer	Rolled over to 2019
	Pentoxifylline	5	**III**	Suggestion against	• The panel suggests that **systemic pentoxifylline**, administered orally, not be used to prevent OM in patients undergoing bone marrow transplantation	Rolled over to 2019
Natural & miscellaneous	Pilocarpine	6	**III**	Suggestion against	• The panel suggests that **systemic pilocarpine**, administered orally, not be used to prevent OM in patients receiving RT for H&N cancer	Rolled over to 2019
		7	**II**	Suggestion against	• The panel suggests that **systemic pilocarpine**, administered orally, not be used to prevent OM in patients receiving high-dose CT, with or without TBI, for HSCT	Rolled over to 2019

* Key: "New in 2019"—guideline statement determined in 2019 based on new evidence; "confirmed in 2019"—guideline statement confirmed/enhanced in 2019 based on new evidence; "rolled over to 2019"—guideline statement determined in 2014 and no new evidence for this intervention until 2019.

** For the detailed protocols see the full text in the 2019 guidelines paper.

BCoG, bacitracin, clotrimazole, and gentamicin (as a lozenge); BOC, basic oral care; CHX, chlorhexidine; CT, chemotherapy; GM-CSF, granulocyte macrophage colony-stimulating factor; H&N, head and neck; HSCT, hematopoietic stem cell transplantation; KGF-1, keratinocyte growth factor 1; LoE, level of evidence; NGP, no guideline possible; OM, oral mucositis; PBM, photobiomodulation; PTA, polymyxin, tobramycin, and amphotericin B (as a lozenge or a paste); PTP, physical therapy parameters; RT, radiotherapy; RT-CT, radiochemotherapy; TBI, total body irradiation.

Source: Elad S, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2020;126(19):4423–4431.

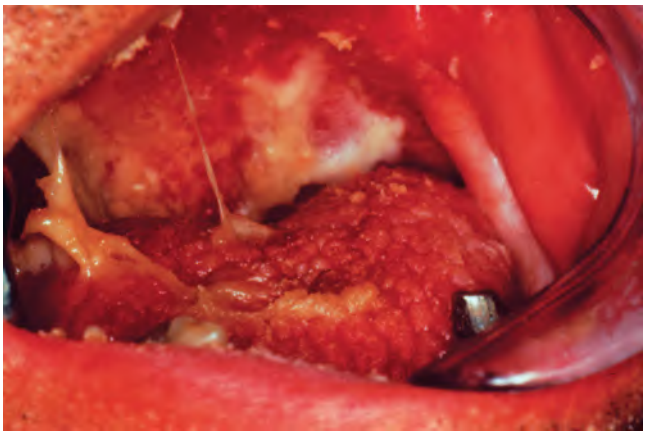

Figure 20-14 Salivary hypofunction.

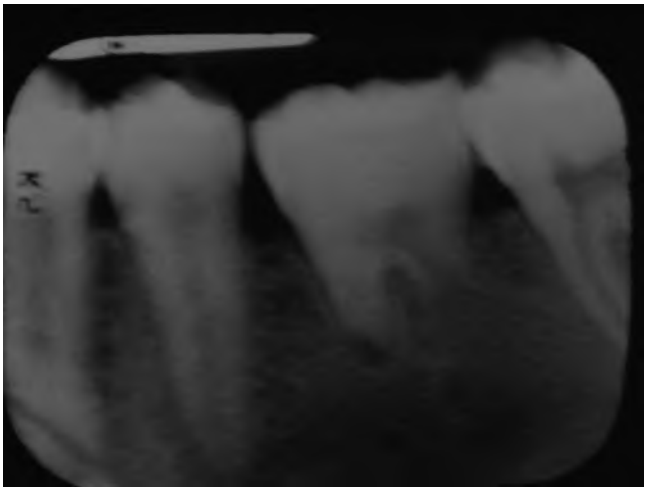

Figure 20-15 Dental root alteration as a result of childhood treatment for neuroblastoma and conditioning total body irradiation prior to hematopoietic stem cell transplantation.

HSCT.[64] The mean area of the mandibular central incisor, first, and second molar was significantly smaller in individuals post HSCT, and the vertical growth of the face was significantly reduced, especially in the lower third, compared to healthy controls.[65] Children undergoing HSCT had significantly more growth reduction in vertical craniofacial variables compared to healthy children.

Positive correlations were found between discoloration of the deciduous teeth and liver transplantation, between enamel hypoplasia and kidney transplantation, and between treatment with CSA and its dose and blood concentration.[66] Additionally, pulp stones were present in 13% of kidney versus 8% of liver recipients, more often in those treated with CSA than with tacrolimus. The presence of pulp stones correlated with the administration of glucocorticoids. Jawbone abnormalities affected 30% of kidney recipients and 12% of liver recipients, including foci of density and reduced bone density. Jaw abnormalities were also associated with glucocorticoid treatment.[66]

Neurologic Complications

Patients treated with targeted therapy and immunotherapy may report oral mucosal sensitivity (dysesthesia) without any abnormal clinical findings. This dysesthesia was most frequently associated with sunitinib and sorafenib.[61] It is unclear what analysis was done to eliminate known factors that contribute to oral burning; however, the literature refers to the condition as burning mouth syndrome.

Face transplant requires a long period for the establishment of reliable neurologic connections, and during this recovery time numbness in the trigeminal branches that were reconnected is expected. There are a limited number of reports on face transplantation, but the range of time for regaining sensation is 3–24 months.[67,68] This also applies to tooth vitality. Interestingly, an abnormal vitality test in which a stimulus to an upper premolar evoked a response in the upper incisors was reported.[68]

Vitamin Deficiency–Related Oral Lesions

Iron deficiency is common in patients with end-stage renal disease. Anemia improved within 1 year of kidney transplant, although iron deficiency increased.[69] The extent of the role of iron deficiency in post-transplant oral mucosal atrophy is unclear.

Intestinal transplant recipients may experience long-term intestinal insufficiency with pan-vitamin deficiency. The dentist may encounter the oral manifestations of malnutrition, including hypovitaminosis. The effect of vitamin deficiency is reviewed elsewhere.[70]

DENTAL TREATMENT

There are several principles in the approach to dental treatment for transplant patients, in particular the timing of the dental treatment relative to the transplant procedure: pre transplant, during transplant, and post transplant. Additionally, there are considerations specific to certain types of transplants. These considerations will be presented separately.

Pre-transplantation Considerations

General

The main consideration before the transplant is to eliminate dental infections that may impede transplantation. The process of evaluation and treatment planning prior to transplant is often referred to "clearance," and this process requires coordination with the transplant team. The concern is that sites of asymptomatic infection may flare up while the patient is immunosuppressed or hospitalized for the transplant procedure. Clearance involves a thorough evaluation of the dentition, periodontium, and oral mucosa. Controversy exists regarding the optimal radiographic examination for these patients. Some dentists feel that a full mouth series is necessary and others prefer a panoramic film and bitewings. There is consensus, however, on the importance of having access to recent dental radiographs.

Considering dental management goals, the treatment plan differs significantly to that of a routine treatment plan for a healthy patient. While eliminating foci of infection, sites of acute infection are prioritized, particularly if these sites are symptomatic. The treatment plan needs to be definitive and eliminate these foci as quickly as possible. Occasionally, chronic dental infections may be considered a priority as well. However, it is often clear that not all dental needs can be addressed before transplant, and elective dental treatment in patients with life-threatening end-stage disease should be postponed until the medical condition permits.

Although immunosuppression for solid organ transplants is not associated with neutropenia, the approach used in cancer patients prior to chemotherapy highlights the types of dental conditions considered as potential sites of infection. A list of dental conditions that put patients at risk for infection during times of immunosuppression includes nonrestorable teeth (e.g., those with severe periodontal disease, gross decay that involves the pulp), symptomatic teeth, and partially erupted third molars with a history of pericoronitis.[71] Furthermore, teeth posing risk for food impaction should be considered as high priority.

The more severe the immunosuppression, the more definitive dental treatment should be. Therefore, in patients undergoing HSCT, treatment decisions are determinative. On the other hand, in patients undergoing solid organ transplantation with a relatively short period of immunosuppression, dental needs that are not categorized as high priority may be postponed. In such cases, the patient should be informed about these unmet dental treatment needs and advised to follow up with their primary dentist post transplant when routine dental treatment has been approved.

During dental clearance, the patient should be advised to follow up with the dental team periodically, since there may be an extended waiting period until the actual date of transplant. Periodic dental checkups and hygiene visits are important during this time, and the low-priority dental needs may be addressed if the medical condition permits.

Specific organ dysfunction poses unique challenges. Transplant-specific considerations are detailed below. Occasionally multiorgan transplants are performed, to include heart–lung, lung–kidney, lung–liver, and kidney–pancreas transplants. In such cases, aspects related to each transplanted organ need to be followed.

Liver Transplant

The main concern in patients with end-stage liver disease is bleeding. In liver transplant candidates, the potential for bleeding is unpredictable. On top of the coagulopathy there is secondary portal hypertension that leads to destruction of platelets in the spleen, and patients may be resistant to platelet transfusions. The complexity of hemostasis impairment is driven also by the presence of anemia, reduced thrombopoietin production, and vitamin K deficiency, which may be seen in this patient population. Furthermore, preoperative coagulation tests may not correlate with the level of bleeding during an operation. Specifically, in the Model for End-Stage Liver Disease (MELD), preoperative prothrombin time (PT), preoperative partial thromboplastin time (PTT), preoperative INR, and preoperative platelet count were not statistically significant in predicting postoperative bleeding.[72]

A major bleeding episode following a dental extraction has been reported.[73] This type of bleeding may develop despite preoperative systemic coagulation-promoting medication and fresh plasma preoperatively, and may be life-threatening.[73]

A preoperative tool to assess bleeding risk pre liver transplant has been proposed.[72] In this study, patients were placed into three risk groups (minimal, moderate, high) based on the number and complexity of teeth to be extracted as well as any planned adjunctive preprosthetic procedures. The study found a relatively high rate of severe bleeding (6%, 12.5%, and 50% for low, moderate, and severe risk groups, respectively). Despite a more aggressive preoperative management protocol for the high-risk patients, 5/10 (50%) experienced prolonged postoperative bleeding, with 3/5 (60%) requiring hospital admission, and 1/5 (20%) experienced a significant prolongation of their inpatient stay.

More recently a few cohorts showed only minor bleeding when platelet transfusions were administered preoperatively. However, most of the studies reported no correlation

between the preoperative platelet count or INR and the risk for bleeding, highlighting the unpredictable nature of this bleeding risk. Notably, all these studies were conducted in Europe or Brazil; therefore, the availability of local hemostatic agents varies.[74–76] One study suggested a low risk of bleeding following tooth extraction in patients with liver cirrhosis, INRs of 2.5 or less, and platelet counts of 30,000/mm^3 or greater, and bleeding was controlled with local hemostatic measures.[77] Nevertheless, the unpredictability of the bleeding risk remains an issue. A lab test named thromboelastography (TEG) may be used in this patient population to guide the decisions about platelets and other blood products transfusions in order to reduce the bleeding risk.[78]

While risks associated with oral infection are well known, there is no consensus regarding the level of inflammatory disease that would hamper the transplant procedure and scope of dental therapy required in the pre/post-transplant patient to prevent oral infection.[79] Accordingly, although many publications support a minimal approach, the cutoff between minimal dental treatment and avoiding dental treatment is unclear.

Accordingly, the current view is that a dental examination before transplantation is essential, and that the nature of dental treatment may have to be modified according to patient health status. Importantly, infections from dental sources in the immediate term following transplantation appear to be rare or have not been reported because they were managed.[80] Therefore, the risk for dental treatment–related bleeding before liver transplant may outweigh the risk of infection in the period immediately after a liver transplant.

Consequently, a selective approach is needed for foci of infection when one of the following exists: acute dental infection that manifests as pain, fever, lymphadenopathy, extraoral swelling, intraoral swelling, and vestibular tenderness together with tenderness to percussion. These signs likely indicate an acute dentoalveolar abscess and justify extraction of the involved tooth. Risk for aspiration is another indication for dental intervention prior to liver transplant. For signs of low- to moderate-level infection, the transplant team and the patient should be informed, but the extraction may need to be postponed until after liver transplant (approximately 3 months). Although this empiric approach seems to be a reasonable inference from the literature, there are few data from clinical trials to support it.

Another concern in patients with end-stage liver disease is the ability to metabolize medications. Medications are often adjusted pre transplant because of altered hepatic metabolism (Table 20-7). These changes may be either dose reduction, longer intervals between doses, or complete avoidance of certain drugs. The dentist should be familiar with the available tools to identify medications that need to be altered in this population. There are several open databases that offer this information (e.g., ePocrates, UpToDate).

The necessity for antibiotic prophylaxis in patients pre liver transplant has been discussed in the literature, including whether prophylaxis is needed due to the vulnerability of these patients and risk for peritonitis, or whether an antibiotics is harmful to the failing liver.[81] Furthermore, considering that spontaneous bacterial peritonitis caused by *Streptococcus viridans* has only been noted in patients with multiple dental infections, it is possible that a surgical procedure on an infected site will cause a bacteremia.[82] A cohort study in 346 liver transplant candidates reported that routine extractions without antibiotic prophylaxis can be performed safely, 86% of patients had no complications, and 14% had minor complications.[74] This dilemma indicates that each patient should be assessed individually, and a consultation with an infectious diseases specialist may be needed.

Kidney Transplant

Kidney transplantation is the optimal modality of treatment for patients with end-stage kidney disease (ESKD). It is associated with improved quality of life, lower medical costs, and improved survival.[83] The shorter the period of time on dialysis, the better the results achieved by transplantation, and the best results are seen with preemptive transplantation.[84]

Some medical complications in patients with ESKD may influence pretransplantation dental clearance. Hypertension and congestive heart failure may develop due to fluid retention and production of vasoactive hormones via the renin-angiotensin system.[85] Therefore, vital signs should be measured prior to the dental exam, and monitored continuously if the values are elevated. Blood pressure readings above 180/110 mm Hg are an indication to postpone dental treatment and refer for medical evaluation.

Reduced synthesis of erythropoietin can lead to anemia. Uremia might increase bleeding tendency due to a qualitative platelet dysfunction (decreased platelet aggregation and impaired platelet adhesiveness). Therefore, invasive dental procedures should be delivered gradually and hemostasis should be achieved between treatment steps (for example, scaling in segments to confirm hemostasis prior to moving to the next segment). Hemostatic agents should be available to minimize postoperative bleeding.

Altered cellular immunity associated with uremia may put patients with ESKD into an immunocompromised state.[86] It is important to educate patients about unique considerations and stress the importance of oral hygiene to prevent infection.

The distribution, metabolism, bioavailability, and rate of excretion of many drugs are altered, and dosage adjustment of dose or frequency is required. Potentially nephrotoxic agents should be considered carefully, for example nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, acyclovir, and tetracycline (Table 20-7).

Table 20-7 Medication considerations in patients with liver or kidney failure*.

	Dose Change Advised	
Drug	**Renal Dosing**	**Liver Dosing**
Acetaminophen**	CrCl 10–50: give q6h CrCl <10: give q8h HD: usual dose q8h; no supplement after dialysis PD: usual dose q8h; no supplement	(Not defined) Hepatic impairment: consider decreasing dose
Acyclovir (per os)	CrCl <10: 200 mg PO q12h (for usual dose of 200 mg x5/d) (for usual dose of 400 mg x3/d) HD: 200 mg PO q12h, on dialysis days admin. after dialysis; give additional dose as supplement PO after dialysis PD: not defined	(Not defined) Hepatic impairment: caution advised
Amoxicillin**	CrCl 10–30: 250–500 mg q12h CrCl <10: 250–500 mg q24h; info: do not use 875 mg tab for CrCl <30 HD: 250–500 mg q24h, on dialysis days administer after dialysis; consider supplement during and after dialysis if next maintenance dose not due right after dialysis PD: 250 mg q12h; no supplement; info: do not use 875 mg tab for CrCl <30	(Not defined)
Cephalexin	CrCl 50–90: give usual dose q6–8h CrCl 10–50: give usual dose q8–12h CrCl <10: give usual dose q12–24h HD: give usual dose q12–24h, on dialysis days administer after dialysis; consider supplement if next maintenance dose not due right after dialysis PD: give usual dose q12–24h; no supplement	(Not defined)
Clavulanic acid with amoxicillin**	CrCl 10–30: 250 mg/125–500 mg/125 mg q12h CrCl <10: 250 mg/125–500 mg/125 mg q24h; info: do not use 875 mg/125 mg tab for CrCl <30 HD: 250 mg/125–500 mg/125 mg q24h, on dialysis days administer after dialysis; consider supplement during and after dialysis if next maintenance dose not due right after dialysis PD: 250 mg/125 mg q12h; no supplement; info: do not use 875 mg/125 mg tab	Hepatic impairment: caution advised; amoxicillin/clavulanate-associated hepatic impairment Hx: contraindicated
Clindamycin	(No adjustment)	(No adjustment)
Codeine sulfate	CrCl 10–50: decrease dose by 25%, titrate slowly CrCl <10: avoid use HD/PD: avoid use	(Not defined) Severe impairment: caution advised
Diazepam	Renal impairment: no adjustment; info: caution advised, metabolite accumulation possible HD/PD: no adjustment; no supplement	Mild to moderate impairment: caution advised Severe impairment: contraindicated
Ibuprofen	CrCl >60: no adjustment CrCl 30–60: not defined, caution advised CrCl <30: avoid use Advanced renal disease: avoid use HD/PD: avoid use	(Not defined) Hepatic impairment: caution advised

(*Continued*)

Table 20-7 (Continued)

	Dose Change Advised	
Drug	**Renal Dosing**	**Liver Dosing**
Lidocaine	Mild to moderate impairment: no adjustment Severe impairment: not defined, caution advised with prolonged infusion HD/PD: not defined	(Not defined) Hepatic impairment: caution advised
Metronidazole	Renal impairment: no adjustment HD: no adjustment, on dialysis days administer after dialysis; consider supplement if next maintenance dose not due right after dialysis PD: no adjustment; no supplement	Child–Pugh Class A or B: caution advised Child–Pugh Class C: decrease dose 50%
Minocycline	Renal impairment: decrease usual dose and/or frequency, amount not defined, max 200 mg/24h HD/PD: not defined	(Not defined) Hepatic impairment: caution advised
Naproxen	CrCl >60: no adjustment CrCl 30–60: not defined, caution advised CrCl <30: avoid use Advanced HD/PD: avoid use	(Not defined) Hepatic impairment: caution advised
Tetracycline	if usual regimen bid - Renal impairment: consider decreasing frequency HD: give usual dose q24h; no supplement after dialysis PD: give usual dose q24h; no supplement	(Not defined) Hepatic impairment: caution advised

* Includes drugs commonly used in dentistry.
** Refers to the immediate-release form; for information about the extended-release form please see the source.
CrCl, creatinine clearance; HD, hemodialysis; Hx, history; PD peritoneal dialysis.
Source: Adapted from ePocrates, https:// online.epocrates.com/home, accessed February 2020.

As kidney disease progresses, hemodialysis is life-saving. The efficiency of hemodialysis is much lower than a functioning kidney, therefore ESKD patients on hemodialysis are in a constant state of kidney failure and uremia. The risk for bleeding is increased from the use of heparin during hemodialysis. Infective endocarditis (IE) occurs more frequently in hemodialysis patients due to the vascular access. About 2%–6% of chronic hemodialysis patients develop IE and the incidence is 50–60 times higher than in the general population.[87] IE is usually related to bacteremia associated with repeated manipulation of the vascular access, particularly central venous catheters. According to the American Heart Association (AHA) statement regarding patients with nonvalvular-cardiovascular device, including hemodialysis, antibiotic prophylaxis is recommended for patients with these devices if they undergo incision and drainage of infection at other sites (e.g., abscess).[88] Additionally, if the patient has a history of IE, the AHA guidelines for the prevention of IE should be followed.[89]

Considering that the fistula is a life port for patients on hemodialysis, it is critical when measuring blood pressure not to place the cuff on the arm used for the dialysis access. Since fluid is restricted to avoid volume overload, attempts should be made to minimize water from the dental handpiece (high-speed, ultrasonic scaler) and manual instrumentation is preferred. Likewise, rubber dam and power suction will reduce water intake.

Hemodialysis patients with poor electrolyte balance are at risk for arrhythmia and overvolume complications. This is most noticeable after a weekend interval between hemodialysis sessions. Therefore, special consideration should be made if an emergency dental visit occurs on the morning following the weekend or a similar prolonged period without dialysis.

Patients with kidney failure develop changes in bone metabolism, termed renal osteodystrophy. Dentists should be aware that manifestations of renal osteodystrophy include tooth mobility, malocclusion, pulp stones, enamel hypoplasia, bone demineralization, decreased trabeculation of cancellous bone, decreased thickness of cortical bone, radiolucent giant cell lesions, and jaw fracture (spontaneous or after dental procedures). If giant cell tumors are present in the jaws, the transplant team should be informed, and the patient should be followed up to ensure that the lesions

resolve spontaneously when kidney function returns to normal. Likewise, osteodystrophy may result in abnormal bone healing after extraction, therefore extractions should be as atraumatic as possible and wound healing post extraction should be confirmed.[85]

Kidney failure may be a complication of an underlying chronic disease, such as diabetes. These comorbidities should be addressed concomitantly.

As home hemodialysis is becoming more common, it has a marked impact on the patient's vitality, quality of life, and independence from the hemodialysis unit. These factors indirectly influence dental care.

Heart Transplant

Patients awaiting a heart transplant are usually poor candidates for outpatient dental treatment. The majority of these patients have severe CAD or congestive heart failure. Both conditions can progress to life-threatening complications during invasive dental treatment. The sole effect of stress and/or pain can cause adverse outcomes in these patients. The cardiovascular reserve of these patients is small and they are therefore much better candidates for elective dental treatment after transplantation. Some patients awaiting heart transplant may not leave the hospital until they receive their new heart.

For urgent dental problems, individually tailored treatment includes adequate anxiolysis, close monitoring, and profound local anesthesia. In a cohort of 32 patients with refractory heart failure receiving dental treatment in a specialized hospital department, adverse systemic effects were reported as arrhythmias (25%) and pulmonary congestion (19%), of whom five required medical treatment.[90] Both adverse reactions were seen in patients undergoing dental extraction or periodontal treatment. Therefore, pre–heart transplant patients undergoing dental clearance should be monitored closely. The preferred position for dental treatment is semi-supine in order to avoid pulmonary congestion. Measures to avoid unintended fluid intake should be used, such as a rubber dam and power suction. Dentists should be certified in basic life support and have a routine in place for medical emergencies (see Chapter 14 regarding congestive heart failure).

Some pre–heart transplant patients have a left ventricular assist device (LVAD). LVAD offers patients a therapeutic option that provides circulatory support while awaiting transplantation, or it may be a permanent alternative to transplantation (i.e., "destination therapy").[91] Most patients have LVADs with a nonpulsating continuous-flow pump and therefore blood pressure does not fluctuate and there is no practical way to measure blood pressure and heart rate in the conventional fashion. In these cases, dentists can get an impression about patient vitality by assessing clinically adequate perfusion by skin color, capillary refill following light pressure, and mentation status.

In addition, LVAD patients are maintained on a consistent anticoagulation regimen, and therefore have an increased bleeding tendency and risk of thromboembolic events.[92] Unfortunately, there are no robust data regarding dental treatment complications in patients with LVAD. In a retrospective review of charts of 29 patients with LVAD who underwent oral surgical procedures, bleeding as defined in this study was documented in 17 patients and bleeding correlated with the INR level.[93] In a retrospective study of 32 LVAD patients undergoing dental extractions who were monitored for bleeding complications, several approaches were applied preoperatively, including holding warfarin treatment, changing to heparin drip, or continuing with warfarin.[94] The average postoperative change in hemoglobin level was -0.79 $\pm$ 1.45 g/dL. Only 1 patient (3%) required a postoperative blood transfusion and there were no surgical interventions due to bleeding. The authors concluded that minor oral surgical procedures can be performed safely in patients being supported on LVAD therapy.

Although data to support the practice are lacking, many of those managing these patients prefer to have them covered with prophylactic antibiotics prior to invasive dental procedures.

Lung Transplant

The common indications for a lung transplant are chronic obstructive pulmonary disorder (COPD), interstitial lung disease, pulmonary hypertension, and cystic fibrosis. The disease-specific modifications to dental treatments are described elsewhere in this book. Most patients awaiting lung transplant are on oxygen therapy and have difficulty breathing. Combustible sources near patients on oxygen therapy must be avoided. This may be relevant for some types of laser therapy in the dental office. Narcotic medications that cause respiratory depression should be considered carefully. These chronic conditions may result in extrapulmonary complications, which should also be addressed.

Mechanical ventilation and/or extracorporeal life support (ECLS) have advanced and are being used more often prior to transplant. Considering the proximity of the lines to the endocardium in the right atrium, antibiotic prophylaxis should be considered prior to dental treatment manipulating the gingiva, periapical area, or oral mucosa. The principles outlined in the 2007 AHA guidelines for prevention of IE may be applied in this scenario, although no specific data are available to demonstrate ECLS-associated risk for IE. These patients may be on anticoagulants, and protocols to establish hemostasis should be employed.

Intestinal Transplant

Intestinal transplantation is indicated for patients with gut failure due to life-threatening complications of parenteral nutrition or underlying gastrointestinal disease such as desmoid tumor, congenital mucosal disorders, and ultrashort bowel syndrome.[95] The 1-, 5-, and 10-year graft survival rates are 71%, 50%, and 40% and the patient survival rates are 77%, 58%, and 47%, respectively.[96] In some cases, other organs are transplanted simultaneously from the same donor. When advanced liver disease is present, the liver is replaced as well. The pancreas and duodenum are also often transplanted.[97]

Candidates for intestinal transplantation are severely malnourished.[98] Vitamins C, E, and K may be low in patients with short bowel syndrome. Theoretically, manifestations of vitamin C and K deficiencies may result in spontaneous gingival bleeding and excessive postoperative bleeding. Therefore, dentists should monitor coagulation tests and have local hemostatic agents available.

Normally, approximately 80% of immune cells reside in the gut. After transplantation, the gut is repopulated with recipient cells, whereas the genotype of the epithelium remains largely that of the donor, making the organ highly chimeric and immunogenic.[97] The large lymphoid load and the reaction due to this immunologic discrepancy between donor and recipient cells put the patient at risk for immunologic complications.[99] Therefore, relatively high doses of immunosuppressant are administered and the pretransplant dental clearance should be determinative.

Pancreatic Transplant

Patients awaiting pancreatic transplants have a significant glucose management challenge and therefore serum glucose levels must be considered before dental treatment. These patients may be poor wound healers and may have "brittle insulin-dependent diabetes"; that is, they may experience sharp alterations in blood glucose levels and be prone to both ketoacidosis and insulin shock (see Chapter 16 on diabetes mellitus and endocrine diseases). Pancreatic dysfunction may be accompanied by hepatic failure. Hence, coagulation complications and medication and local anesthetic metabolism must be considered when performing dental procedures in these individuals.

Hematopoietic Stem Cell Transplant

Most HSCT patients have been through induction and have endured consolidation chemotherapy to treat a hematologic malignancy. Many of these patients are pancytopenic and prone to infections and bleeding. They are poor candidates for routine outpatient dental treatment. Other patients may have had a significant remission of their disease with normal blood counts, allowing emergency dental treatment before HSCT.

Blood counts should be addressed during the pretransplant clearance exam. It remains unclear if the bacteremia from periodontal probing alone can increase the risk of bacteremia and septicemia while a patient is neutropenic, although studies in patients with OM demonstrated an increased risk for septicemia.[100] If the patient is leukopenic (white blood cell $<1 \times 10^9$ cells/L) or neutropenic (neutrophil count $<0.5 \times 10^9$ cells/L), antibiotic prophylaxis is indicated for invasive treatments.[100] Ideally, invasive tests or treatments should be combined to maximize the benefit of each antibiotic prophylactic course. For example, probing of gingival depth, scaling, and elimination of advanced decay may be performed in one session. Most of the pre-HSCT patients will have a central catheter inserted before their dental evaluation. This alone is not an indication for antibiotic prophylaxis.

Anemia is rarely a limiting factor; however, extreme anemia may cause sudden hemodynamic changes, and the transplant team should be informed before dental treatment. Platelet count is a critical parameter prior to dental intervention. Uncontrolled bleeding may occur following simple dental procedures such as scaling, therefore measures to avoid bleeding should be applied. The decision about platelet transfusion prior to dental treatment is ambiguous, with no clear cutoff line. Generally speaking, a platelet count below 20,000/μL is a red flag and if invasive dental procedures are indicated, platelet transfusion should be considered. Severe bleeding may occur at higher platelet counts, especially in the presence of an additional coagulopathy, and clinician discretion is needed.

Since immunosuppression induced by the HSCT conditioning regimen may be severe, eradication of potential sites of infection should be determinative. Furthermore, often the timeline for delivering dental treatment is very short. Therefore, compromises may be needed regarding treatment, for example extractions may be prioritized over endodontic treatment.

Prompt consultation with the hem/oncologist is recommended and the discussion may address the need for blood product transfusion, the timeline to complete dental clearance, inclusion of sufficient time for postextraction wound healing, and potential foci of infection that will remain during HSCT. The transplant team may prefer to delay invasive dental procedures and proceed with the HSCT.

Face Transplant

Face transplantation is indicated for patients with severe facial damage and disfiguration, usually associated with trauma. Since it was first performed in 2005, a few dozen cases have been published in the literature, reporting impressive restorative ability and improved quality of life.[101] In many cases the oral soft and hard tissues are also damaged

by trauma and transplantation may include the jaws and dentition. Therefore, the role of the dentist is significant in surgical planning and follow-up, and is not limited just to dental clearance. Considering the mental status of the patient and limited intraoral access, compliance with oral hygiene should be stressed and hygiene aids adjusted to accommodate the altered anatomy.[102]

Presurgical evaluation of the donor dentition should be performed not only for treatment planning, but also to reduce the risk of odontogenic infection post transplantation.[68] The outcome of this complex surgical procedure relies on close attention to occlusal relationships, temporomandibular joint (TMJ) dynamics, dental health, and the intraoral donor–recipient soft tissue interface.[103] Maxillofacial prosthodontists may be involved in the fabrication of a prosthetic donor mask for the donor's remains.[104]

Post-transplantation Considerations

The post-transplantation period can be divided into the immediate period, the stable period, and the chronic rejection period. The patient is most susceptible to both rejection and severe infection in the immediate post-transplantation period, which extends to when the transplanted organ is functioning appropriately. No elective dental procedures should be performed at this time of immunosuppression, and emergency treatment should only be provided after consultation with the transplantation physician.

The stable post-transplantation period begins when the transplanted organ is functioning appropriately. It is during this time that problems relating to immunosuppression, and side effects of immunosuppressive medications may become apparent. Dental treatment planning must consider these factors. This stage lasts for a variable amount of time (patients may remain stable for years) and is considered the best period for elective dental treatment.

Patients post solid organ transplant may have numerous dental needs.[22] Considering immunosuppression, a dentoalveolar abscess may manifest atypically and a bacterial infection requires prompt antibiotic therapy. Culture and sensitivity testing are advised. It is extremely important to provide oral hygiene instruction and to discuss with the patient the importance of appropriate hygiene to prevent oral infections.

Antibiotic prophylaxis prior to dental treatment may be proposed by the transplantation physician. This is an empiric decision and the indications and contraindications require further evidence-based research. Considerations that support the use of antibiotic prophylaxis include the nature and degree of immunosuppression, history of infections, signs of rejection, and nature of the dental procedure (e.g., invasiveness). Given the nature of HSCT, immunosuppression is deeper and if an urgent dental procedure is needed, antibiotic prophylaxis will be required when the patient is neutropenic. If antibiotic prophylaxis is indicated, a consultation with an infectious disease specialist may help determine the best antibiotic(s) in light of the post-transplant oral flora and concurrent antibiotic exposure.

Corticosteroid supplementation may also be required due to adrenal suppression associated with high-dose chronic corticosteroid use. This supplementation may help avoid cardiovascular collapse during stressful procedures including general anesthesia, and it is recommended when the stress of the procedure or the patient's perception of the stress (pain) of the procedure is increased. Some have questioned the need for supplementation for limited surgical procedures, such as removal of gingival overgrowth via gingivectomy under local anesthetic. Steroid supplement for limited dental procedures is not needed as long as the patient's medical and emotional status are stable.

Another consideration during the stable post-transplantation period involves medication interactions, as several antirejection immunosuppressive agents interact with medications that a dentist may prescribe. For example, CSA levels are affected by anti-inflammatory drugs such as ibuprofen and naproxen, antifungals such as itraconazole and fluconazole, and antibiotics such as clarithromycin. Reviewing potential interactions between the transplant patient's medications and those the dentist intends to prescribe is prudent. As the development and use of immunosuppressive agents evolve, dentists will need to be familiar with the newer medications and the potential risk of interactions with medications used in dentistry.

It may be reasonable to offer dental implant–based restorations considering the improved life expectancy of transplant recipients. A clinical trial demonstrated that dental implants are feasible in patients post liver transplant.[105] Patients were followed for 8 years while treated with immunosuppressive agents. More research is warranted, however, in order to understand the determinants of complication-free implant procedures in patients post liver transplant, or any other solid organ transplant.

Given the high risk for malignant transformation in patients post HSCT and post solid organ transplant, any abnormal tissue should be assessed closely, including delayed postextraction wound healing.

Many HSCT and solid organ transplant patients are treated with bone-modifying agents, such as bisphosphonates and denosumab for steroid-induced osteoporosis. Additionally, multiple myeloma patients are treated with intravenous bisphosphonates. Dentists will find this information in the medical chart or by consultation with the medical team, and the protocols for patients at risk for osteonecrosis of the jaws should be followed.

The stable post-transplantation period ends when a grafted organ begins to fail, heralding the chronic rejection period. Laboratory parameters indicating organ failure and biopsies are used to confirm this process. For dentists, these patients are often the most complicated to manage, since the organ is failing and the patient remains immunosuppressed. Only emergency dental treatment is indicated, and the transplantation physician's input is essential. The treating dentist must consider the ramifications of organ failure and make appropriate provisions.

In addition to the above general post-transplant considerations for dental management, there are specific considerations for face transplant and HSCT. Face transplantation may affect the dentition, occlusion, and sensation.[68] Mucosal constriction due to trauma and surgical scarring may limit mouth opening and impair oral hygiene, function, and access for dental treatment. Mouth opening may also be restricted due to TMJ trauma or dysfunction. There may be malocclusion in patients with a grafted maxilla. There may be palatal fistulas at suture points of the donor and the recipient.[97] Acute episodes of graft rejection are common within the first year of transplantation.[106] Although mucosal graft rejection is not as common as seen in the skin, it has been described in the literature and the dentist should be able to identify it.[41]

The engraftment phase post HSCT may take place within 2–3 weeks; however, the immune reconstitution may take months. Therefore, decisions about the timing of routine dental care are individualized, and will range from a few months post transplant to a year. In the interim the patient should be encouraged to maintain good self-care practices.

There is controversy in the literature regarding changes in the oral microbiome following HSCT, with most studies showing a shift toward enterococci and increases in *Klebsiella pneumoniae*, *Pseudomonas* spp., *Candida albicans*, staphylococci, and enteric bacilli.[11,107,108] Variation between studies may be partially explained by different types of transplant, the intensity of the conditioning regimen, the chemotherapy courses, and the timing of bacterial testing. Patients have shown some benefit from chlorhexidine mouth rinses during this period.

Oral complications of HSCT and cGVHD may affect dental treatment. If dry mouth develops, preventive measures should be applied, including moistening the mouth, fluoridation, and frequent dental evaluations. Toothpastes need to address the gingival and mucosal sensitivity associated with cGVHD, and therefore neutral pH, mint-free toothpastes are advised.

Gingivitis and gingival recession post HSCT are common.[23] cGVHD may affect the gingivae and periodontium, and atrophy may result in thin gingival tissues. There is anecdotal evidence linking gingival recession to cGVHD.[109]

cGVHD may manifest as a progressive limitation of mouth opening, and dental treatment may be challenging. If there is limited access to the posterior teeth, extractions may be the only treatment option, and may need to be performed by an oral surgeon.

Considering that the conditioning regimen for HSCT includes cytotoxic agents and occasionally TBI, maxillofacial and dental developmental abnormalities affect about 55%–63% of pediatric HSCT patients.[64] These abnormalities include agenesis, root hypoplasia with arrested root development and shortened or tapered V-shaped roots, and smaller than normal or crowded teeth. These affect the occlusion and increase the tendency for dental decay. Orthodontic treatment may be considered to realign the occlusion.

SUMMARY

There are a wide range of oral considerations in the transplantation population. Dentists need a strong knowledge base in medicine and oncology to minimize adverse outcomes from provision of oral healthcare. As this challenging population grows, so does the need for qualified dental practitioners to treat them. Advances in the treatment of transplant patients pose new challenges in dental diagnosis and management, in particular with the nature and timing of dental procedures and preventive protocols.

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21

Infectious Diseases

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Bacterial, viral, and fungal infections are some of the most common chief complaints in oral medicine. When encountering an oral infection, we believe that practitioners should always ask the following questions. First, does the patient have an infection? Microbiology specimens collected from a nonsterile site in the oropharynx will likely be positive; these results may simply represent normal colonization. Clinicians should carefully consider the organism involved and the clinical scenario that prompted the specimen to be collected. Second, does this infection represent a localized or disseminated process? Some patients with unusual oral fungal infections (e.g., *Cryptococcus* and histoplasmosis) may warrant further investigation for disseminated disease. Third, does this infection provide any clues to associated conditions or underlying medical comorbidities that require further evaluation? Oral manifestations of sexually transmitted infections (STIs), such as gonorrhea, chlamydia, and syphilis, should prompt clinicians to evaluate for other STIs. Episodes of thrush with any clear underlying cause and/or evidence of Kaposi sarcoma (KS) should prompt clinicians to consider whether the patient may have HIV. Although such questions seem rudimentary, we strongly encourage oral medicine clinicians to consider developing and following a consistent approach, such as the one outlined above, with each patient. Such approaches minimize the chance of inappropriately treating colonization and missing a potentially disseminated infection or an important associated condition.

One of the newest frontiers in oral medicine is understanding how bacteria and viruses interact with hosts. These interactions are complex, and research in this field has several titles; some examples include the microbiome, virome, and resistome. For simplicity, we will provide a little more detail about the microbiome, which is currently the best-studied field. The human oral microbiome contains over 1000 bacterial and fungal species.[1,2] Furthermore, the oral microbiome varies by location in the mouth. For example, different combinations of organisms exist in the gingival sulcus, tongue, cheek, and palate.[2–4]

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

The oral microbiome plays a very important role in oral and systemic health by inhibiting pathogen colonization (colonization resistance), antagonizing pathogens by producing antimicrobial substances such as bacteriocin, and developing local and systemic immunity. Furthermore, oral bacteria can reduce nitrate to nitrite, which after gastric absorption becomes nitric oxide, which is essential for the vascular health.[5,6] The human oral microbiome also harbors a diverse range of antimicrobial resistance genes (ARGs), including resistance to tetracycline, amoxicillin, and gentamicin, which may act as a significant reservoir for ARGs to be transferred to pathogenic microbes.[7]

BACTERIAL INFECTIONS

Bacterial infections are common causes of concern in oral medicine. Several different infections are addressed in other chapters, such as angular cheilitis in Chapter 4 on "Red and White Lesions of the Oral Mucosa"; necrotizing gingivitis (NG) in Chapter 3 on "Ulcerative, Vesicular, and Bullous Lesions"; and bacterial sialadenitis in Chapter 9 on "Salivary Gland Diseases." The remainder of this chapter will focus on atypical bacterial infections, such as STIs, actinomycosis, and tuberculosis (TB).

The term sexually transmitted infections is now preferred over the historical term sexually transmitted diseases. This newer terminology acknowledges that some patients may have asymptomatic infections, which are still important and require treatment. The four most common bacterial STIs are chlamydia, gonorrhea, syphilis, and trichomoniasis (technically protozoa). These four organisms cause 376 million new infections in the world per year. In response, the World Health Assembly has led ambitious efforts to end STIs by 2030.[8]

Chlamydia

Epidemiology

Chlamydia is caused by *Chlamydia trachomatis*, an obligate intracellular gram-negative bacterium. Chlamydia is the most reported STI worldwide. Based on prevalence data from 2009 to 2016, the estimated pooled global prevalence of chlamydia in 15–49-year-old women is 3.8% (95% uncertainty interval [UI]: 3.3–4.5) and in men 2.7% (95% UI: 1.9–3.7).[9] In 2016, 403,807 cases of chlamydia were reported in 26 European Union (EU)/European Economic Area (EEA) member states, with an overall notification rate of 185 cases per 100,000 population.

Clinical Presentation

Patients acquire chlamydia via vaginal, anal, or oral sex with an infected partner. Chlamydia commonly causes genital infections in the cervix, urethra, or epididymis. Cervicitis is often asymptomatic in women. Urethritis manifests as pain or difficulty urinating, with or without cervical or penile discharge. Men who engage in receptive anal intercourse can also develop prostate infections.[10,11] Extragenital infections commonly present as pharyngitis and conjunctivitis.

In women, chlamydia infections can ascend to the fallopian tubes, ovaries, or uterus, causing pelvic inflammatory disease (PID). Left untreated, PID can lead to scarring, infertility, and ectopic pregnancies. Infections can also rarely ascend into the abdomen and cause liver abnormalities as well. Complications among males include infections of the epididymis and testes. Both male and female patients can also rarely develop a reactive arthritis.

Some *Chlamydia trachomatis* strains have an atypical presentation. Specifically, serovars (serologic variants) L1, L2, and L3 cause lymphogranuloma venereum (LGV), which manifests as genital ulcers with lymphadenopathy and requires different antibiotic management. LGV is managed differently than standard *Chlamydia trachomatis* infections and is more common in Africa, India, Southeast Asia, and the Caribbean. However, outbreaks have been reported outside of these areas. Due to breakdown of the mucosal barriers, patients with chlamydia are at greater risk of acquiring other STIs, including HIV.[10,11]

Diagnosis

Chlamydia trachomatis is generally diagnosed via nucleic acid amplification testing (NAAT) on cervical, ureteral, oral, rectal, or urinary specimens.[10]

Treatment

Doxycycline and azithromycin are the preferred antibiotics to treat *Chlamydia trachomatis* infections. Antibiotic recommendations between these two agents are often dictated by national and regional susceptibility data. For example, the British Association for Sexual Health and HIV (BASHH) recommends doxycycline.[10] However, either agent is considered acceptable in the United States.[12]

Oral/Facial Considerations

Patients can also acquire chlamydia infections in the oropharynx via oral sex. Oral infections are often asymptomatic, but fever and lymphadenopathy may occur. Tonsillar infections typically manifest as erythema with small punctate lesions. Lesions may also occur uncommonly in other locations in the mouth and are described as being erythematous, pustular, erosive, or ulcerated.[13]

Gonorrhea

Epidemiology

Gonorrhea is caused by *Neisseria gonorrhoeae*, a gram-negative bacterium. The 2016 global incidence of gonorrhea

was 0.9% (95% UI: 0.7–1.1) in women and 0.7% (95% UI: 0.5–1.1) in men. Among men and women aged 15–49 years, there were 87 million new cases of gonorrhea in 2016 globally.[8] In Europe, gonorrhea is more common in men, and 48% of all reported cases were in men who have sex with men (MSM). Gonorrhea is more common in younger individuals.[14] In the United States, recent trends demonstrate an increase in the incidence of gonorrhea.[15]

Clinical Presentation

Gonorrhea infects the same anatomic sites as chlamydia, and symptoms between the two infections overlap. For example, patients can also develop cervicitis, urethritis, epididymitis, conjunctivitis, and pharyngitis. Similarly, women can develop PID, ectopic pregnancy, and infertility as a complication. Gonorrhea can also be asymptomatic, like chlamydia. However, gonorrhea can manifest a disseminated infection, which classically involves the joints.

Diagnosis and Treatment

Like chlamydia, gonorrhea is diagnosed via NAAT. This can be performed in the urine and on swabs from the urethra, cervix, vagina, or oropharynx. Patients with suspected gonorrhea should be referred to a genitourinary medicine clinic for specimen collection, culture, partner notification, and treatment.[16] First-line therapy to treat gonorrhea is ceftriaxone. However, recent increases in antimicrobial resistance to ceftriaxone have been observed.[17] Like chlamydia, gonorrhea damages mucous membranes, which increases the risk of HIV and other STIs.[18,19]

Oral/Facial Considerations

Oropharyngeal gonorrhea is often asymptomatic.[20] When symptomatic, it can present with nonspecific multiple ulcers, fiery red oral mucosa, pseudomembrane, painful pharyngitis, atypical gingivitis, and lymphadenopathy (see Figures 21-1 and 21-2).

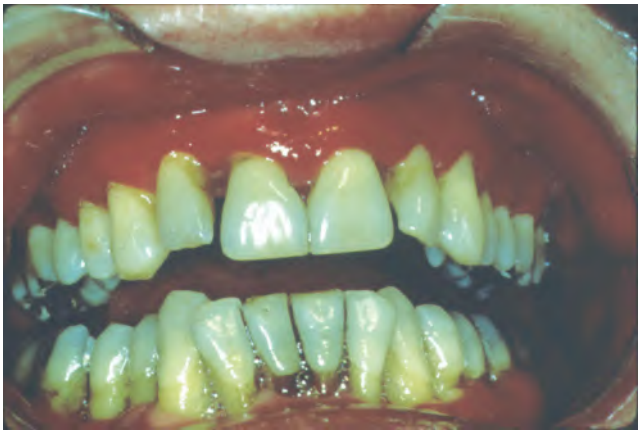

Figure 21-1 Gonococcal gingivitis.

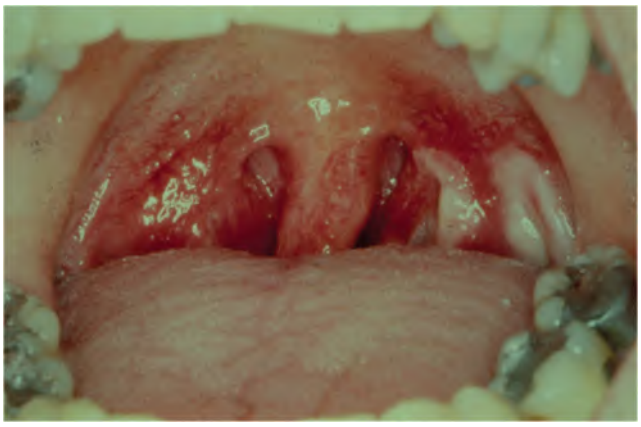

Figure 21-2 Gonorrhea: pseudomembranes in the fauces. *Source*: Courtesy of Dr. Stephen Challacombe.

Syphilis

Epidemiology

Syphilis is caused by *Treponema pallidum,* a spirochete bacterium. It is acquired primarily through sexual contact. The estimated pooled global prevalence of syphilis is 0.5% (95% UI: 0.4–0.6) for both men and women, with regional values ranging from 0.1% to 1.6 %.[8] Like chlamydia and gonorrhea, syphilis is more common in younger individuals and MSM. Recent trends suggest that the incidence of syphilis has been increasing.[21,22]

Clinical Presentation

Syphilis is often considered the "great imitator" because patients can present in a variety of ways. In general, active syphilis infections can be divided into primary, secondary, and tertiary stages. Primary infections occur generally within the first month of exposure. Patients will classically present with a painless genital ulcer (chancre) at the initial inoculation site (Figure 21-3A, B). However, some patients may not develop or recall developing an ulcer. In secondary syphilis, patients develop a disseminated infection, which manifests as a diffuse rash (classically on the palms and soles).[22–24] In tertiary syphilis, which is very rare, patients classically present with a cardiovascular infection or a syphilitic gumma. Cardiovascular manifestations classically are aneurysms. However, patients may also present with aortic regurgitation and coronary ostial occlusive disease.[25]

Syphilis may be passed from an infected mother to her child during pregnancy, causing congenital syphilis. Patients with congenital syphilis may have deformed bones, severe anemia, jaundice, hepatomegaly, splenomegaly, blindness, deafness, meningitis, or skin rash.[22–24]

Diagnosis

Syphilis is diagnosed using a combination of treponemal and nontreponemal tests (Figure 21-3C, D). Consultation with a physician is strongly considered when interpreting

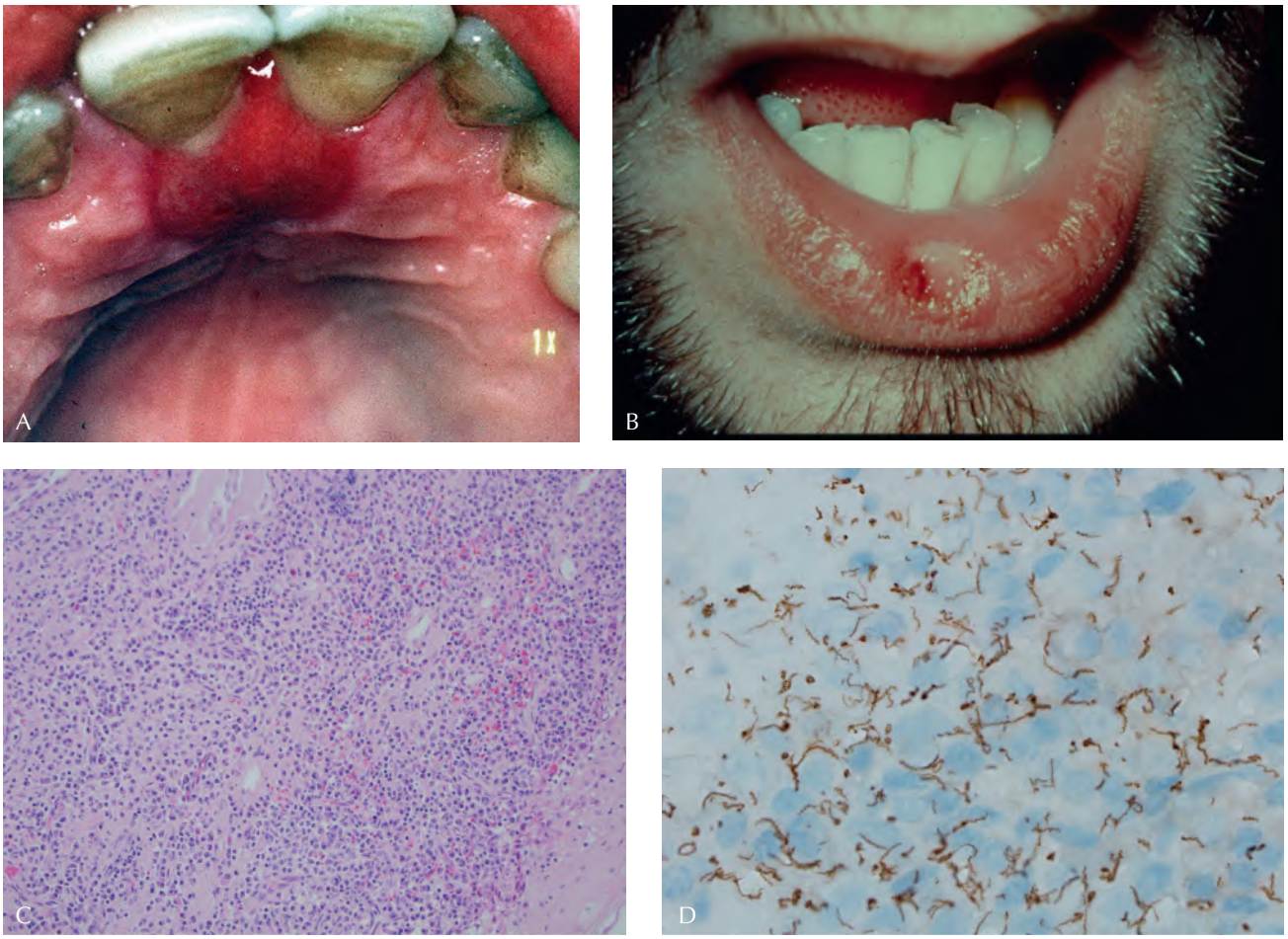

Figure 21-3 (A) Syphilitic patch on the hard palate of primary syphilis. Reproduced with permission from Alam F, Argiriadou AS, Hodgson TA, Kumar N, Porter SR. Primary syphilis remains a cause of oral ulceration. *Br Dent J*. 2000;189:352–354. (B) Primary syphilis: irregular ulceration of the lower lip. *Source*: Courtesy of Dr Stephen Challacombe. (C) H&E and an immunohistochemical stain for a syphilitic oral lesion. The H&E shows polyclonal plasmacytosis, which can be found in syphilis. (D) The immunohistochemical stain shows spirochetes.

syphilis diagnostic test results. Treponemal antibody tests will remain positive after patients receive treatment. Quantitative nontreponemal tests should decline after treatment, but the results may never return to negative.[24]

Treatment

Syphilis is treated based on the duration and severity of disease. Consultation with a physician is strongly recommended prior to initiating syphilis treatment. In general, early syphilis (<1 year) is usually treated with a single dose of intramuscular (IM) benzathine penicillin G. Late syphilis (>1 year) is treated with IM penicillin once weekly for three consecutive weeks. Patients who have evidence of neurologic involvement (neurosyphilis) require intravenous (IV) penicillin for 10–14 days.[26]

Oral/Facial Considerations

Approximately 15% of patients with primary syphilis will present with highly infectious intraoral chancres, as either solitary or multiple lesions. Chancres typically present as painless, sometimes necrotic, ulcers with a rolled border and associated lymphadenopathy. Common sites of occurrence are the lips, tongue, palate, and nostrils. Lymphadenopathy commonly accompanies these lesions. As mentioned previously, the lesions heal spontaneously without treatment.[13] If there is a clinical concern for syphilis, patients should still seek medical care, even if the lesion has healed.

Typical oral lesions in secondary syphilis are described as a mucous patch, which presents as thickened whitish plaque affecting the oral mucosa. Necrosis and sloughing may occur. Commonly affected sites include the tongue, lip, buccal mucosa, and palate. These patients may also present with mucosal ulcers and erythematous macular lesions.[27] Syphilis-related gummas classically occur on the hard palate, but may also occur on the soft palate and the alveolus. A gumma begins as a swelling, which eventually ulcerates and then goes through repeated phases of healing and breakdown. Bone destruction of the hard palate may occur with

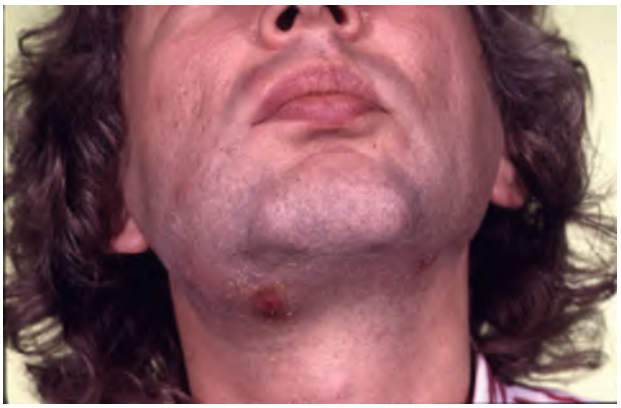

Figure 21-4 Sublingual swelling and discharge from actinomycosis. *Source*: Courtesy of Dr Stephen Challacombe.

palatal perforation and, in some cases, oral nasal fistula. A gumma may erode into underlying blood vessels.[28]

Infants with congenital syphilis may also develop orofacial malformations, including Hutchinson's notched incisors, mulberry-shaped molar teeth, corneal keratitis, frontal bossing, saddle nose, and hard palate defects.[23]

Actinomycosis

Epidemiology

Actinomyces spp. naturally colonize the oropharynx (Figure 21-4), gastrointestinal tract, and pelvis in humans. Infections with *Actinomyces* spp. (called actinomycosis) rarely occur. The annual incidence is fewer than 1/300,000 per year. The incidence of actinomycosis has thought to have declined due to an overall improvement in oral hygiene over time. The male:female ratio is between 1.5:1 and 3:1.[29–32] Risk factors for acquiring actinomycosis include poor oral hygiene; local tissue damage by trauma, recent surgery, or irradiation; intrauterine devices (IUDs) for pelvic infections; and diabetes.[32,33]

Clinical Presentation

Actinomycosis commonly occurs in the orocervical (50%), thoracic (20%), and abdominal pelvic regions (20%). Over time, the infection will slowly erode through facial planes and develop chronic sinus tracts. Most infections are thought to occur due to muscular injury, allowing the bacteria to penetrate into body areas and grow in an anaerobic environment.[31,32]

Diagnosis

The differential diagnosis for actinomycosis includes cancer, TB, appendicitis, pneumonia, and PID. Most cases are diagnosed when a biopsy reveals classic gram-positive filamentous bacteria with or without "sulfur granules." However, the term sulfur granules is a misnomer. These granules are actually composed of a protein–polysaccharide complex and are mineralized by host calcium. Although difficult to achieve, actinomycosis can sometimes be cultured under anaerobic conditions. Other diagnostic approaches, such as immunohistologic, polymerase chain reaction (PCR), and serologic techniques, are generally not commercially available.[31,32]

Treatment

Actinomycosis is treated with a prolonged course of systemic antibiotics with or without surgery. Penicillin-based antibiotics (penicillin, amoxicillin, amoxicillin-clavulanate) are preferred.[31,32]

Consultation with an infectious diseases doctor is recommended to assist with antibiotic monitoring and treatment duration.

Oral/Facial Considerations

Orocervicofacial actinomycosis classically develops after dental manipulation, oral trauma, or in the setting of poor oral hygiene. Patients generally present soft tissue swelling, in or near the mandible. However, infections also occur in the check, chin, and maxilla. Like other forms of actinomycosis, patients will slowly develop sinus tracts with or without sulfur granules. Complications include myositis and osteomyelitis. The differential diagnosis includes malignancies and granulomatous diseases.[30,31,34]

Tuberculosis

Epidemiology and Clinical Presentation

TB is caused by *Mycobacterium tuberculosis*. Individuals acquire TB by inhaling airborne particles from other infected people. Once inhaled, TB proliferates inside of alveolar macrophages. When enough macrophages are recruited, local complexes of enlarged lymph nodes can be seen on a chest radiograph. These are called "ghon complexes," where TB can remain dormant for decades. Patients who initially develop TB (also called the primary disease stage) generally have fevers and other nonspecific symptoms. Once primary TB symptoms resolve, patients are considered to have latent TB. This means that they likely still have residual TB bacteria, which can reactivate at some point later in life.

Only about 10% of patients will develop reactivation TB later in life. When reactivated, TB generally presents with a chronic respiratory infection with cough, fevers, night sweats, and weight loss. Patients classically have an upper lobe cavitary lesion on chest radiographs. However, TB can reactivate anywhere in the body.[35,36]

TB is a major global health problem. Worldwide there were 10.0 million (range: 9.0–11.1 million) individuals

Table 21-1 Risk factors for tuberculosis (TB).

Risk Factor	Comment
HIV	Persons living with HIV are 15–22 times more likely to develop TB than persons without HIV In 2018, 251,000 death from HIV-associated TB were reported
Diabetes	A person with diabetes has a 2–3 times higher risk for acquiring TB Diabetes can worsen the course of TB and TB can worsen glycemia control for people with diabetes
Malnutrition	Malnutrition increases the risk of TB and TB can lead to malnutrition
Tobacco	Tobacco smoking increases the risk of TB by 2–3-fold and is associated with poor TB treatment results
Harmful use of alcohol	Harmful use of alcohol increases the risk of TB 3-fold and it is also a strong risk factor for poor TB treatment adherence

Source: World Health Organization, 2020.

diagnosed with TB in 2018.[37] Although the incidence of TB remains stable in most nations, multidrug- and extensively drug-resistant TB remains a growing public health concern.[38]

Medical risk factors for TB include HIV, diabetes, malnutrition, smoking, and alcohol use (Table 21-1).[39–41] Societal risk factors for TB include overcrowding, poorly ventilated housing, malnutrition, smoking, stress, social deprivation, and poor social capital.[42] In industrialized countries, most cases occur in minority groups, particularly recent immigrants from countries with high TB endemicity.

Latent TB can be diagnosed two different ways. The most common approach is tuberculin skin testing on the forearm with purified protein derivative (PPD), a mycobacterial antigen. Interferon gamma release assays (IGRA), are blood tests that detects sensitization to *Mycobacterium tuberculosis*.[35,38,43] In the United States, the Centers for Disease Control (CDC) recommend screening certain high-risk populations for latent TB (Table 21-2). Patients with a positive screening test should be evaluated for the presence of active TB disease. However, a negative latent TB screening test should not be used to rule out active TB.

Diagnosis

Active TB is generally diagnosed via culture of the bacterium. To improve the test sensitivity, serial sampling of respiratory tract specimens is common. Special acid-fact bacteria (AFB) stains can aid in diagnosis, but these are nonspecific. Newer PCR-based platforms are often used in conjunction with standard AFB stains and culture.[35,38,43]

Table 21-2 High-risk groups recommended for purified protein derivative testing.

1) People who have spent time with someone who has tuberculosis (TB) disease
2) People with HIV infection or another medical problem that weakens the immune system
3) People who have symptoms for TB disease (fever, night sweats, cough, and weight loss)
4) People from a country where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia)
5) People who live or work somewhere in the United States where TB disease is more common (homeless shelters, prison or jails, some nursing homes)
6) People who use illegal drugs

Source: Centers for Disease Control, 2018.

Table 21-3 Treatment for tuberculosis (TB) infection.

Category	Medication Regimens*
Latent TB	Isoniazid monotherapy daily for 9 months Rifampicin-based treatment daily for 4 months Isoniazid and rifapentine weekly for 3 months Isoniazid and rifampicin-based treatment daily for 3 months
Active TB without central nervous system involvement	Isoniazid (with or without pyridoxine), rifampicin, pyrazinamide, and ethambutol for 2 months, then isoniazid (with or without pyridoxine) and rifampicin for a further 4 months
Active TB with central nervous system involvement	Isoniazid (with or without pyridoxine), rifampicin, pyrazinamide, and ethambutol for 2 months, then isoniazid (with or without pyridoxine) and rifampicin for a further 10 months

* Modify the treatment regimen according to drug susceptibility testing. Management of these cases should be done by a multidisciplinary team including TB team, Infectious Disease, Microbiology, and Oral Medicine. Some treatment regimens may vary based on local guidelines.
Source: National Institute for Health and Care Excellence. *Tuberculosis*. Updated September 2019. www.nice.org.uk/guidance/ng33.

Treatment

Patients with latent TB receive different treatment regimens than those with active disease. Those with latent TB require a prolonged course of one or two antibiotics. They are often screened for underlying medical problems prior to initiating therapy.[44] Patients with active TB generally receive a combination of four different antibiotics when they start treatment (Table 21-3). Adherence to antibiotics is frequently monitored via directly observed therapy. After a couple of weeks of therapy, treatment regimens are generally modified based on adherence, tolerability, and clinical response. The usual course of therapy is six to nine months and involves several drug regimens (Table 21-3).[44] However, antibiotic selection

and treatment regimens may vary if patients have known or suspected drug-resistant TB. Drug-resistant TB is more challenging to treat and may require IV antibiotics.[38,45] Patients with multidrug- or extensively drug-resistant TB require often require complex antibiotic treatment regimens for a prolonged period of time. Despite these intensive regimens, patients with extensively drug-resistant TB frequently have poor outcomes.[44,46]

Public health efforts to combat TB include educational interventions, vaccination, screening high-risk patients, contact tracing, and early diagnosis and treatment.[44] Bacillus Calmette-Guerin (BCG) is a live vaccine made from a weakened strain of *Mycobacterium bovis*. BCG continues to be administered in many developing countries, but it is not routinely used in the United States and is rarely administered in the United Kingdom. Contact tracing to identify and screen close contacts of recently diagnosed TB patients is considered an important part of combating TB. In hospital settings, patients are placed in airborne isolation, with precautions such as N95 respirators to reduce TB transmission to healthcare workers.[44,47,48]

Oral/Facial Considerations

Oral manifestations may occur in up to 3% of patients with long-term active TB. Lesions may occur in the oral tissues and the neck lymph nodes. The latter is termed scrofula. Oral lesions can be found in various soft tissues and very occasionally in supporting bone. Oral lesions may be primary or secondary to pulmonary tuberculosis. Stellate ulcers affecting the dorsal surface of the tongue are a classic presentation. A TB oral ulcer usually has undermined edges and a granulating floor, but the clinical picture can be variable. Lesions may also affect the gingiva, floor of the mouth, palate, lips, and buccal mucosa (Figure 21-5). Macroglossia, parotitis, intraosseous lesions, periauricular swelling, and trismus have been reported in some oral TB cases.[49]

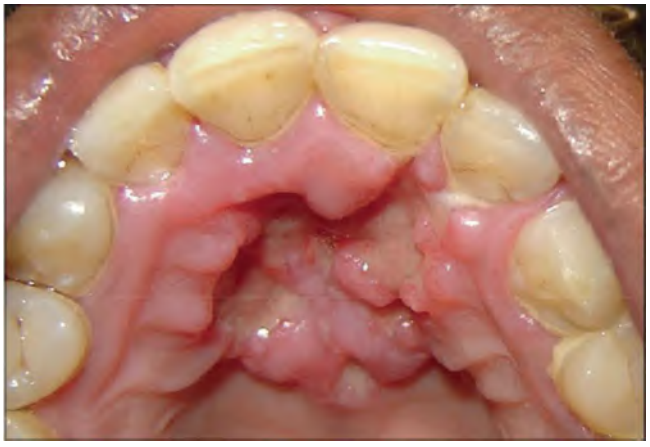

Figure 21-5 Palatal tuberculosis ulcer in a patient with pulmonary tuberculosis.

Standard fluid-resistant masks likely provide some protection against TB for dental healthcare personnel. However, routine dental care should be deferred in patients who remain contagious with TB. In the United States, patients with TB are no longer considered contagious if they meet the following criteria: (1) three consecutive AFB sputum smears collected at 8–24-hour intervals; (2) compliant with an adequate treatment regimen for at least two weeks; and (3) improvement in symptoms. If oral care must be provided for a patient who is contagious with TB, patients should be placed in a negative-pressure room and healthcare workers should wear an N95-, FFP2-, or FFP3-level respirator. If an oral medicine provider plans on treating a patient with active TB, it is strongly recommended to consult with an infection prevention specialist or hospital epidemiologist, who may be able to share clinic- or hospital-specific protocols. TB protocols may recommend scheduling the patient as the last case of the day to minimize exposure to other patients and staff. TB patients should be instructed to wear a surgical mask while in patient care areas. High-efficiency particulate air (HEPA) filters may also be used to filter out TB. Consultation with the multidisciplinary TB team is strongly recommended in these cases.[44,47,50]

FUNGAL INFECTIONS

Candidiasis, which accounts for the vast majority of oral fungal infections, is described in detail as part of Chapter 4, "Red and White Lesions of the Oral Mucosa." Other fungal infections can be divided into those that generally infect immunocompromised or immunocompetent patients. *Aspergillus*, *Rhizopus* (mucromycosis), *Fusarium*, and *Cryptococcus* generally arise as opportunistic infections in immunocompromised patients. If a patient is diagnosed with one of these infections, oral medicine providers should consider referring or screening them for an underlying immunodeficiency. Other fungi such as *Coccidioides immitis*, *Histoplasma capulatum*, *Blastomyces dermatitis*, *Paracoccidioides brasiliensis*, and dermatophytes also infect immunocompetent subjects.[51,52] A thorough history and physical examination should be performed for patients with atypical fungal pathogens, as these pathogens can also cause disseminated infections. Furthermore, oral medicine clinicians should strongly consider consultation from an infectious diseases specialist to assist with diagnosis and management of unusual oral fungal infections.

In this section we discuss less common fungal infections, which can have oral manifestations including the following:

- Common endemic mycoses in the Americas include blastomycosis, histoplasmosis, and paracoccidioidomycosis in

Central and South America. Primary infection occurs through the respiratory tract, with dissemination to the skin and viscera via hematogenous and lymphatic spread.[52]

- Nonendemic fungal infections include aspergillosis, cryptococcosis, and mucormycosis. This group of fungal infections often presents as solitary oral ulcers. However, reactive epithelial and pseudoepitheliomatous hyperplasia may lead to heaped-up, exophytic mucosal lesions potentially misinterpreted as squamous cell carcinoma (SCC). Early diagnosis and treatment of mucormycosis is crucial to prevent local invasion and disfigurement of the oral and maxillofacial tissues.[51]

Blastomycosis

Epidemiology

Blastomyces dermatitidis is a dimorphic fungus that can grow either as a yeast or in mycelial form. Most cases occur in the United States and Canada. It is a normal inhabitant of soil and agricultural and construction workers are at highest risk of infection, particularly those working in the Mississippi and Ohio River Valleys, around the Great Lakes, and near the St. Lawrence Seaway. This geographic distribution has led to the designation by some as "North American blastomycosis." However, cases of blastomycosis infections have also been described in Mexico and Central and South America.[53]

In the United States, the yearly incidence is about 1–2 cases per 100,000 population; Wisconsin has the highest rates in the US with between 10 and 40 cases per 100,000 population. Some 1,216 blastomycosis-related deaths occurred during 1990–2010 in the United States, with an overall age-adjusted mortality rate of 0.21 per 1 million person-years.[54]

Clinical Presentation

Both immunocompetent and immunocompromised individuals can develop blastomycosis. Risk factors for blastomycosis include outdoor activities such as forestry work, hunting, and camping. Immunosuppressed patients, such as HIV patients, solid organ transplant patients, and those receiving tumor necrosis factor (TNF) antagonists, are also at higher risk for developing blastomycosis.[54,55]

Patients with blastomycosis generally present with pneumonia due to inhaling fungal spores. Immunocompetent patients frequently present with indolent symptoms such as malaise, low-grade fever, and mild cough. If the infection goes untreated, the signs and symptoms may progress to include dyspnea, weight loss, and production of blood-tinged sputum.[56] Some patients develop acute respiratory distress syndrome, with a mortality rate of up to 50–89%.[55] Disseminated blastomycosis occurs more frequently in immunosuppressed individuals such as those with HIV or organ transplant recipients.[56]

Most blastomycosis infections are localized to the lung, but 25–40% will develop extrapulmonary infection leading to cutaneous, osteoarticular, genitourinary, or central nervous system (CNS) disease. This is usually due to the spread of organisms from the pulmonary lesions through the lymphatic system. The skin lesions (typically on exposed surfaces) start as subcutaneous nodules, slowly progressing to well-circumscribed indurated ulcers.[57]

Diagnosis

The differential diagnosis for blastomycosis is broad and includes other fungal pathogens and atypical bacteria, including tuberculosis. Blastomycosis can be diagnosed using real-time nucleic acid detection, antibody identification through enzyme immunoassay, antigen detection, biopsy, and culture on Sabouraud agar.[58–60] Blastomycosis characteristically has broad-based unipolar budding yeast forms on histology.[58] Clinically, it is diagnosed via a positive blastomycosis antibody in the setting of a compatible clinical presentation, including appropriate epidemiologic risk factors.

Treatment

All cases of blastomycosis should be treated to prevent extrapulmonary dissemination.[56] Mild to moderate pulmonary disease can be treated with azole-based antifungals. Itraconzole for up to 12 months is a common regimen. Moderately severe pulmonary disease should be initially treated with lipid formulation of amphotericin B (AmB) for one to two weeks or until improvement is noted. This is followed by oral itraconazole therapy. Serum levels of itraconazole should be determined after two weeks from the treatment to ensure adequate drug exposure.[56,61] Table 21-4 details the treatment recommendation for disseminated and CNS blastomycosis according to the current guidelines.[56]

Oral/Facial Considerations

Oral lesions are rarely the primary site of infection. Indeed, most cases of oral involvement demonstrate concomitant pulmonary lesions on chest radiographs. The most common appearance of the oral lesions of blastomycosis is a nonspecific, painless ulcer with indurated borders and verrucous mucosal hyperplasia, often mistaken for SCC.[62–64]

Histoplasmosis

Epidemiology

Histoplasmosis is caused by the fungus *Histoplasma capsulatum*, a dimorphic fungus with both yeast and mycelial forms. Infection results from inhaling dust contaminated with droppings, particularly from infected birds or bats.

Table 21-4 Blastomycosis treatments.

Pulmonary	**Moderate to severe** Lipid formulation amphotericin B (AmB) 3–5 mg/kg per day *or* AmB deoxycholate 0.7–1 mg/kg per day for 1–2 weeks or until improvement *then* Itraconazole 200 mg 3 times per day for 3 days, *then* 200 mg twice per day for a total of 6–12 months **Mild** Itraconazole 200 mg 3 times per day for 3 days, *then* 200 mg once or twice per day for a total of 6–12 months Itraconazole serum level should be done 2 weeks after treatment
Disseminated	**Moderate to severe** Lipid formulation AmB 3–5 mg/kg per day *or* AmB deoxycholate 0.7–1 mg/kg per day for 1–2 weeks or until improvement *then* Itraconazole 200 mg 3 times per day for 3 days, *then* 200 mg twice per day for at least 12 months **Mild** Itraconazole 200 mg 3 times per day for 3 days, *then* 200 mg once or twice per day for a total of 6–12 months **Osteoarticular blastomycosis** At least 12 months of antifungal therapy Itraconazole serum level should be done 2 weeks after treatment
Central nervous system	Lipid formulation AmB 5 mg/kg per day for 4–6 weeks *then* Fluconazole 800 mg per day, *or* itraconazole 200 mg 2–3 times per day, *or* voriconazole 200–400 mg twice per day for at least 12 months or until resolution of cerebrospinal fluid abnormalities Itraconazole serum level should be done 2 weeks after treatment
Immunosuppressed patients	Lipid formulation AmB 3–5 mg/kg per day *or* AmB deoxycholate 0.7–1 mg/kg per day for 1–2 weeks or until improvement *then* Itraconazole 200 mg 3 times per day for 3 days, *then* 200 mg twice per day for at least 12 months Itraconazole serum level should be done 2 weeks after treatment Lifelong suppressive therapy with oral itraconazole 200 mg per day if immunosuppression cannot be reversed

Additional medication notes: Amphotericin is nicknamed "amphoterrible" because it is associated with substantial side effects, including chills, nausea, vomiting, and electrolyte disturbances. Caution should be employed when using amphotericin with ganciclovir or valganciclovir. Itraconazole is generally well tolerated. Itraconazole can cause QT prolongation and is also a CYP3A4 inhibitor.
Consider reviewing potential drug interactions prior to prescribing any new medications.
Management of these cases should be done by a multidisciplinary team, including Infectious Disease, Microbiology, and Oral Medicine.
Source: Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;46(12):1801–1812.

An African form of this infection is caused by a larger yeast, *H. huboisii*, which is considered a variant of *H. capsulatum*.[65]

Histoplasmosis is the most common systemic fungal infection in the United States and presents primarily as pulmonary disease; in endemic areas such as the Mississippi and

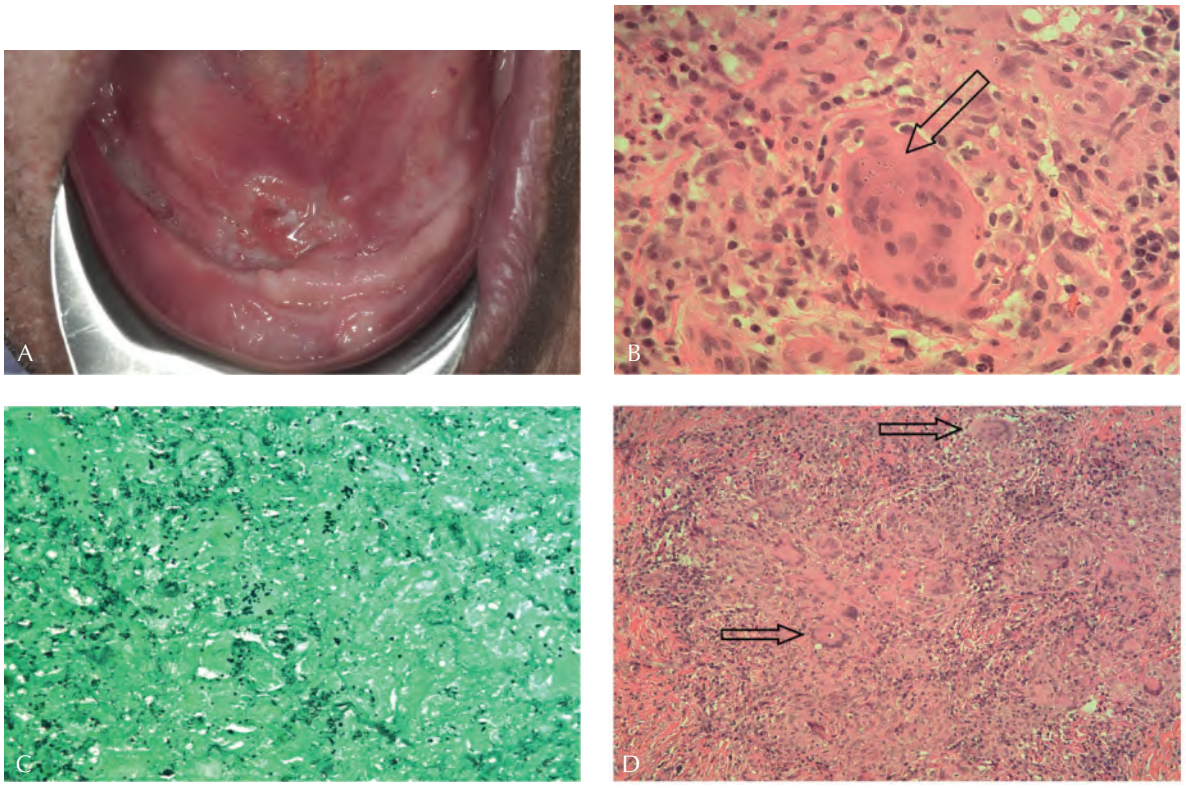

Figure 21-6 (A) Histoplasmosis. (B) H&E staining (20×) shows a giant cell with numerous small round fungal organisms. (C) Gomori methenamine silver staining shows the fungal organisms stained black. (D) H&E staining (10×) shows granulomas with multinucleated giant cells. Courtesy of Dr. Ross Kerr.

Ohio River valleys, serologic evidence of previous infection may be found in 60–90% of the population. The incidence of histoplasmosis in adults aged 65 years and older was calculated as 3.4 cases per 100,000 population in the United States in general and 6.1 cases per 100,000 population in the Midwest. Outbreaks of occupationally acquired histoplasmosis have been reported among agricultural workers and laborers in endemic areas. Particularly at risk are individuals working with aerosolized topsoil or dust with bat or bird droppings.[65,66] Symptomatic histoplasmosis is more prevalent among people with immunosuppression. In Latin America, histoplasmosis is one of the most common opportunistic infections among HIV-infected individuals, leading to a 30% mortality rate.[65]

Clinical Presentation

In many cases primary infection is mild, manifesting as a self-limiting pulmonary disease that heals to leave mediastinal fibrosis and calcification, which can be identified on chest radiographs. In a small percentage of cases, progressive disease results in cavitation of the lung and widespread dissemination of the organism. Common locations for disseminated disease include the liver, spleen, adrenal glands, intestinal tract, and meninges. Patients with the disseminated form of the disease may develop anemia and leukopenia secondary to bone marrow involvement. Immunosuppressed or myelosuppressed patients are more likely to develop a severe disseminated form of the disease, and disseminated histoplasmosis is one of the infections that characterize AIDS.[65]

Diagnosis

Antigen detection via enzyme immunoassay can be performed in blood, urine, cerebrospinal fluid (CSF), and bronchoalveolar lavage (BAL) samples for rapid diagnosis of disseminated and acute pulmonary histoplasmosis. Clinically, urine histoplasma antigen is commonly used to diagnose invasive infections. Of note is that chronic pulmonary disease can have a low antigen burden, making the test insensitive.[67] Other possible diagnostic methods are antibody detection via immunodiffusion, and identification of histoplasma DNA via various PCR techniques. It is important to note that there is some cross-reactivity with *Blastomyces* infections.[68,69] In disseminated disease, peripheral blood smear may show the organisms engulfed by white blood cells. Sputum fungal culture and bronchoalveolar lavage can also be performed. Histopathology of the involved tissue can demonstrate the characteristic 2–4 μm diameter budding yeast cells (Figure 21-6).[70]

Treatment

Immunocompromised patients with disseminated histoplasmosis are generally treated with liposomal AmB and/or itraconazole. Patients with moderate to severe disease should initially receive amphotericin-based therapy. Alternatives to amphotericin and itraconazole include voriconazole and posaconazole.[71] Fluconazole should not be used, as it is not thought to be active against *H. capsulatum*. Antifungal selection and duration are based on a combination of factors including duration of symptoms and severity of presentation.[70] Corticosteroids, such as methylprednisolone during the first one to two weeks of the antifungal therapy, should be considered for patients who develop respiratory complications including hypoxema and significant respiratory distress.[70,72] Antifungal therapies and steroids have limited benefit for patents with fibrosing mediastinitis, a rare complication from histoplasmosis.

Oral/Facial Considerations

Oral manifestations of histoplasmosis are most common in patients with disseminated disease (66%). Oral manifestations of histoplasmosis are also common in subacute (31%) and acute (19%) infections.[52] However, primary oral involvement has also been reported. In one study, 3% of HIV-positive patients in an endemic area had oral lesions of histoplasmosis, and oral histoplasmosis had been reported as the first sign of AIDS.[73] Patients diagnosed with histoplasmosis should be tested for HIV infection and evaluated for disseminated disease.

Oral mucosal lesions begin as an area of erythema that becomes a papule and eventually forms a painful, granulomatous-appearing ulcer, often with an indurated border, on the gingiva, palate, or tongue. Some lesions can appear fungating. Cervical lymphadenopathy may also be present. The differential diagnosis of oral histoplasmosis includes SCC, other chronic fungal infections, and lymphoma. Ulcers present for weeks or months may represent other lesions of infectious etiology (other deep fungal, mycobacterial, treponemal, or parasitic), traumatic ulcerative granuloma, SCC, lymphoma, or other malignancy.[74]

Paracoccidioidomycosis

Epidemiology

Paracoccidioidomycosis is caused by *Paracoccidioidomycosis brasiliensis*. About 15,000 cases of paracoccidioidomycosis have been reported since 1930. It occurs in South and Central America; however, the majority of cases have been reported in Brazil.[75,76] *Paracoccidioidomycosis brasiliensis* infections are thought to be due to inhalation of spores from colonized soil and/or wood. Like other dimorphic fungi, paracoccidioidomycosis has both a mold and a yeast form.

Clinical Presentation

Similar to tuberculosis, most patients are asymptomatic after an initial infection. The organism can be dormant within lymph nodes for many years and then reactivate later in life. The disease affects primarily men (15:1 ratio men,women) over 30 years of age. When reactivated, the infection involves primarily the oral mucosa, the lungs, and the skin. Other potential sites of involvement are the gastrointestinal tract, the liver, the bones, the CNS, and the male genitourinary tract. In severe cases, signs and symptoms may mimic those of TB and include fever, weight loss, and productive cough with bloody sputum. Paracoccidioidomycosis can occur in immunocompetent and immunocompromised individuals; however, symptoms usually get worse more quickly in immunocompromised patients such as HIV-infected subjects.[77]

Diagnosis

Paracoccidioidomycosis can be identified by direct examination of sputum or biopsy from ulcers or pus draining from lymph nodes. A 10% potassium hydroxide (KOH) preparation should be used to observe paracoccidioidomycosis yeasts. The microorganism is then isolated in culture.[78–80]

Treatment

The preferred agents to treat paracoccidioidomycosis are azole antifungals, with itraconazole being preferred due to lower relapse rates. AmB is generally avoided in patients with mild or moderate illness due to higher toxicity.[81] Trimethoprim/sulfamethoxazole (cotrimoxazole) is also used for the treatment of paracoccidioidomycosis.[82] However, patients treated with cotrimoxazole generally require a longer treatment duration.

Oral/Facial Considerations

Oral mucosal lesions are a prominent feature of paracoccidioidomycosis and present as ulcers; oral complaints are often the presenting symptoms of these patients. Lesions of the gingival mucosa are most common, followed by the palate and lips. The lesions are frequently painful. Ulcerative lesions with crusting also occur on the facial skin and may infiltrate subcutaneously.[83]

Aspergillosis

Epidemiology

Organisms of the fungal genus *Aspergillus* cause multiple infections, including invasive aspergillosis, chronic necrotizing aspergillosis, allergic bronchopulmonary aspergillosis, and aspergilloma. Commonly found in soil, on plants, in decaying organic matter, and in dust from houses and building materials, *Aspergillus* spp. represent a variety of

organisms that are ubiquitous in the environment. Colonization of the respiratory tract in humans occurs. Thus, oral medicine clinicians should carefully consider whether a positive *Aspergillus* culture is compatible with an infection or simply colonization. *A. fumigatus* complex is generally considered the most pathogenic species.

The epidemiology of *Aspergillus* infections varies based on disease presentation. Immunocompromised patients, particularly those receiving chemotherapy, classically present with a fungal pneumonia from *Aspergillus*. In addition to the lungs, invasive aspergillosis can involve the CNS, bones, eyes, heart, and kidneys.[84,85]

Clinical Presentation

There are many risk factors that are strongly associated with acquiring invasive aspergillosis, such as allogeneic stem-cell transplantation, prolonged severe neutropenia (>10 days), immunosuppressive therapy, chronic granulomatous disease, solid organ transplantation, acute leukemia, aplastic anemia, and preexisting cavity (aspergilloma). Moreover, other risk factors weakly associated with increased risk for acquiring invasive aspergillosis include advanced chronic lung disease, primary immunodeficiency, HIV infection, diabetes, cystic fibrosis, severe burns, malnutrition, multiple myeloma, immunocompromised patients, age >55 years, and smoking.[84]

Diagnosis

Invasive aspergillosis has a high mortality rate; therefore, early diagnosis is crucial to improve prognosis. The diagnosis of invasive aspergillosis is still challenging, as microscopy and culture of lower respiratory specimens have low sensitivity. It is also often difficult to obtain tissue for histopathology from critically ill patients. Invasive diagnostic procedures such as bronchoscopy with BAL and/or biopsy, percutaneous transthoracic computed tomography (CT)-guided needle aspiration, and video-assisted thoracoscopic biopsy can show the characteristic angular, dichotomously branching, septate hyphae. Culture confirmation to distinguish *Aspergillus* spp. from other fungi with similar morphologic features is important (Figure 21-7). False-negative results occur with specimens obtained from unaffected areas. Thus, lack of positive fungal smear or culture does not rule out the diagnosis. Tissue biopsy for histopathology is the historical gold standard method for diagnosing invasive aspergillosis. PCR based on amplification of *Aspergillus*-specific fungal gene is promising, but often not commercially available.[84] Serum biomarkers such as *Aspergillus* galactomannan antigen and serum beta-D-glucan are frequently used in clinical settings. However, false-positive galactomannan results are common in patients who receive certain types of IV antibiotics. Serial galactomannan values improve the sensitivity and specificity of the test; however, the sensitivity is low in those receiving antifungal drugs as prophylaxis. Serum immunoglobulin (Ig) G antibodies to *Aspergillus* can be used to diagnose aspergilloma.[84]

Figure 21-7 *Aspergillus niger* spores. Source: spoonielife.wordpress.com. Reproduced with permission.

Due to the limitations of available diagnostic tests, immunocompromised patients frequently receive empiric treatment for invasive aspergillosis if they have a compatible syndrome (e.g., a malignancy on immunosuppressive chemotherapy and evidence of fungal pneumonia on CT scan), regardless of test results.

Prophylaxis

Patients with hematologic malignancies commonly may receive antifungal prophylaxis. The choice of agent is based on a variety of factors, including anticipated duration of immunosuppression, antineoplastic regimen, and local epidemiology.

Treatment

Aspergillus spp. are usually sensitive to the following antifungal drugs: AmB; azoles such as voriconazole, posaconazole, and isavuconazole; or echinocandins such as caspofungin and micafungin. Voriconazole is the preferred agent to treat invasive *Aspergillus* infections. Combination therapy with multiple antifungal agents is occasionally administered. Reversal of the underlying immune deficiency or surgical resection of the infected focus may also be combined with antifungal therapy to treat invasive aspergillosis.[84,86,87]

Oral/Facial Considerations

Oral colonization with *Aspergillus* spp. is common, although oral infections are rare. Oral medicine clinicians may also see allergy-mediated disease, such as allergic pulmonary aspergillosis and allergic fungal rhinosinusitis. These conditions are best managed by referral to medical providers, such as pulmonary specialists and otolaryngology to aid in diagnosis and management. Therapy may include corticosteroids and surgical debridement; antifungal agents are sometimes adjunctive treatments.[85,86]

Cryptococcosis

Epidemiology

Cryptococcosis is a worldwide infection that develops after fungal spores are inhaled from soil contaminated from bird droppings, primarily with two species, *Cryptococcus neoformans* and *C. gattii*. The infection is common in immunocompromised patients with one of the following underlying conditions: AIDS, steroid exposure, transplantation, liver disease, malignancy, and sarcoidosis.

The incidence is particularly high in HIV patients, with an estimated 220,000 cases of cryptococcal meningitis occurring worldwide each year resulting in nearly 181,000 deaths. Most cryptococcal meningitis cases occur in sub-Saharan Africa.

Clinical Presentation

The clinical presentation of cryptococcal infections is variable. Patients may have an insidious presentation with months of fatigue, lethargy, and memory loss. However, other patients may have an acute illness with sudden onset of fevers and headaches. Meningoencephalitis and meningitis are two of the most dreaded complications. Symptoms include fever, headache, lethargy, and mental changes and can lead to permanent neurologic damage.[88,89]

Diagnosis

Cryptococcosis can be diagnosed via microscopic examination, culture of tissue or body fluids, PCR, or serologic testing. Cryptococcal antigen testing of the blood CSF is a rapid test that is highly sensitive and specific for invasive infections.[90,91]

Treatment

In resource-limited settings with a high prevalence of cryptococcal meningitis and no access to cryptococcal antigen screening, primary prophylaxis with itraconazole or fluconazole may be effective in HIV-positive patients with a CD4 count of <100 cells/μL. Treatment of an active cryptococcal infection depends on many factors, such as the site of involvement, the immune status of the host, and the disease severity. Consultation with an infectious diseases physician is strongly recommended for patients with severe cryptococcal infections, particularly those with CNS involvement. AmB with or without flucytosine is the mainstay of therapy. Furthermore, close monitoring and CSF pressure during treatment may be required. Flucytosine is sometimes added to AmB to improve clearance of CSF cryptococcosis. Less severe infections are treated with fluconazole or itraconazole. Fluconazole is generally preferred due to superior tolerability and absorption. Treatment requires long courses of medication of at least six months or longer. Lifelong maintenance therapy may be required in patients with cryptococcal meningoencephalitis.[89,90,92]

Oral/Facial Considerations

Oral lesions of cryptococcosis may occur in patients with disseminated disease and immunosuppression. They have been described as ulcers and tumor-like nodules occurring on the gingiva and tongue (Figures 21-8 and 21-9).[91,93]

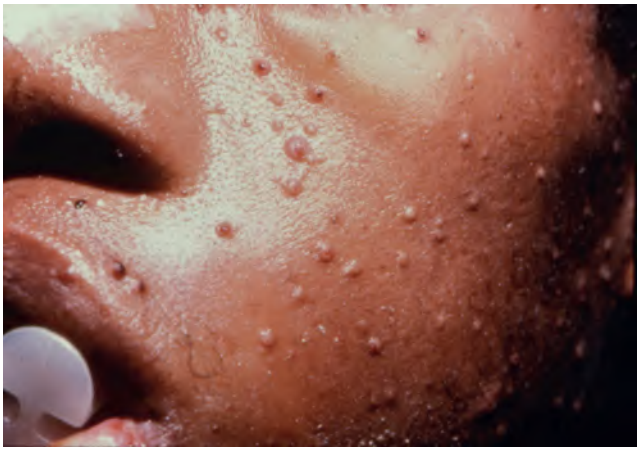

Figure 21-8 Cryptococcus lesions on the face.

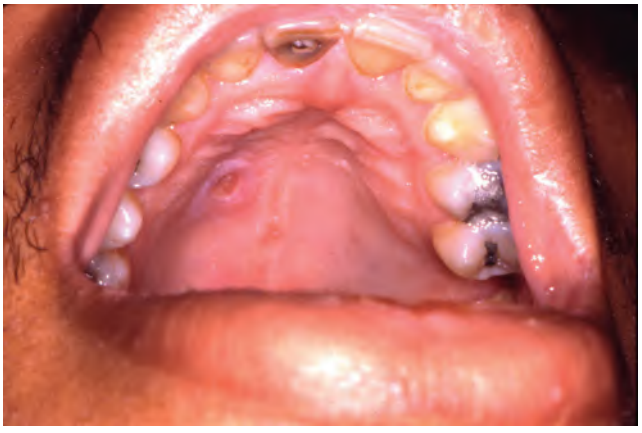

Figure 21-9 Cryptococcus lesion on the palate.

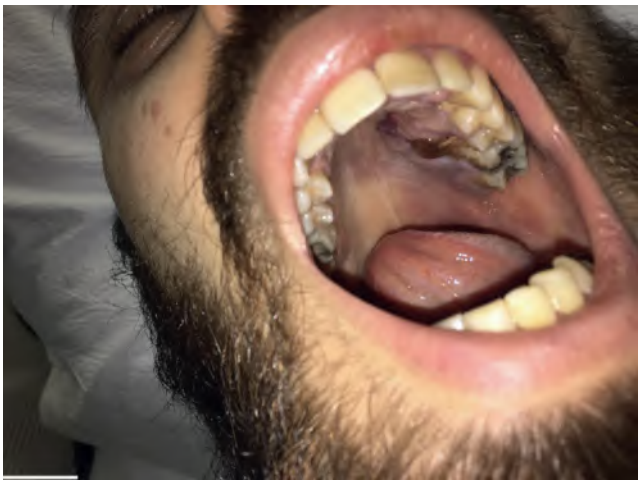

Figure 21-10 Mucormycosis in a patient with acute myelogenous leukemia. Courtesy of Dr. Katherine France, DMD, MBE.

Mucormycosis

Epidemiology

The term mucormycosis describes infections caused by the class of fungi known as the mucorales. Mucorales include *Rhizopus*, *Mucor*, and *Lichtheimia* (formerly *Absidia*).[94] The term "zygomycosis" has also been used for these infections. These organisms are typically found in the soil and decaying organic matter. These fungi are highly pathogenic when identified in a sterile site. However, in nonsterile sites they can be cultured from the human nose, throat, and oral cavity of healthy asymptomatic individuals. Infection classically occurs in patients with decreased host resistance (Figure 21-10), such as those with diabetic ketoacidosis, hematologic malignancies, solid organ or bone marrow transplants, history of corticosteroid therapy, graft-versus-host disease, patients with severe trauma or burns, and patients on deferoxamine therapy. Premature neonates are also considered vulnerable for acquiring the disease.[95–97]

Clinical Presentation

Mucormycosis is characterized by arterial invasion and a fulminant course, frequently resulting in death. The hallmark of infection is the formation of emboli, with resulting necrosis of involved tissue. Mucormycosis may present as a pulmonary, sinus, rhinocerebral, skin, or disseminated infection. The three most common forms of mucormycosis are rhino-orbiti-cerebral in diabetics, pulmonary in patients with hematologic malignancies or transplants, and infections from direct tissue inoculation related to combat or natural disasters.[95,98,99]

Treatment

The judicious use of immunosuppressants like corticosteroids, and adequate control of diabetes, may help in reducing the risk of infection with mucormycosis. Additionally, the use of rooms equipped with HEPA filters and the use of masks for patients with severe immunosuppression are possible preventative measures. Posaconazole is used as a secondary preventative measure in patients expected to continuing to be immunosuppressed after completing the therapy for mucormycosis.[95]

Diagnosis

Early diagnosis is essential for improved survival and reduced morbidity from extension and dissemination of disease. Negative cultures do not rule out mucormycosis because the fungus is frequently difficult to culture; instead, a biopsy for culture and direct examination should be performed. The histopathology shows necrosis and nonseptate hyphae, which are best demonstrated by a periodic acid–Schiff stain or the methenamine silver stain. Necrosis and occlusion of vessels are also frequently present. Newer techniques of identification include the use of PCR; however, this is not generally commercially available.[100]

Treatment

First-line therapy consists of a combination of aggressive surgical debridement and antifungal therapy. Although there are no randomized controlled trials, liposomal AmB is considered the drug of choice. Second-line treatment includes azoles, specifically posaconazole and isavuconazole. Echinocandins, such as caspofungin, are also sometimes used in combination with other antifungals.[95,101–103] The mortality rate is 50–100% in spite of therapy.[94]

Oral/Facial Considerations

The rhinomaxillary form of the disease, a variant of the rhinocerebral form, begins with the inhalation of the fungus. The fungus invades blood vessels, causing direct tissue toxicity, thrombosis, and ischemia. The fungus may spread from the oral and nasal region to the brain, causing death in a high percentage of cases. The most common symptoms of the rhinomaxillary form include proptosis, loss of vision, nasal discharge, sinusitis, and palatal necrosis.[103]

The most common oral manifestation of mucormycosis is ulceration of the palate, which results from necrosis due to invasion of a palatal vessel. The lesion is characteristically large, deep, and may lead to exposure of underlying bone. Ulcers from mucormycosis have also been reported on the gingiva, lip, and alveolar ridge. The differential diagnosis for oral mucormycosis is broad. Solitary mucosal ulcers of several weeks' and months' duration may represent lesions of other infectious etiology, traumatic ulcerative granuloma, SCC, lymphoma, or other malignancy. The initial manifestation of the disease may be confused with pain from an odontogenic infection or conventional bacterial maxillary sinusitis. More advanced disease with ulcer and palatal

perforation may suggest an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (e.g., Wegener granulomatosis).[98,103]

VIRAL DISEASES

Viruses are unique since they need a host cell to survive, unlike bacteria and fungi. Viruses can cause acute, chronic, and latent infections. Viruses can also be associated with malignancies, either via chronic inflammation or DNA damage. The most relevant viruses to the orofacial region include the families *Herpesviridae* and *Papillomaviridae*. However, there several other systemic viral infections that can present with oral and orofacial manifestations (Table 21-5). The majority of viral infections affecting the orofacial region are self-limiting in otherwise healthy individuals, while atypical presentations with systemic complications are more likely to occur in immunocompromised hosts.[106]

Transmission of viruses in a clinical setting from patient to dental healthcare personnel (DHCP) can be reduced by following simple steps. First, all DHCPs should receive routine vaccines for viral illnesses, including hepatitis B. DHCPs should always follow standard infection control procedures when caring for patients. Third, DHCPs should report any occupational exposures and follow local postexposure prophylaxis guidelines to minimize the chance of acquiring a viral infection from a patient. Appropriate diagnosis of oral viral infections is critical, especially to distinguish it from other infections, as some of them may well be malignant or have the potential to turn sinister.

Herpes Group of Viruses

The herpes group of the *Herpesviridae* family includes eight DNA viruses in three subclasses as alpha, beta, and gamma herpes viruses. Alpha herpes viruses include the herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), and varicella-zoster virus (VZV, HHV-3). Beta herpes viruses are cytomegalovirus (CMV, HHV-5), human herpesvirus-6 (HHV-6), and human herpesvirus-7 (HHV-7). Gamma herpes viruses consist of Epstein–Barr virus (EBV, HHV-4) and human herpesvirus-8 (Kaposi sarcoma herpes virus or KSHV, HHV-8).[107–110]

Alpha Herpes Viruses

Herpes Simplex Virus

HSV-1 generally affects the areas above the waistline and HSV-2 mainly causes genital lesions or lesions below the waistline. However, HSV-1 and -2 can affect either area, including the oral cavity (Figures 21-11 and 21-12). Primary infection of HSV-1 occurs either during childhood as gingivostomatitis or, if not exposed then, as pharyngotonsillitis in an adult. Latent reactivation of HSV-1 most commonly manifests as herpes labialis or a common cold sore. However, atypical forms and severe disseminated forms can occur in immunocompromised individuals. The main mode of transmission of HSV-1 is through contaminated saliva and transmission may occur via kissing a child.

Both primary and secondary or recrudescent infections are self-limiting. Immunosuppression, ultraviolet sun exposure, stress, changes in weather, especially the colder months, could all attribute to the initiation of herpes labialis. Primary infection is common among children and young adults, either asymptomatic or in the form of gingivostomatitis, following a usual course of fever, headache, irritability, loss of appetite, lethargy, hypersalivation, and cervical lymphadenopathy. The majority who suffer from recurrent herpes labialis may experience a prodromal phase of tingling, burning sensation, itching, mild pain, and/or fever. Clinically, single or multiple small erythematous papules that develop and form vesicles appear on either upper or lower lip, which may or may not coalesce. They will either rupture or may heal by crusting, leaving no noticeable scar in most circumstances. An atypical clinical presentation may occur in immunocompromised patients and the elderly. The healing may be prolonged with pain in the immunocompromised patient. There may be widespread vesicles with ulcerations involving large areas of the lip mucosa and adjacent cutaneous surfaces of the perioral region. The diagnosis is clinical. However, HSV DNA using molecular diagnostic techniques can be considered in atypical cases and immunocompromised patients. Antiviral treatment is often recommended for immunocompromised patients and in moderate to severe infection in otherwise healthy individuals. Oral or systemic acyclovir, 200 mg tablets, 5 times daily for 7 days or topical application of 5% acyclovir cream every 4 hours for 5 days is the recommended dose. Valacyclovir 1–2 mg twice daily may be used for prophylaxis.

Patients rarely present with ocular manifestations of HSV. Those with a history of HSV who are complaining of ocular pain or blurry vision should be referred to a physician for further evaluation. Patients may also present with neurologic complications from HSV infections. These include encephalitis, meningitis, and Bell's palsy. These symptoms can present with or without oropharyngeal disease.

Varicella-Zoster Virus

Children who acquire VZV develop chickenpox, a diffuse rash. Nonimmune adults who acquire VZV generally have a more severe presentation. Chickenpox can lead to orofacial lesions such as vesicles, especially over the facial skin and the oral mucosa, in addition to the cutaneous lesions of the

Table 21-5 Signs and symptoms of common orofacial manifestations of viral infections.

Orofacial Signs and Symptoms	Usual Site[†]	Disease Associated	Possible Virus Associated	Underlying Factors to Be Considered
Erythema, ulceration	Lips, oral mucosa	Erythema multiforme	HSV	Drug reactions?
Vesicle and/or bullae	Oral mucosa Gingivostomatitis in a child (primary) Pharyngotonsillitis in an adult (primary)	Herpes simplex infection	HSV-1	
	Lips	HSV—herpes labialis	HSV-1	Secondary infection Latent
	Localized depending on the affected nerve	Herpes zoster	VZV	Past history of chickenpox
	Oral mucosa, lips, hand, and foot	Hand, foot, and mouth disease	Enterovirus	
	Oral mucosa	Pemphigus vulgaris?	HSV? CMV?	
Ulceration	Lips	Erythema multiforme	HSV?	
	Oral mucosa	HIV disease	CMV	
	Oral mucosa	Behçet's syndrome	HSV? CMV?[104,105]	Immunodeficiency
	Soft palate/oropharynx	Herpangina	Coxsackie	
White patches	Lateral border of the tongue, (bilateral)	Hairy leukoplakia	EBV	HIV
White growths	Oral mucosa, perioral region	Papilloma	HPV	Other sexually transmitted diseases
Prodromal tingling sensation	Lips	Herpes simplex secondary infection	HSV	
	Face, oral mucosa, and lips (unilaterally)	Herpes zoster	VZV	Immunosuppression, HIV
Pain	Localized lip lesion	Herpes simplex	HSV	Immunosuppression
	Localized depending on nerve involved	Herpes zoster	VZV	Past history of chickenpox
Pigmentation (with or without swelling)	Palate, gingiva	Kaposi sarcoma	HHV-8	Immunosuppression, HIV
Swelling	Palate, oral mucosa	Lymphoma	EBV	Immunosuppression, HIV
	Salivary (parotid) glands	Mumps	Paramyxovirus	

[†] Oral mucosa = nonspecific site, include mucosa covering the entire oral cavity and tongue.
CMV, cytomegalovirus; EBV, Epstein–Barr virus; HHV, human herpesvirus; HPV, human papillomavirus; HSV, herpes simplex virus; VZV, varicella-zoster virus.
Source: Adapted from Nair RG, Salajegheh A, Itthagarun A, Pakneshan S, Brennan MT, Samaranayake LP. Orofacial viral infections—an update for clinicians. *Dent Update*. 2014;41(6):518–520, 522–524. doi:10.12968/denu.2014.41.6.518.

trunk. Vesicles normally do not survive in the oral cavity, leaving an erythematous papular lesion. If not secondarily infected with bacteria, the lesions on the facial skin will usually heal without scarring.

Once a person has had chickenpox, VZV remains latent in sensory ganglia until reactivation and replication, resulting in herpes zoster (shingles). Herpes zoster generally affects those above the age of 50 years or the immunocompromised. It is characterized by a unilateral, distinctive painful vesicular rash over a dermatome, corresponding to the sensory ganglion where the VZV is latent (Figures 21-13 and 21-14). Orofacial manifestations are within the ophthalmic, maxillary, and mandibular nerve distribution of the trigeminal nerve. Maxillary and mandibular distribution may lead to intraoral vesicles and painful ulcerations. Preventative therapy includes vaccination against VZV.

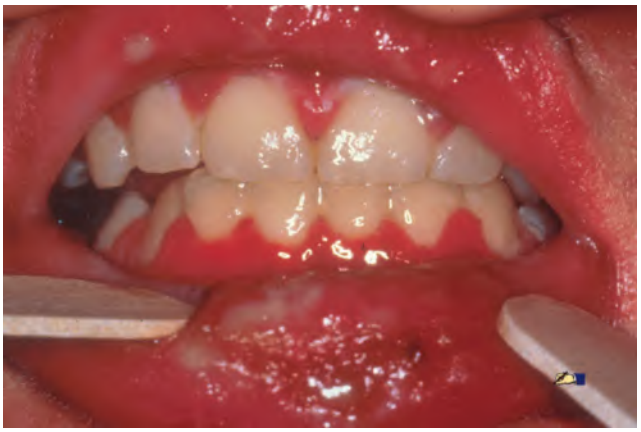

Figure 21-11 Primary herpes involving lips and gingiva.

Antiviral therapy is not indicated for chickenpox in otherwise healthy individuals, but may be considered in children 12 years or older, patients with chronic cutaneous or pulmonary disease, patients on short to intermittent courses of aerosol corticosteroids, and those on long-term salicylates. Treatment is based on symptomatic relief and antiviral drugs. In general, antiviral therapy reduces the acute symptoms of pain and malaise, limits the spread and duration of the skin lesions, and may prevent the development of postherpetic neuralgia and reduce ophthalmic complications. Strict hand washing, wearing of gloves, and vaccination of staff against VZV is important in prevention of transmission of herpes virus in the clinical setting.

Like HSV, VZV complications may be ocular, such as herpes zoster ophthalmicus and acute retinal necrosis. Other

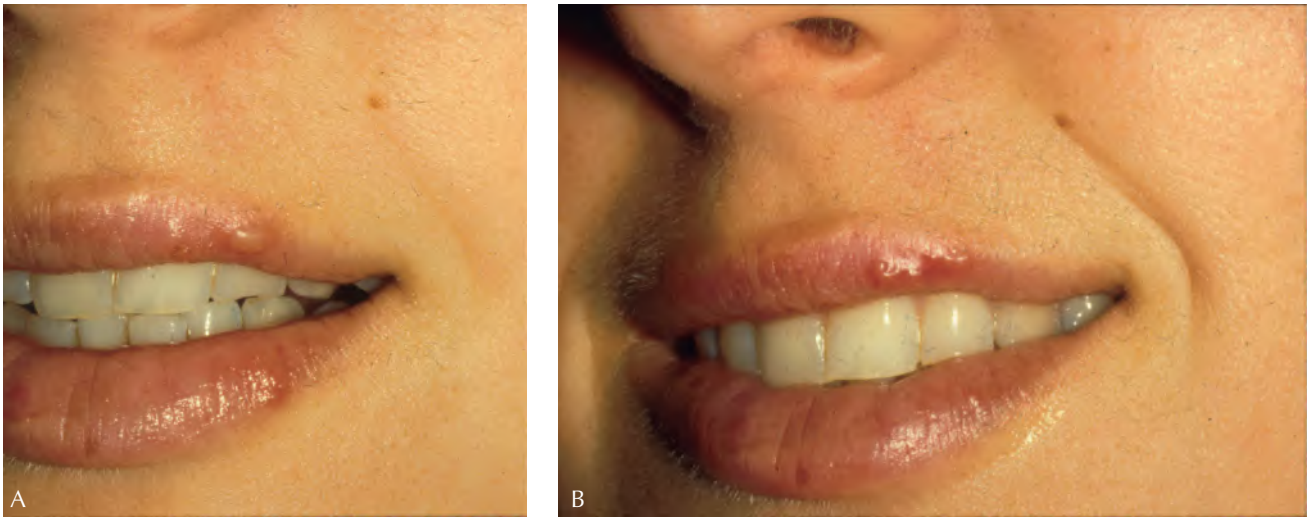

Figure 21-12 (A) Secondary herpes simplex lesions of the upper lip, one hour following prodrome stage. (B) The same herpetic lesions five hours following prodrome stage.

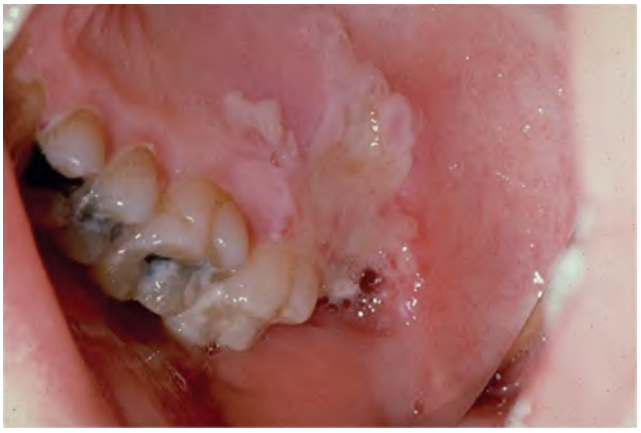

Figure 21-13 Herpes zoster.

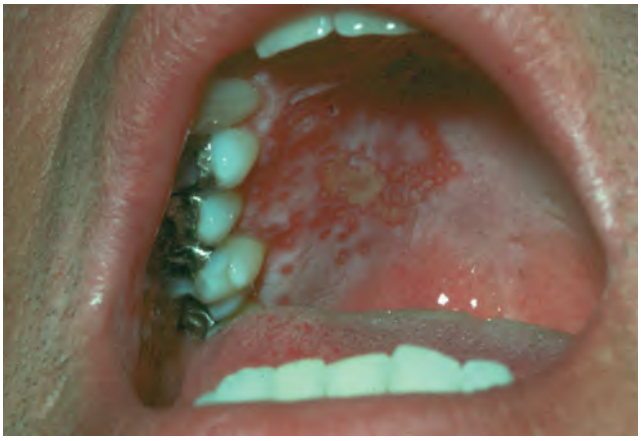

Figure 21-14 Herpes zoster.

neurologic complications include aseptic meningitis and encephalitis. Oral medicine providers should also be aware that altered taste and oral lesions can be a manifestation of Ramsay Hunt syndrome, a triage of ipsilateral facial paralysis, ear pain, and vesicles in the auricle. VZV infections can be treated with acyclovir and valacyclovir.

Beta Herpes Viruses

Cytomegalovirus

CMV is known to cause mononucleosis-like disease characterized by pharyngitis, lymphadenopathy, and fever in a healthy immunocompetent individual, requiring no specific therapy. In the orofacial region, the mononucleosis-like disease can present with palatal petechiae and submandibular lymphadenopathy. This virus also has been implicated in nonspecific oral ulcers (Figures 21-15 and 21-16) and salivary gland disease, especially in HIV-infected patients. CMV can be diagnosed via antibody testing, PCR, and histopathology.

CMV can reactivate in immunocompromised patients and in any body tissues. Common syndromes include retinitis, colitis, and pneumonitis. Patients may also present with a nonspecific CMV syndrome with evidence of fevers, myelosuppression, and CMV viremia.

CMV infections are generally treated with ganciclovir and valganciclovir.

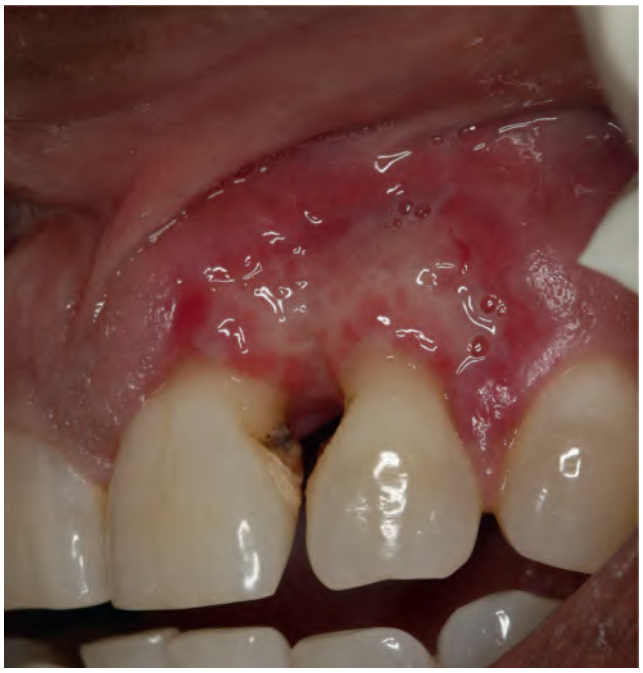

Figure 21-15 Cytomegalovirus lesion on the gingiva. Courtesy of Dr. Eric Stoopler, DMD.

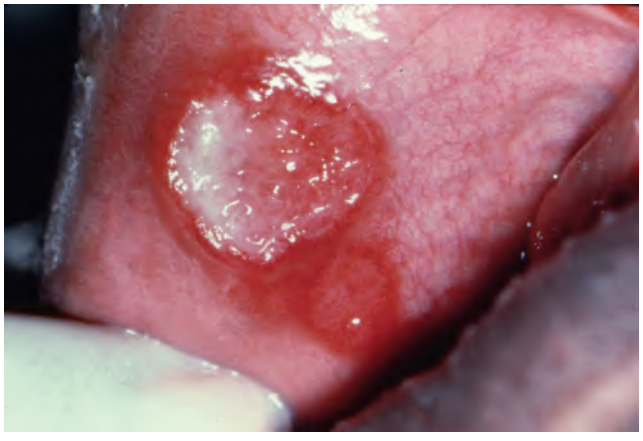

Figure 21-16 Cytomegalovirus lesion of the buccal mucosa.

Human Herpesvirus-6

HHV-6 is one of the first "ancient" human herpes viruses identified by molecular characterization. The main mode of viral transmission is through contaminated saliva. HHV-6 is present in the saliva of a large proportion of the healthy adult population. The primary infection is usually asymptomatic and commonly occurs during childhood by age 2 years. The clinical form is called exanthema subitum or roseala infantum (also called sixth disease). This biphasic disorder usually runs a benign course, causing fever, then a maculopapular rash on subsidence of fever at the end of the fourth febrile day. Uvulo–palatoglossal junction ulcers are useful early signs. The condition requires no antiviral treatment. Recent reports have emphasized the critical role of HHV-6 in the etiology of human oral SCC.[111] However, it is unclear whether the virus acts in combination with other carcinogens as a so-called co-carcinogen.

HHV-6 has been associated with several other conditions in immunocompromised patients, including encephalitis. It can be detected using PCR or paired serologic testing. HHV-6 can be treated with ganciclovir and foscarnet.

Human Herpesvirus-7

HHV-7 was first identified in 1990 and is closely related to HHV-6. It establishes latency in macrophages and T lymphocytes and reactivates frequently, with asymptomatic virus shedding through saliva. Most children acquire infection by the age of 3–4 years, and seronegative individuals are at risk of infection at any age. The spectrum of diseases caused by primary HHV-7 infection is similar to HHV-6, with milder clinical presentation. Diagnostic testing for HHV-7 is rarely performed. However, PCR and serologic testing platforms exist. Severe complications due to HHV-6 and -7 are treated with ganciclovir and its derivatives, foscarnet, or cidofovir.

Gamma Herpes Viruses

Epstein–Barr Virus

EBV can cause local or systemic infections and benign or malignant diseases of the orofacial region. They include

infectious mononucleosis or glandular fever, oral hairy leukoplakia (OHL), a white patch on the side of the tongue with a hairy appearance, and malignancies such as lymphomas (non-Hodgkin and Burkitt) and nasopharyngeal carcinoma.[112]

Clinical features of infectious mononucleosis are pharyngitis, cervical lymphadenopathy, generalized arthromyalgia, and associated fever and malaise. Classically, patients with EBV infections will develop a morbilliform rash following administration of amoxicillin. Symptomatic treatment is indicated such as antipyretics, analgesics, and anti-inflammatories, with no specific antiviral drug treatment. One important complication of mononucleosis includes splenic rupture. Patients with EBV who complain of significant abdominal pain should be referred for medical evaluation. OHL is a classic feature of immunosuppression, HIV disease, and iatrogenic immunosuppression such as cancer therapy. Clinically, lesions appear as white corrugated patches, commonly on the lateral border of the tongue and gingiva (Figure 21-17).

EBV-related lymphomas may present as a swelling and/or an ulcer in the oral cavity and orofacial region (Figure 21-18). Lymphomas and nasopharyngeal carcinomas need more aggressive cancer therapies, depending on the type and stage of the disease. Lymphomas generally manifest as painless anterior cervical lymphadenopathy.

Human Herpesvirus-8

HHV-8 is associated with KS, which is most commonly found in patients with HIV disease or AIDS. KS infection in non-HIV patients is rare and is classically associated with older males of Mediterranean decent. HHV-8 has been found in all the different types of KS affecting humans, hence it is known as Kaposi sarcoma herpes virus. KS seen in HIV disease or AIDS-associated KS is usually asymptomatic, with either purple or bluish macules or swellings affecting the orofacial skin and oral mucosae. However, KS lesions can occur anywhere in the body, including the lungs and other organs. In the oral cavity, the hard palate is the most common site, though other areas of the oral cavity could be involved. Management may include intralesional injections of cytotoxic drugs or sclerosing agents, and surgery is warranted only to restore esthetics such as the labial gingivae, for example.[113] Antiretroviral therapy (ART) has significantly improved the management of orofacial KS associated with AIDS. Systemic chemotherapy is used in patients with severe disease.

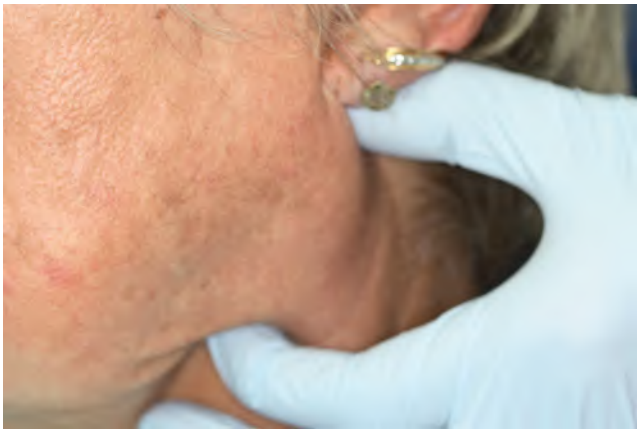

Figure 21-17 Lymphoma of the anterior cervical lymph nodes.

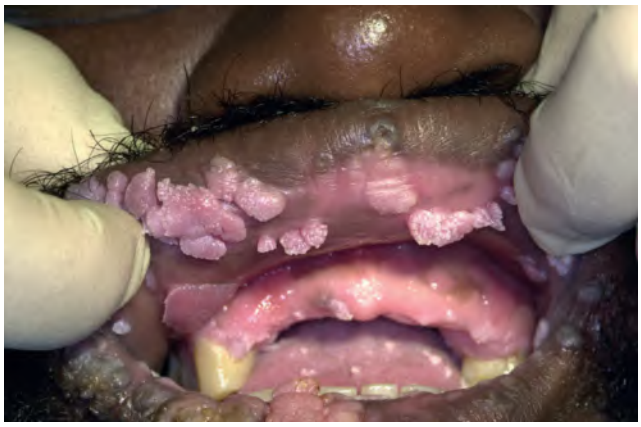

Figure 21-18 Human papilloma virus–related warts on the oral mucosa.

Human Papilloma Virus

The *Papillomaviridae* family is a group of double-stranded circular DNA viruses commonly found in the oral and oropharyngeal mucosa, tracheobronchial mucosa, and anogenital region. They are grouped into more than 100 types and HPV types 16 and 18 have been implicated in oral, oropharyngeal, and tonsillar carcinomas (Figures 21-19 and 21-20). More recently, there has been an increasing understanding of the risk factors of HPV in oropharyngeal cancers, especially the risk of orogenital sexual activity.

Orofacial manifestations of HPV are verruca vulgaris or the common wart on the perioral skin; oral papilloma of the oral mucosa; focal epithelial hyperplasia; and condyloma accuminatum, a sexually transmitted disease. Heck's disease or focal epithelial hyperplasia is a rare benign lesion attributed to subtypes 13 or 32 (Figure 21-21). Clinically, it presents as multiple white or mucosal-color papules or nodular lesions affecting the oral mucosae.

Management of HPV infection depends on the clinical presentation such as papilloma (Figure 21-22), typically using complete surgical excision and/or topical drug therapy. Laser and cryotherapy are not recommended due to lack of a tissue for histopathologic evaluation and a possible seeding of the

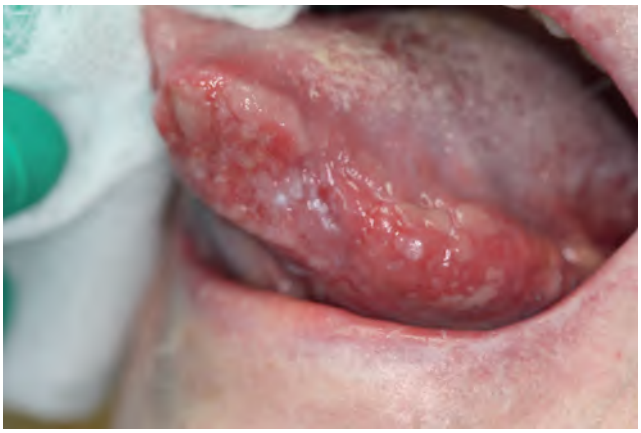

Figure 21-19 Squamous cell carcinoma of the tongue secondary to human papillomavirus with evidence of lichen planus.

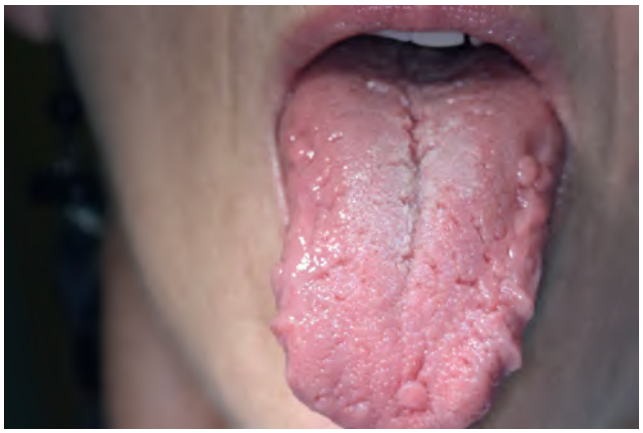

Figure 21-21 Heck's disease (human papillomavirus of the tongue).

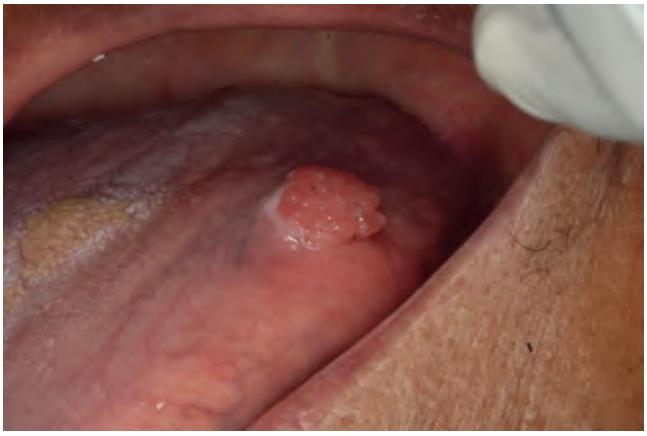

Figure 21-20 Squamous cell carcinoma of the tongue with a human papillomavirus-positive papillomatous growth.

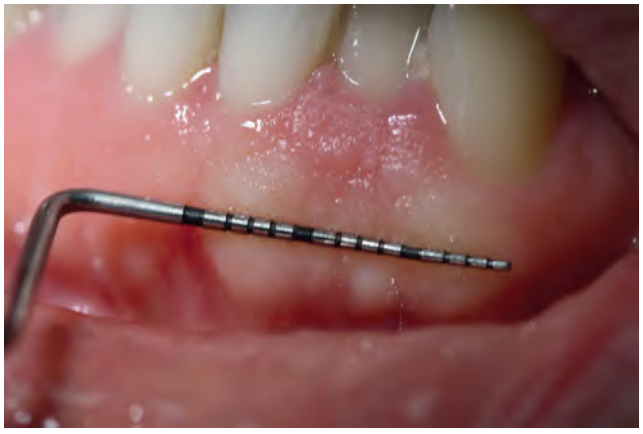

Figure 21-22 Papilloma on the gingiva.

lesion to the surrounding tissue in the process. HPV vaccines are currently available and have a clear role in preventing many anogenital cancers and conditions related to HPV infection. The effectiveness of HPV vaccines in preventing oral HPV infection and cancer is unknown. Studies are underway to evaluate the long-term efficacy of the vaccine against both anogenital and non-anogenital endpoints.[114,115]

Coxsackie Virus

Coxsackie virus causes hand, foot, and mouth disease (strain A16) and herpangina. These viruses can pass through the oral mucosa and small intestine and the regional lymph nodes. Clinical features of hand, foot, and mouth disease include a mild prodrome followed by sparse distribution of vesicles with an erythematous halo affecting the oral mucosa, hands, and feet. Painful ulcerative lesions occur anywhere in the oral cavity, but are commonly found on the hard palate, tongue, and buccal mucosa. The enanthem (mucosal lesions) begins as 2–8 mm erythematous papules, a short vesicular stage, and yellow-gray ulcers with an erythematous halo. Lesions may coalesce and the tongue may become red, edematous, and painful, interfering with oral intake. Oral lesions heal without treatment within 5–7 days. Outbreaks of hand, foot, and mouth disease are common in daycare facilities. No specific treatment is necessary except for isolation of the patient, especially children, to avoid spread of the disease in a community.

Herpangina is also a disease of early life, with an incubation period of four days followed by an abrupt onset of fever with malaise, headache, and neck or back pain. The oral mucosal lesions consist of 1–2 mm gray-white papulovesicular lesions that progress to ulcers surrounded by an erythematous halo or rim, and the oropharynx may appear diffusely hyperemic. Lesions are distributed on the anterior tonsillar pillars, soft palate, uvula, and tonsils, and usually last for a week. Common complaints of affected patients are anorexia, dysphagia, and sore throat.

Hand, foot, and mouth disease and herpangina are typically diagnosed clinically. Only symptomatic treatment is necessary such as antipyretics, analgesics, and anti-inflammatories, if necessary.

Other Viruses with Orofacial Manifestations

Measles is caused by an RNA virus of the paramyxovirus group of the respiratory tract and skin through droplet infection, mainly affecting infants and young children. With an increase in measles vaccine coverage or a decrease in population density, the age distribution shifts toward older children. The first dose of the measles–mumps–rubella (MMR) vaccine should be given between 12 and 13 months of age and the second before school entry, but it can be given routinely at any time from three months after the first dose. In temperate climates, annual measles outbreaks typically occur in the late winter and early spring, while in tropical climates, a combination of high birth rates and variable associations of measles outbreaks with the rainy season creates highly irregular large outbreaks.

Measles is a highly contagious disease after an incubation period of about 10–12 days. Constitutional symptoms such as fever, malaise, conjunctivitis, coryza, and cough start and last for a week, followed by hyperpyrexia. Pathognomonic Koplik's spots are punctate blue-gray lesions surrounded by an erythematous ring (so-called grains of sand on a red background) on the buccal mucosa. They appear 1–2 days prior to the onset of the rash and remain for 2–3 days. Pinpoint raised red lesions on the soft palate may coalesce and the entire oropharynx turns red, lasting for 6–7 days. Other features include Herman spots on the tonsils as bluish-gray areas. Treatment is mainly based on supportive measures such as fluids and antipyretics.

Molluscum contagiosum is a disease due to a large DNA virus. Molluscum is primarily a disease of childhood. The clinical presentation includes asymptomatic, multiple flesh-colored, dome-shaped papules of the skin with a central depression. Lesions generally resolve in a few months. However, patients who are immunocompromised or deficient, such as those who are HIV infected, are more prone to develop severe disease. The diagnosis is typically clinical. When needed, treatments include physical destruction of the lesions with cryotherapy or curettage. Topical treatments have also been used, but none is particularly effective.

Congenital and Neonatal Viral Infections

Many organisms including viruses can infect the fetus and impair its development. The responsible organisms have been widely known as TORCH: **t**oxoplasma gondii, **o**ther microorganisms, **r**ubella virus, **c**ytomegalovirus, and **h**erpes viruses.[116] Awareness of occupational health hazards such as risk for pregnant female oral healthcare workers and pregnant patients is important in preventing such cross-infection, though it is very rare.[117]

Rubella

Rubella affects the fetus through a primary infection of the mother, but rare cases have been reported after a secondary infection or reinfection of the mother. The risk of fetus infection is highest in the first trimester (just before conception and during the first 8–10 weeks of gestation); the majority of infants infected at this age suffer from congenital defects and the treatment of the infants with congenital rubella is mainly supportive. Features of congenital rubella include congenital cataracts, congenital heart defects, sensorineural deafness, mental retardation, growth retardation, hepatosplenomegaly, jaundice, purpuric rash, or signs of meningoencephalitis. The majority of survivors progress poorly, with growth impairment and hearing, visual, and cardiac defects. Oral complications include hypoplastic enamel of both primary and permanent dentition.[118]

Cytomegalovirus

The neonatal disease rate is probably highest for children of women who have had a primary infection in the first half of pregnancy. Most infants with congenital CMV exhibit no signs of infection; however, infants with asymptomatic CMV infection may later develop neurologic deficits like microcephaly, intellectual disability, and motor defects, behavioral problems, and sensorineural hearing loss. Congenital CMV is perhaps the most common cause of congenital nongenetic sensorineural hearing loss.[119]

Herpes Simplex Virus Types 1 and 2

Transmission of HSV infection of the newborn usually occurs during pregnancy, intrapartum, and postnatally. Intrauterine viral transmission is highest during the first 20 weeks of gestation and may lead to abortion, stillbirth, and congenital anomalies. Manifestations of congenital HSV include skin lesions and scars, eye lesions (chorioretinitis, microphthalmia, and cataract), neurologic damage (intracranial calcifications, microcephaly, seizures, and encephalomalacia), growth, and psychomotor development retardation. Neonates infected intrapartum or postnatally by HSV can present with the disease localized to the skin, eye, and/or mouth, or can deteriorate rapidly as a result of respiratory distress, shock, multiorgan failure, disseminated intravascular coagulopathy, or encephalitis, with high rates of neurologic morbidity among survivors.

Varicella-Zoster Virus

Infection with the virus causing chickenpox, VZV, during early gestation can lead to either fetal loss or congenital varicella syndrome, which is a rare complication of infection with maternal varicella before 20 weeks of pregnancy. It can be associated with severe anomalies like dermatomal scarring, limb hypoplasia, ocular abnormalities, low birth weight, neurologic defects, and early death. Primary disease

in the mother around the time of delivery leads to neonatal infection. When maternal clinical infection occurs under 5 days prior to delivery to 2–5 days post delivery, a severe form of neonatal chickenpox is possible.[120]

Hepatitis Virus

Hepatitis viruses cause inflammation of the liver known as hepatitis. There are five main clinical types: hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), hepatitis D (HDV), and hepatitis E (HEV), with different modes of transmission, severity, and geographic distribution. Out of the five, types B and C lead to chronic disease, causing liver cirrhosis, cancer (hepatocellular carcinoma), and deaths. According to the World Health Organization (WHO), it is estimated that 325 million people globally live with the dangerous variants, HBV and/or HCV. Out of the 325 million, about 257 million were living with chronic HBV infection in 2016 and 71 million with chronic HCV infection as of 2015.

HAV infection can lead into mild to severe illness and is transmitted through contaminated food and water or from an infected individual (fecal–oral route). The majority of infected individuals recover completely after a short illness, with immunity lasting lifelong and mortality reported within a small group. HAV is prevalent in countries where there is a lack of clean water, sanitation, among MSM, and in persons who inject drugs (PWIDs). The treatment of HAV infections is supportive care. Prevention is through the HAV vaccine.

HBV infection presents as either an acute or a chronic disease, transmitted through contact with blood or other body fluids and vertical transmission from an infected mother to a child. Those who are chronically infected are prone to complications such as liver cirrhosis and hepatocellular carcinoma. HBV is highly contagious. Several antiviral medications are effective in treating HBV. Tenofovir (with or without emtricitabine) is preferred. Alternative agents include lamivudine, emtricitabine, adefovir, and entecavir. Once a person develops HBV, there is no cure. It is generally diagnosed via serologic testing (Table 21-6). The best mode of prevention is through an effective vaccination against HBV.

HCV generally presents as a chronic disease with varying degrees of disease severity, including cirrhosis and liver cancer. HCV is highly infectious and can be transmitted through a very small quantity of infected blood, such as in case of the bore of a needle. The main mode of HCV transmission is through injecting drug use, accidental exposure, and unsafe conditions in healthcare practices, and transfusion of infected blood. Sexual activities are thought to play a minor role in HCV transmission.[121] Diagnosis is by testing for anti-HCV antibodies. However, many patients spontaneously clear HCV infections, so HCV ribonucleic acid (RNA) is required to confirm an active chronic infection. In chronic HCV infection, the two main concerns are liver damage, leading to cirrhosis, and hepatocellular carcinoma. A liver ultrasound is generally the screening test of choice for both. Patients with active HCV should be managed by antiviral medications, which are curative. Modern HCV direct-acting antiviral (DAA) treatment regimens feature fixed-dose combination pills. At the time of publication, the two most common are glecaprevir/pibrentasvir and sofosbuvir/velpatasvir; however, several other regimens also exist. Treatment is selected based on virus genotype, prior treatment history, and antiviral resistance. Treatment courses vary from 8 to 24 weeks. Unfortunately, there are no effective HCV vaccines available yet.[122,123]

HDV requires HBV for its replication, hence it occurs as a super-infection or simultaneously with HBV and can be

Table 21-6 Common serologic patterns of hepatitis B (HBV) and C virus (HCV) infection.

Serologic Result	Interpretation
HBV	
HbsAg *neg*, anti-HBc *pos*, anti-HBs *pos*	Immunity from natural infection
HBsAg *neg*, anti-HBc *neg*, anti-HBs *pos*	Immunity from vaccination
HBsAg *pos*, anti-HBc *pos*, IgM anti-HBc *pos*, anti-HBs *neg*	Acute infection
HBsAg *pos*, anti-HBc *pos*, IgM anti-HBc *neg*, anti-HBs *neg*	Chronic infection
HBsAg *neg*, anti-HBc *pos*, anti-HBs *neg*	Recovering from acute infection, *or* False-positive anti-HBc, thus susceptible *or* "Low-level" chronic infection Resolving acute infection
HCV	
Anti-HCV reactive	A repeatedly reactive result is consistent with current HCV infection, *or* past HCV infection that has resolved, *or* biologic false positivity for HCV antibody Test for HCV RNA to identify current infection
Anti-HCV reactive, HCV RNA detected	Appropriate counseling and referral for medical care and treatment
Anti-HCV reactive, HCV RNA not detected	No further action required in most cases

anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HbsAg, hepatitis B surface antigen; IgM, immunoglobulin M.

chronic. The main mode of transmission is through infected blood, body fluids, and, though rare, vertical transmission from mother to child, among PWIDs, and through hemodialysis. HDV can be treated with interferon-based regimens. There is no vaccine for HDV, so the best prevention is vaccination for HBV.

HEV is also a highly infectious virus and can lead to serious illness and death. The main mode of transmission is through the fecal–oral route via contaminated water. It has been recorded globally and commonly in Southeast Asia. Pregnant women are at particularly high risk of complications from HEV. There is a vaccine available in China, but it is unavailable in the rest of the world.

Orofacial Manifestations and Considerations

Hepatitis viruses cause serious liver damage and its consequences, especially susceptibility to bleeding and contraindications of certain drugs that depends upon the severity. There are several physical signs of end-stage liver disease, such as icterus or yellowing of the mucous membrane, including the oral cavity, due to jaundice, petechial hemorrhages and ecchymosis, palmar erythema, Dupuytren's contracture of the palm, urticaria, gynecomastia, and spider nevi. However, these features are nonspecific and may be present from other conditions, including alcohol-related liver disease.

With regard to orofacial structures, sialosis affecting the parotid glands and a close relationship with oral lichen planus, Sjögren syndrome, and sialadenitis has been documented. Halitosis with fetid odor, cheilitis, atrophic tongue, xerostomia, bruxism, and crusted perioral rash have also been reported.

Considering modern oral health practices, there is no cause for concern in treating hepatitis patients as long as all infection control measures are in place. If a healthcare professional is infected, they must avoid patient care during the infectious stages with active signs and symptoms of the disease.

Potential exposure to hepatitis virus in an oral health practice may include needle stick or other sharps injury, contact with potentially infectious body fluids, and exposure to mucus membranes. DHCP should report any bloodborne exposures. Depending on the nature of the exposure, baseline serologic data may be obtained from both the patient and the dental healthcare worker. Exposed healthcare workers should be monitored closely after exposure and, depending on the nature of the exposure, postexposure prophylaxis (PEP) may be ordered.[124]

Human Immunodeficiency Virus

HIV is an RNA-based retrovirus that integrates into the DNA of and replicates in a subset of T cells called CD4 cells. These CD4 cells help coordinate immune system responses. If left untreated, the CD4 cell count will deplete over time, leaving individuals at risk for a variety of infections. If the CD4 cell counts drop to very low levels, patients can develop a syndrome called acquired immunodeficiency syndrome (AIDS). However, if initiated on ART in a timely fashion, people living with HIV have the same life expectancy as HIV-negative individuals.[125]

Early diagnosis, appropriate timely management, and long-term retention in care for HIV patients remain major public health challenges. It is estimated that about 69,000 HIV-positive people have died and 1.7 million new infections were reported in 2019 alone. However, new infections have reduced by 39% and HIV-related deaths by 51%, and more than 15 million lives were calculated to have been saved due to ART between 2000 and 2019.

AIDS is a stage where the body's immune system is severely compromised due to HIV. Due to advances in ART and substantial public health efforts to engage HIV-infected individuals in care, fewer people are developing AIDS over time.

The definition of AIDS is when the CD4 count falls below 200 cells/mm^3 of blood, or when the patient develops one or more opportunistic infections regardless of their CD4 count. HIV is generally diagnosed with a combined antibody/antigen immunoassay, followed by an HIV PCR. Early diagnosis and treatment of HIV are essential for two reasons. First, early treatment may prevent patients from developing AIDS. Second, patients who are on treatment and have an undetectable viral load are not able to transmit the virus to others.

Transmission of HIV occurs mainly through body fluids such as blood, semen, vaginal secretions, or vertical transmission from an infected mother to her child while pregnant or during delivery and by breast milk.

Risk factors for HIV transmission include unprotected anal or vaginal sex, presence of other sexually transmitted diseases, contaminated needle and other equipment sharing among PWIDs, blood transfusions, tissue transplantation, and needle stick injuries. Vertical transmission from an HIV-infected mother to child may also occur if the mother's infection is not controlled.

Antiretroviral regimen for a treatment-naïve patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor. Pharmacokinetic (PK) enhancers (also known as a booster) may also be included in ART regimens to reduce pill burden. Most modern HIV regimens are fixed-dose combination pills that will include three active agents.

An ART regimen should not be stopped unless discussed with a medical provider.[12,126]

Orofacial Manifestations and Considerations

Orofacial manifestations of HIV are variable. Patients with acute HIV (recent infection) may present with a mononucleosis-type syndrome with fevers, pharyngitis, and lymphadenopathy. Later oral manifestations of HIV include pseudomembranous or erythematous candidiasis, angle cheilitis, OHP, NG, necrotizing periodontitis, linear gingival erythema, KS, non-Hodgkin lymphoma (group 1), and melanotic hyperpigmentation, HSV infection, and HPV infection (group 2). There has been a major reduction in candidiasis, OHL, KS, and HSV infection since the advent of ART. HIV-associated salivary complications include xerostomia, Sjögren syndrome–like illness, sialosis, salivary gland benign lymphoepithelial cysts within salivary glands, diffuse infiltrative lymphocytosis syndrome (DILS), mucous extravasation, and even ranula.[127]

In a small group of ART recipients, immune reconstitution may be dysregulated, leading to opportunistic infection and complications. This immune dysregulation is called immune reconstitution inflammatory syndrome (IRIS), with possible manifestations in the mouth as atypical viral and fungal infections and KS. IRIS is generally managed with supportive care.

Another unwanted effect of ART is lipodystrophy, where there is a redistribution of adipose tissue of the face, leading to esthetic concerns (Figure 21-23). In addition to the face, lipoatrophy may affect buttocks, arms, and legs. Lipohypertrophy or excessive fat accumulation can also be an undesirable side effect over the abdominal and mammary regions and the neck. Atrophy of fat from the bilateral face can affect a patient's self-esteem, social isolation, and depression. Lipodystrophy also has been associated with insulin resistance, hyperlipidemia, and endothelial dysfunction, leading to cardiovascular complications. Lipodystrophy is less common with newer ART regimens.

In a healthcare setting, if exposure to HIV is suspected, appropriate action must be taken. The HIV status of the source individual should be determined. Depending on the nature of the exposure, PEP medication regimens using three or more forms of ART may be administered. Follow-up should include counseling, baseline and follow-up HIV testing, and monitoring for drug toxicity and complications, if any.

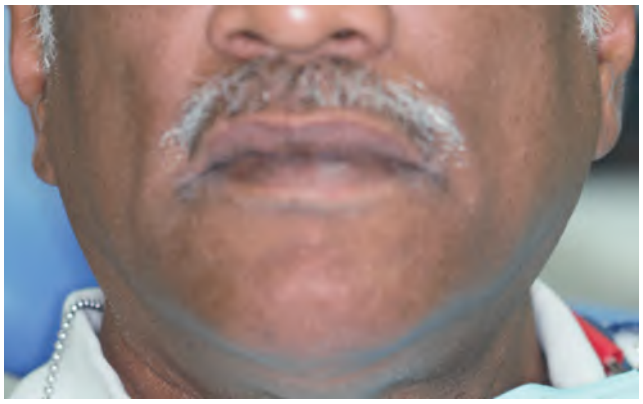

Figure 21-23 Lipoatrophy of the face and sialosis due to HIV.

Coronaviruses

Coronaviruses are enveloped single-stranded RNA viruses that cause a variety of infections in both humans and animals. The virus is named because of its crown-like appearance on electron microscopy. Two genera of coronavirus, α and β, infect humans. Alpha coronaviruses are one of the causes of the common cold. Beta coronaviruses include several important human pathogens, including the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV-1 and SARS-CoV-2).

MERS-CoV, a novel zoonotic infection that likely originated from camels, was first identified in 2012 in Saudi Arabia. Patients with MERS-CoV typically present with a respiratory tract infection that can progress to pneumonia and death in up to one-third of patients.[128] Human-to-human transmission is thought to be limited. The WHO tracks MERS-CoV cases here: https://www.who.int/emergencies/mers-cov/en/.

SARS-CoV-1, a zoonotic infection that may have originated from palm civets, was first identified in Guandong Province in China in 2003. Patients with SARS-CoV-1 also typically present with an influenza-like illness that can progress to pneumonia and death in approximately 15% of patients. Like MERS-CoV, human-to-human transmission is thought to be limited with adequate infection control precautions. There are no current cases of SARS-CoV-1 infections. However, it has reemerged four times since 2003. The WHO tracks SARS-CoV-1 cases here: https://www.who.int/ith/diseases/sars/en/.

SARS-CoV-2 is a zoonotic virus that likely originated in bats in Wuhan, China at the end of 2019.[129] Coronavirus disease 2019 (COVID-19) is the name of the clinical syndrome for patients infected with SARS-CoV-2. Patients with COVID-19 often present with influenza-like illness symptoms, with fevers, cough, fatigue, and myalgia. However, other presentations include anosmia, dysgeusia, and diarrhea. Furthermore, a substantial proportion of patients may have no symptoms at all.[130]

The virus is primarily transmitted via large respiratory droplets. Aerosols and surfaces are other potential additional sources of transmission. Live virus can be detected in aerosols in carefully curated laboratory settings.[131] However, the clinical significance of these findings remains controversial. A 2020 systematic review of real-world data demonstrates no substantial transmission of SARS-CoV-2 from patients to healthcare workers wearing standard surgical masks while

caring for COVID-19-infected patients.[132] Respirators (e.g., N95) continue to be recommended by the CDC during aerosol-generating procedures and during procedures in the nose, throat, oropharynx, and respiratory tract.[133]

The incubation period is up to 14 days.[134] The virus spike protein binds to the receptor-binding domain of the cellular receptor angiotensin-converting enzyme 2 (ACE2), which is distributed throughout the respiratory tract, the ducts of salivary glands, and the conjunctiva.[135,136]

At the time of this writing, the current gold standard for diagnosing COVID-19 is NAAT, which is thought to have good sensitivity and excellent specificity. However, false negatives can occur, and a single negative test should not rule out the disease in symptomatic patients. Similarly, NAAT simply detects SARS-CoV-2 virus material and cannot differentiate between live and dead virus. Therefore, a positive test does not necessarily mean that someone is contagious. SARS-CoV-2 antibody testing is also commercially available. The sensitivity and specificity of these tests vary depending on the manufacturer. There are also significant limitations to interpreting antibody tests. For example, a positive test should not be interpreted as immunity to SARS-CoV-2 as some antibody tests do not evaluate for the presence of neutralizing antibodies. Similarly, patients who have a positive antibody test may still be contagious to others. Patients may also have a negative antibody test and still have COVID-19 if they present within the first few days of symptoms.[137]

Dentistry is classified as one of the highest-risk professions for transmitting COVID-19.[138,139] Until further research on COVID-19 transmission dynamics in dental settings is performed, dentists should wear the following personal protective equipment:

- FFP3 (Europe) or N95 (USA) respirator.
- Disposable gown.
- Gloves.
- Eye protection (goggles or face shield).

In case of the unavailability of FFP3 respirators (99.95% filtration of 0.3 micron particles), N95 (95% filtration of 0.3 micron particles; cannot be used in Europe as not CE marked) or FFP2 (94% filtration of 0.3 micron particles) masks were considered to provide enough protection provided that they are face-fit tested for the specific user.[140,141] This has been reviewed in multiple sources.

Current (2021) evidence-based treatments for COVID-19 include remdesivir and dexamethasone.[142,143] However, dozens of other agents are under active investigation throughout the world. At the time of this writing, SARS-CoV-2 vaccines are also an active area of research, with several commercially available worldwide.[144,145]

Vaccines against SARS-CoV-2

Since the beginning of the worldwide pandemic in early 2020, over 100 new vaccines have been developed worldwide with the objective of producing long-lived protective immunity. These fall into four main groups:

- Inactivated viral product vaccines.
- Protein-based vaccines.
- Viral vector vaccines.
- Genetic vaccines.

In addition, short-lived passive immunization protection has been developed using monoclonal antibodies.

Inactivated vaccines are produced relatively easily and are usually administered intramuscularly. They are, however, limited by the productivity of the virus in cell culture, as well as the safety measures needed to grow large amounts of SARS-CoV-2.

Recombinant protein vaccines can be divided into recombinant spike protein–based vaccines, recombinant RBD (part of the spike protein)-based vaccines, and virus-like particle (VLP)-based vaccines.

In *viral vector vaccines* viruses, like adenoviruses, are modified to carry SARS-CoV-2 genes, including replication of the whole spike protein. They enter host cells to create coronavirus viral proteins or replicate and expose the coronavirus proteins on their surface.

Genetic vaccines are based on mRNA, which can be incorporated into muscle cells and protein expressed, or plasmid DNA, which can be produced at a large scale in bacteria and contain expression promoters and the gene that encodes the spike protein. The advantage of these technologies is the possibility of large-scale production.

Monoclonal antibodies against COVID-19 are not preventive measures like vaccines, but treatments. They are laboratory-made monoclonal antibodies that mimic those produced naturally or by vaccines. The monoclonal antibodies are usually directed against the spike proteins.

Oral Manifestations

A systematic review from September 2020 covered the spectrum of oral signs and symptoms of patients with COVID-19.[146] Gustatory impairment was the most common oral manifestation, with a prevalence of 45%. Taste disorders were 38% for dysgeusia and 35% for hypogeusia, while ageusia had a prevalence of 24%. Oral mucosal lesions varied and included white and erythematous plaques, irregular ulcers, small blisters, petechiae, and desquamative gingivitis. The tongue, palate, lips, gingiva, or buccal mucosa may have been affected. The authors concluded that taste disorders may be common symptoms in patients with COVID-19 and should be considered in the scope of the disease's onset and progression. They also reported that oral mucosal lesions are more likely to present as coinfections and secondary manifestations with multiple clinical aspects.

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22

Disorders of the Endocrine System and of Metabolism

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ENDOCRINE DISEASES

The term "endocrine" was coined by Starling to contrast the actions of hormones secreted internally (hence *endo*crine) from those substances that are secreted onto external surfaces (exocrine, e.g., sweat or saliva).[1] The term "hormone" is derived from the Greek *hormân*, "to set in motion, stimulate," a derivative of *hormé* meaning "impetus" or "impulse." This describes well the dynamic actions of hormones and their ability to induce cellular responses and their regulation of the major physiologic processes of growth, reproduction, metabolism, and the maintenance of homeostasis (e.g., glucose and calcium). The release and actions of hormones are controlled by means of predominantly negative "feedback loops," as exemplified by the hypothalamus-pituitary-adrenal (HPA) axis (see Figure 22-1).

The most common endocrine disorders are (Figure 22-2):[2]

- Diabetes mellitus.
- Obesity.
- Thyroid disorders: hypothyroidism, hyperthyroidism, goiter.
- Menstrual disorders and/or hirsutism, usually due to polycystic ovarian syndrome (PCOS).
- Hypogonadism (in association with erectile dysfunction).
- Osteoporosis and metabolic bone disease.
- Subfertility (delay or difficulty in conceiving).
- Disorders of growth or puberty.

Endocrine disorders (the "endocrinopathies") are common, and are increasing in frequency. They encompass some of most prevalent of the chronic diseases, including diabetes mellitus[3] and increasingly obesity.[4,5] Endocrine diseases affect the entire system of endocrine glands, the hormones, synthesized and secreted by these glands, and the target organs that are susceptible to the effects of these hormones. Endocrine disorders are complex and their diagnosis is complicated by four interacting components:[6,7]

- The *hypothalamus* (Figure 22-3) contains most of the "sensing" organs and tissues, and is the part of the brain that monitors crucial determinants of homeostasis; that is, water, electrolyte and osmotic balance, metabolism, the fed and fasted state, and the stress response. Additionally, over the course of a lifetime, conception, pregnancy, growth, development, sexual maturation, and senescence are also regulated by the hypothalamus. Various "biologic clocks" exist that are linked into and exert control over the 24-hour circadian rhythm, the 28-day menstrual cycle, and the longer temporal cycles associated with growth, development, and sexual maturation, including as an example the timing of the onset of puberty. The hypothalamus most significantly is the link between the endocrine and nervous systems. The hypothalamus produces releasing and inhibiting factors that control the hormones of the pituitary, as well as other hormones throughout the body, via the pituitary—the second major component of the endocrine system.
- The *pituitary* is a small pea-sized endocrine gland that regulates all of the major endocrine glands located throughout the body. It does this by the release of trophic hormones that stimulate the growth of the other endocrine glands, or by the release of hormones that stimulate the endocrine glands to release the hormones synthesized

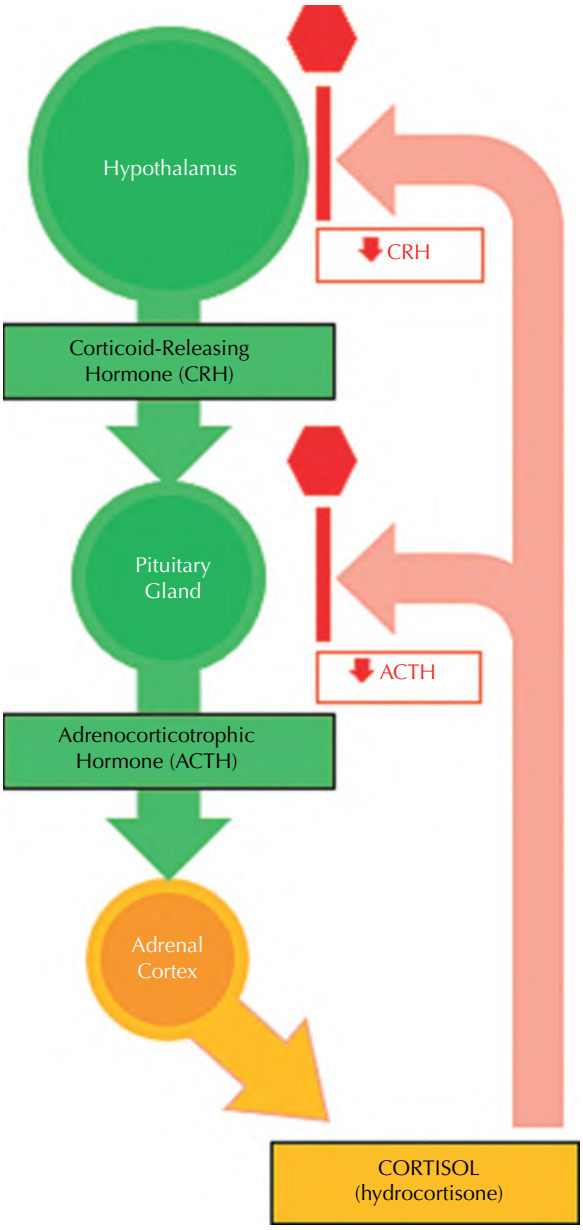


Figure 22-1 The hypothalamus-pituitary-adrenal (HPA) axis is an example of negative feedback inhibition. As the cortisol levels rise, the cortisol induces the hypothalamus to make less corticoid-releasing hormone, so causing the pituitary to make less adrenocorticotrophic hormone, which in turn causes the adrenal gland to produce less cortisol (the reverse applies: a lower cortisol level induces a rise in cortisol production). Courtesy of Mark Schifter.

within that gland itself. Except for oxytocin, all the hormones released by the major endocrine glands are under negative feedback control (meaning that the presence of circulating hormone downregulates further production of that hormone).

- *Major endocrine glands* includes the bilobed thyroid, the four parathyroid glands, the paired adrenal glands (sited atop the kidneys), the endocrine pancreas, and the gonads, testes, and ovaries). These glands synthesize and release the hormones that have the major effects on metabolism, water and electrolyte balance, glucose and calcium homeostasis, the stress response, as well as conception, growth, and development.
- *Hormones* are a class of signaling molecules, produced by endocrine glands that are generally transported by the circulatory system to target organs to regulate physiology and behavior (Box 22-1). Hormone production and function is complex, and includes biosynthesis and storage of a particular hormone in a particular gland, secretion (on receipt of the correct signal—often another hormone—by the gland), transport to the target cells/tissues, and recognition of the hormone by the target cell, via hormonal binding to a cell surface or intracellular receptor, resulting in transmission and amplification of the hormonal signal. The last stage is breakdown of the hormone.

In essence, it is either deficiencies or excess of these hormones of the major endocrine glands that result in significant disease states.[8] Malignancies of the endocrine glands are rare. There are a number of key aspects of endocrine disease about which dentists need to know:

- *Pathophysiology and management of the various endocrine diseases*. This ensures the safe delivery of dental care, the ability to possibly prevent disease progression or worsening morbidity, and to avoid serious potentially life-threatening complications of the patient's disease.
- *Complications that can arise from undiagnosed or poorly managed endocrine disease*. This includes knowledge of potentially life-threatening medical emergencies and the subsequent need to alter treatment planning (including awareness of potential drug interactions) or implement additional measures and resources so as to prevent the likelihood of such emergencies from occurring.
- *Manifestations of the disease in/on the stomatognathic system*. Recognition of the stomatognathic manifestations of endocrine disease is needed for the diagnosis of such conditions and also to identify those patients with poorly controlled or undiagnosed disease.

Hormones

There are five major classes of hormones (classified by their molecular weight and size and their precursor substrates; see Table 22-1),[9] and their function can be broadly classified into three areas of physiologic activity: growth and differentiation; maintenance of homeostasis; and reproduction.

Hormone release is the end-product of a long cascade of intracellular events. Polypeptide hormones, for example, require neural or endocrine stimulation of the cell to initiate

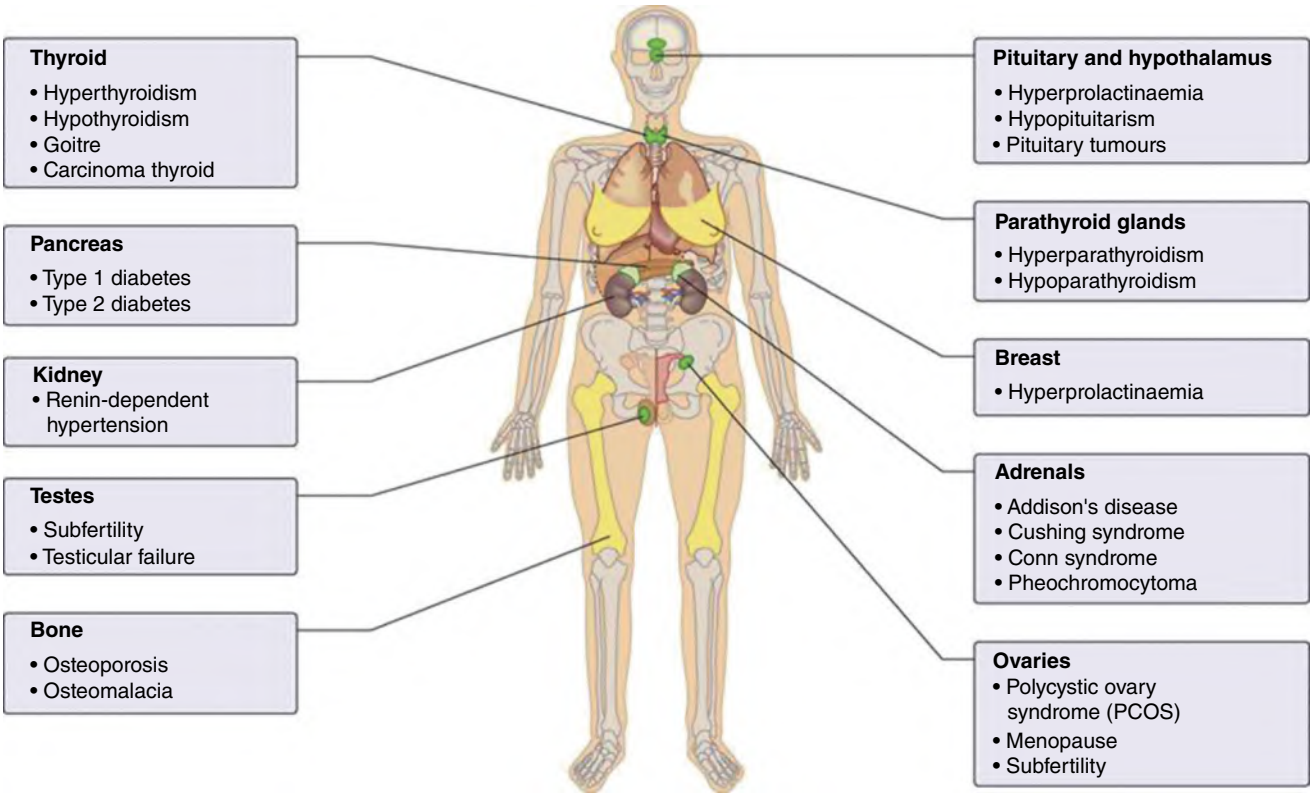


Figure 22-2 The major endocrine organs and common endocrine problems. *Source:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Reproduced with permission.

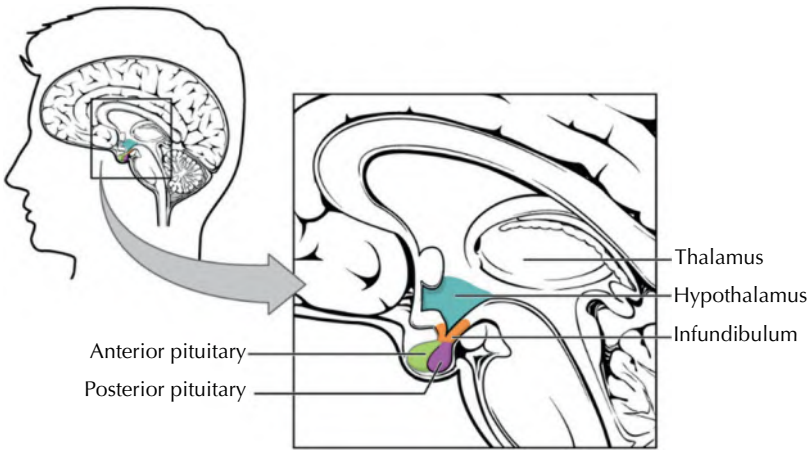


Figure 22-3 Hypothalamus and pituitary in detail. *Source:* Betts JG, Young KA, Wise JA, et al. *Anatomy and Physiology*. Houston, TX: OpenStax; 2013. https://openstax.org/books/anatomy-and-physiology/pages/1-introduction. Creative Commons Attribution License 4.0 license.

transcription from DNA to a specific messenger RNA (mRNA) and subsequent translation into a polypeptide product. This product is often a precursor molecule or "pro-hormone" that is biologically inactive, and is then further processed and packaged into granules, in the Golgi apparatus. These granules are transported to the plasma membrane before release, which is itself regulated by a complex combination of intracellular regulators.

Hormone secretion can be (1) *continuous*, as seen with the thyroid hormones, with a half-life of 7–10 days for T4 and 6–10 hours for T3, and with little variation in levels over the day, month, and year; or (2) *pulsatile*, which is the normal pattern for the gonadotrophins—that is, luteinizing hormone (LH) and follicle-stimulating hormone (FSH)—with a large amount of hormone released in a pulse every 1–2 hours, depending on the phase of the menstrual cycle. Growth hormone (GH) is also secreted in a pulsatile fashion, but with undetectable levels between pulses.

There are major factors that control the release of various hormones over days, for example the circadian rhythm,

weeks, and months, and in the case of the growth and sex hormones over years.[10] The menstrual cycle is an example of a longer and more complex (28-day) biologic rhythm.[11] Other regulatory factors include physiologic "stress" and acute illness, which produce rapid increases in adrenocorticotropic hormone (ACTH) and cortisol, GH, prolactin, epinephrine, and norepinephrine. Over the course of the sleep–wake cycle the secretion of GH and prolactin is increased, especially during the rapid eye movement (REM) phase of sleep. Food intake results in many hormones being released to regulate the body's control of energy intake and expenditure, and these are therefore profoundly influenced by feeding and fasting. Secretion of insulin is increased, while testosterone and GH are decreased after ingestion of food, and secretion of a number of hormones is altered during prolonged food deprivation.

Most hormones are secreted directly into the circulation from the endocrine glands. In contrast to this, the hormones released from the hypothalamus are excreted at much higher concentrations and are confined to the pituitary portal system. Many hormones are bound to proteins within the circulation—it is important to note that only the free (unbound) hormone is available to the tissues and is biologically active. This binding to the plasma proteins serves to buffer against very rapid changes in plasma levels of the hormone and additionally plays a role in regulation of hormonal activity. Many of the tests of endocrine function measure the total rather than the free hormone, giving rise to difficulties in interpretation when the binding proteins are altered in disease states or by drugs. Binding proteins comprise both specific, high-affinity proteins of limited capacity, such as thyroxine-binding globulin (TBG), cortisol-binding globulin (CBG), sex-hormone-binding globulin (SHBG) and insulin-like growth factor (IGF)-binding proteins (e.g., IGF-BP3); and other, less specific,, low-affinity protein carriers, such as prealbumin and albumin.

Box 22-1 Signaling by the Endocrine System

The endocrine system is an information signal system like the nervous system, yet its effects and mechanisms are clearly different. The endocrine system's effects are slow to initiate, and prolonged in their response, lasting from a few hours up to weeks.

- Endocrine signaling relies on hormones that usually travel far via the circulatory system to reach their target organ.
- Paracrine signaling is a form of cell–cell communication in which a cell produces a signal to induce changes in nearby cells, altering the behavior or differentiation of those cells. Paracrine factors diffuse over only a relatively short distance (locally active), in contrast to hormones.
- Autocrine cell signaling entails the cell secreting a hormone or chemical messenger that binds to autocrine receptors *on that same cell*, leading to changes in the cell.

Table 22-1 Major classes of hormones.

Class		Examples	Receptor Types
1	Small neuropeptides	• Gonadotropin-releasing hormone • Thyrotropin-releasing hormone • Somatostatin • Vasopressin	
2	Amino acid derivatives	Catecholamines: • Epinephrine (adrenaline) • Norepinephrine (noradrenaline) • Dopamine • Thyroid hormone	• Interact with cell surface membrane receptors[#]
3	Large proteins[*]	• Insulin • Luteinizing hormone • Parathyroid hormone	
4	Steroid hormones[†]	• Cortisol • Estrogen	• Interact with intranuclear receptors
5	Vitamin derivatives	• Retinoids (vitamin A derivatives) • Vitamin D	• Lipid soluble

[*] Released by the "classic" endocrine glands: pituitary, thyroid, parathyroid, pancreatic islet cells, adrenals, and gonads.
[†] Synthesized from cholesterol-based precursors.
[#] An exception is thyroid hormones, which act via cytoplasmic receptors.

Hormone Receptors

These are broadly divided as follows:

- *Cell surface or membrane receptors*: typically, transmembrane receptors that contain hydrophobic sections spanning the lipid-rich plasma membrane and trigger internal cellular messengers.
- *Nuclear receptors*: these typically bind hormones and translocate them to the nucleus, where they bind hormone-response elements of nuclear DNA via characteristic amino acid sequences (so-called zinc fingers). Abnormalities of hormone receptors can be a rare cause of endocrine disease. The activation of intracellular kinases, phosphorylation, release of intracellular calcium and other "second messenger" pathways, and the direct stimulation of DNA transcription result in some or all of the following:
  - Stimulation or release of preformed hormone from storage granules.
  - Stimulation or synthesis of hormone and other cellular components.
  - Opening or closing of ion (e.g., calcium channels) or water channels (e.g., aquaporin water channels).
  - Activation or deactivation of other DNA-binding proteins, leading to stimulation or inhibition of DNA transcription.

The sensitivity and/or number of receptors for a hormone can be decreased after prolonged exposure to a high hormone concentration (downregulation). Equally, the reverse is true when stimulation is absent or minimal: the receptors are increased in number and/or sensitivity (upregulation).

Primary and Secondary Endocrine Gland Failure

Primary endocrine gland failure occurs when there is dysfunction or removal of the specific end-organ endocrine gland—the thyroid, parathyroid, endocrine pancreas, adrenal glands, or gonads (ovaries and testes). Causes of primary endocrine gland dysfunction or destruction include autoimmune disease, atrophic change, inflammatory or neoplastic infiltration, or complications related to treatment, such as radiotherapy or surgical removal of the gland.

Secondary disorders of the same endocrine axes are caused by diseases of the pituitary gland. The key to diagnosing the site of the disease, either primary or secondary, requires understanding of the negative feedback control system so as to correctly interpret blood tests used in the investigation of endocrine diseases. Primary hormone deficiency due to a disease process of the endocrine end-organ (e.g., thyroid, adrenal, or gonad) will lead to a loss of negative feedback and subsequent elevation in the corresponding anterior pituitary trophic (stimulating) hormone. In secondary gland failure, there will be low or "inappropriately normal" levels of the pituitary trophic hormone in the presence of low end-organ hormone levels; for example, if a patient has low circulating free T3 (fT3) and T4 levels in the context of low thyroid-stimulating hormone (TSH) levels, then the site of the disease is likely to be in or of the pituitary gland.

Investigations of Endocrine Function[12]

See Table 22-2.

Basal Blood Level

Basal hormone levels are especially useful for systems with long half-lives (e.g., T4 and T3, insulin-like growth factor-1 [IGF-1], androstenedione, SHBG) that vary little over the short term and so samples taken at any specific time are satisfactory.

For those hormones that fluctuate in accordance with the circadian rhythm (e.g., testosterone and cortisol), measurements must be taken at an appropriate time of day, which is 11:00 am for testosterone, while the patient is fasted, and between 8:00 and 11:00 am for cortisol, also with the patient fasted. LH/FSH, estrogen, and progesterone vary with time of menstrual cycle, and renin/aldosterone may vary with sodium intake, posture, and age.

Measurement of stress-related hormones (e.g., catecholamines, prolactin, GH, and cortisol) can be problematic, as the patient may be stressed by their attendance at the hospital or by the venipuncture itself, leading to falsely high levels. Sampling via an indwelling cannula at some time after the initial venipuncture overcomes this problem.

Urine Collection

This is done over the course of 24 hours and has the advantage of providing an "integrated mean" of a day's secretion of select hormones, namely the catecholamines and cortisol. However, in practice these results are often complicated by poor patient compliance and incomplete/wrongly timed collection. Age, sex, and weight of the patient are also confounding factors.

Saliva

Salivary analysis has the advantage of avoidance of venipuncture, and is being increasingly used, especially in children (for steroid estimations) or for samples collected at home.[13,14]

Stimulation and Suppression Tests

In general, stimulation tests are used to confirm suspected deficiency, and suppression tests to confirm suspected excessive levels of hormone secretion. These tests are valuable in instances when the secretory capacity of a gland is damaged,

Table 22-2 Diagnosis of endocrine disorders.

Gland/Disease	Hormonal Problem	Diagnostic Assays/Investigations
Acromegaly	Growth hormone (GH) excess	• Plasma GH • Plasma insulin-like growth factor-1
Hyperprolactinemia	Prolactin excess	• Plasma prolactin
Adrenal		
Cushing's syndrome	Excess cortisol	• 24 h urinary free cortisol • 1 mg dexamethasone suppression test • Midnight serum or salivary cortisol
Addison's disease	Low cortisol (and aldosterone)	• Adrenocorticotropic hormone stimulation test
Aldosteronism	Excess aldosterone	• Plasma renin activity • Plasma aldosterone after saline infusion
Pheochromocytoma	Excess epinephrine and/or norepinephrine	• Plasma catecholamines • 24 h urinary catecholamines
Thyroid		
Hyperthyroidism	Excess T4 and/or T3	• Suppressed thyroid-stimulating hormone (TSH; most sensitive test)
Hypothyroidism	Low T4 and/or T3	• Elevated TSH (most sensitive test)
Gonadal Failure/Diseases		
Male—hypogonadism	Low serum testosterone	• Low serum free testosterone levels
Female—ovarian failure	Loss of ovarian estradiol	• Elevated serum gonadotropins (follicle-stimulating hormone and luteinizing hormone)

such that despite maximal stimulation by the trophic hormone, there is diminished output of primary hormone. For example, with the short ACTH stimulation test for adrenal reserve, the healthy subject shows a normal response, while the subject with primary hypoadrenalism (Addison's disease) demonstrates an impaired cortisol response to the injection of cosyntropin (Synacthen®, Mallinckrodt, Dublin, Ireland), a potent ACTH analogue.[15]

Causes of Endocrine Disease

Endocrine diseases can be divided into two major disease states: hormone excess and hormone deficiency (Table 22-3).[16] Hormone resistance can be considered as a separate and distinct third condition,[17] but in practice the effect is one of hormone deficiency.

Hormone Excess

Hormone excess can be caused by autoimmune disorders, the excess therapeutic administration of hormones, or autonomous release with tumors, as can be seen with benign adenomas of the parathyroid, pituitary, and adrenal glands.

Hormone Deficiency

The commonest cause of hormone deficiency is from glandular destruction by autoimmune diseases (Table 22-4) and iatrogenic causes, namely surgery and radiotherapy. Rare cases include infection, inflammation, infarction, hemorrhage, or tumor infiltration. Autoimmune-mediated damage is highly prevalent, as seen with Hashimoto's thyroiditis and that of the pancreatic islet β cells in type 1 diabetes mellitus (T1DM).

Hormone Resistance

Hormone resistance results in a disease state that is similar to that seen with hormone deficiency, but diagnosis is more difficult and complicated as there are usually normal levels of the hormone on testing. The more severe hormone resistance disorders are due to inherited defects in membrane receptors, nuclear receptors, or the pathways that transduce receptor signals. These disorders are characterized by defective hormone action despite the presence of increased hormone levels. The most prevalent acquired forms of functional hormone resistance include insulin resistance in type 2 diabetes mellitus (T2DM) and leptin resistance in obesity.[8,18]

Table 22-3 Endocrine disorders.

Hormone Excess	Examples
Neoplastic	
Benign	• Pituitary adenomas • Hyperparathyroidism • Thyroid nodules (autonomous) • Adrenal nodules (autonomous) • Pheochromocytoma
Malignant	• Adrenal cancer • Medullary thyroid cancer • Carcinoid tumors*
Multiple endocrine neoplasia (MEN)	• MEN1 • MEN2
Autoimmune	• Graves' disease
Iatrogenic	• Cushing's syndrome (excess corticosteroid administration)
Infections/inflammatory	• Subacute thyroiditis
Receptor mutations (for activation)	• Luteinizing hormone (LH) • Thyroid-stimulating hormone • Parathyroid hormone (PTH) receptors
Hypofunction (Hormone Deficiency)	
Autoimmune	• Hashimoto's thyroiditis • Type 1 diabetes mellitus • Addison's disease
Iatrogenic	• Radiation induced • Hypopituitarism • Hypothyroidism
Infectious/inflammatory	• Sarcoidosis of the hypothalamus
Hormone mutations	• Growth hormone (GH) • LH • Follicle-stimulating hormone (FSH) • Vasopressin
Enzyme defects	• 21-Hydroxylase deficiency (congenital adrenal hyperplasia)
Developmental defects	• Turner's syndrome (females)
Nutritional (vitamin) deficiency	• Vitamin D • Iodine
Hemorrhage/Infarction	• Adrenal insufficiency
Hormone Resistance	
Receptor mutations	
Membrane	• GH • Vasopressin • LH • FSH • Adrenocorticotropic hormone • Gonadotropin-releasing hormone • Growth hormone-releasing hormone • PTH • Leptin • Ca^{2+}

Table 22-3 (Continued)

Hormone Excess	Examples
Nuclear	• Androgen receptor • Estrogen receptor • Glucocorticoid receptor • Peroxisome proliferator activated receptor • Vitamin D receptor
Signaling pathway mutations	• Albright's hereditary osteodystrophy
Postreceptor	• Type 2 diabetes mellitus • Leptin resistance

* Of neuroendocrine origin, derived from primitive stem cells of the gut wall, but can occur throughout the body.

Table 22-4 Endocrine glands and autoimmune disease(s).

Clinical Syndrome	Organ	Prevalence (if known*)	Antibody	Antigen
Stimulating				
Graves' disease† Neonatal thyrotoxicosis	Thyroid	1 in 100	Thyroid-stimulating immune-globulin (TSI, TSAb)	Thyroid-stimulating hormone receptor
Destructive				
Autoimmune hypophysitis Selective hypopituitarism (e.g., growth hormone deficiency, diabetes insipidus)	Pituitary specific cells			
Myxedema† (primary hypothyroidism)	Thyroid	1 in 100	Thyroid microsomal Thyroglobulin	Thyroid peroxidase enzyme (TPO) Thyroglobulin
Primary hypoparathyroidism	Parathyroid		Parathyroid chief cell	
Addison's disease‡ (primary hypothyroidism)	Adrenal (adrenal cortex but sparing medulla)			
Type 1 diabetes mellitus	Pancreas beta-islet cells	1 in 500	Autoantibodies to GAD_{67} and GAD_{65}	Glutamic acid decarboxylase (GAD)
Pernicious anemia§ (stomach)	Gastric parietal cell intrinsic factor			
Primary ovarian failure	Ovary	1 in 500		
Primary testicular failure	Testis			
Vitiligo (skin)†	Skin melanocytes		Anti-melanocyte	

* Prevalence for Northern European/Caucasian populations.
Stomatognathic system manifestations:
† Associated with lichen planus, including oral lichen planus.
‡ Hyperpigmentation ("bronzing") and increased number of melanotic macules of the oral mucosa.
§Atrophic glossitis.
Associated diseases include myasthenia gravis and autoimmune liver diseases.

HYPOTHALAMUS AND PITUITARY

Hypothalamus

The hypothalamus (Figure 22-3) contains vital sensors to monitor and control key functions such as appetite, thirst, thermal regulation, the sleeping/waking cycle (circadian rhythm), the menstrual cycle, and the response to stress, exercise, and mood. It serves to integrate the many neural and endocrine inputs to control the release of pituitary hormone-releasing factors. The hypothalamic neurons secrete both pituitary hormone-releasing and pituitary-inhibitory factors (and hormones) via the portal (vein) system, which passes down the stalk into the pituitary.[19]

Pituitary Gland

The pituitary gland is a pea-sized structure situated at the base of the brain within the sella turcica, and is in intimate association with the hypothalamus. It plays a key role in the control of the endocrine system via feedback mechanisms, and hence has been termed the "conductor of the endocrine orchestra."[20]

The pituitary gland is divided into two anatomically, functionally, and developmentally distinct structures: the anterior and posterior lobes.

Anterior Pituitary (Adenohypophysis)

The anterior pituitary hormones (Figures 22-3 and 22-4) are under predominantly positive control by the hypothalamic-releasing hormones, apart from the release of prolactin, which is under tonic inhibition by dopamine. Therefore, pathologic conditions that interrupt the flow of hormones between the hypothalamus and the pituitary gland result in deficiencies of most hormones, but the oversecretion of prolactin. The anterior pituitary is a mixture of cells that produce GH, ACTH, TSH, LH, FSH, and prolactin. ACTH, TSH, FSH, and LH are all intermediaries in their respective endocrine axes; each responds to a specific hypothalamic hormone (Figure 22-5) and, in turn, acts upon an end-organ gland to bring about the endocrine response.

There are five major anterior pituitary axes:

- Gonadotrophin axis.
- Growth axis.
- Prolactin (lactation) axis.
- Thyroid axis.
- Adrenal axis.[21]

The role of the anterior pituitary hormone prolactin is for the initiation and maintenance of lactation. Prolactin levels are increased during pregnancy, breast-feeding, nipple stimulation, stress, and chest wall injury, and by medications with antidopaminergic properties (e.g., antipsychotics).

Posterior Pituitary (Neurohypophysis)

The posterior pituitary (Figures 22-3 and 22-4) is a group of neural cells that are an extension of the hypothalamus and have secretory capacity. The posterior pituitary only secretes two hormones, arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), and oxytocin, both of which are nonapeptides (oligopeptides formed from nine amino acids; Figure 22-5). The primary physiologic functions of oxytocin include contraction of the myoepithelial cells of the alveoli of the mammary gland, which is important during lactation as part of the "let-down response," and contraction of the uterus during childbirth and immediately postpartum.

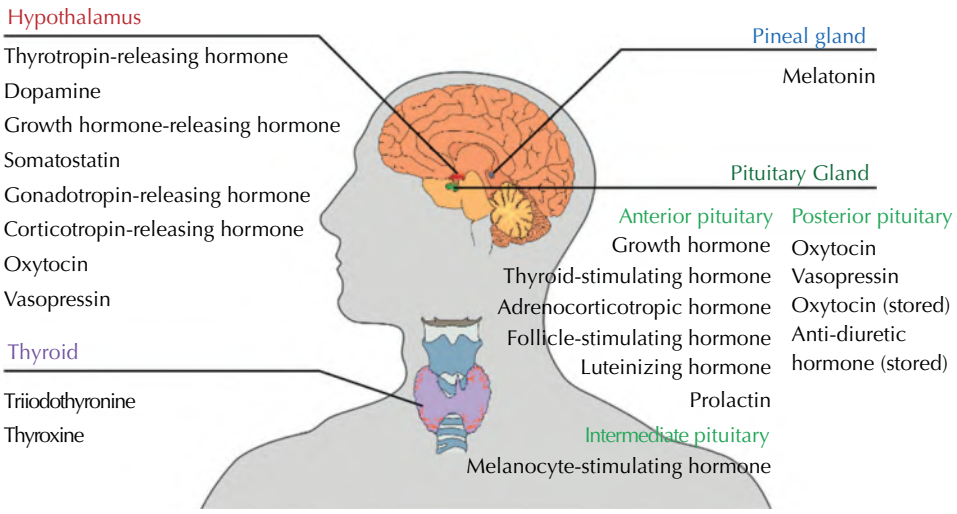


Figure 22-4 Endocrine system in the head and neck region. *Source:* https://commons.wikimedia.org/wiki/File:Endocrine_central_nervous_en.svg. Public domain..

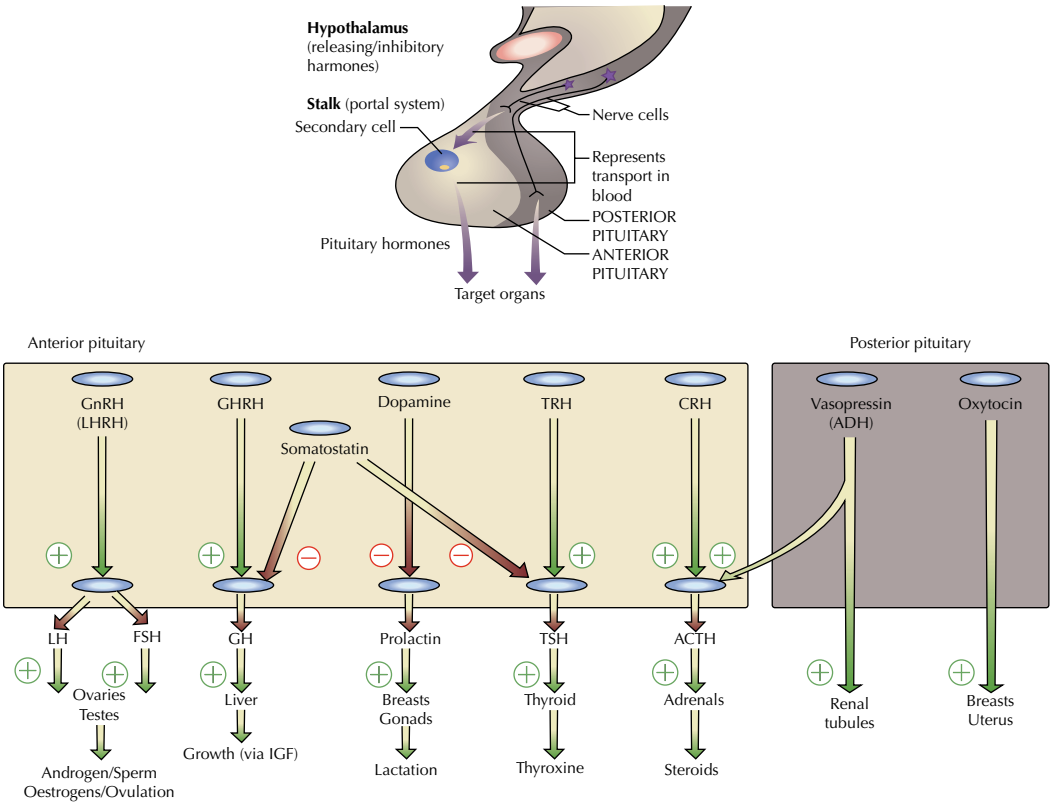


Figure 22-5 The hypothalamic-releasing hormones and their corresponding pituitary trophic hormones. ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; GnHR, gonadotrophin-releasing hormone; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone. *Source:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Reproduced with permission.

Hormone Excess

Hormone excess is seen with pituitary adenomas that are usually benign and slow growing. The symptoms related to the physical enlargement of the adenoma include visual impairment or headache. Occasionally these are detected incidentally as a finding on a magnetic resonance imaging (MRI) or computer tomography (CT) scan. They can result in increased secretion of the hormone(s) produced by the cells represented in these lesions and/or decreased secretion of other hormones due to compression by the tumor. In contrast, pituitary apoplexy (pituitary infarction) has a dramatic presentation with a sudden and severe headache, often with diplopia. Evaluation of masses within the sella turcica is best done with MRI (see Figure 22-6) and evaluation of the hormonal profile.

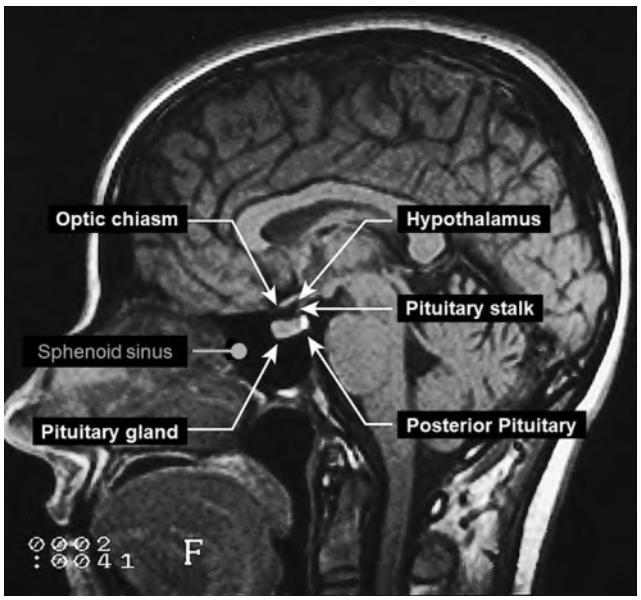


Figure 22-6 Magnetic resonance imaging (MRI) of a sagittal section of the brain, showing the pituitary fossa and adjacent structures. *Source:* Modified from Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Reproduced with permission.

Hypopituitarism

Defects of the hypothalamic-releasing hormones or of the pituitary trophic hormones can be selective or multiple. Selective deficiencies of GH, LH/FSH, ACTH, TSH, and

vasopressin (ADH) are all seen from a variety of causes. Multiple deficiencies usually result from a tumor. There is generally a progressive loss of anterior pituitary function, with GH and the gonadotrophins usually being the first trophic hormones affected. Hyperprolactinemia, rather than prolactin deficiency, occurs relatively early, because of loss of tonic inhibitory control by dopamine. TSH and ACTH secretion is usually the last to be affected. Panhypopituitarism refers to deficiency of all anterior pituitary hormones and it is most commonly caused by pituitary tumors, or as a consequence of the surgery or radiotherapy used in the treatment of such tumors. ADH and oxytocin secretion will only be significantly affected if the hypothalamus is involved, either by a hypothalamic tumor or by suprasellar extension of a pituitary lesion. ADH and oxytocin deficiency is rarely seen with an uncomplicated pituitary adenoma. In general, the symptoms of deficiency of a pituitary-stimulating hormone are the same as primary deficiency of the peripheral endocrine end-organ; for example, TSH deficiency results in primary hypothyroidism and so causes similar symptoms due to lack of thyroid hormone secretion.[22]

Clinical Features

The symptoms and signs will reflect the extent of the hypothalamic and/or pituitary deficiencies, with mild deficiencies being generally clinically silent.

- *Secondary hypothyroidism* and *adrenal failure* both lead to tiredness and general malaise.
- *Hypothyroidism* results in weight gain, slowed mentation, slowness of action, dry skin, and cold intolerance.
- *Hypoadrenalism* causes mild hypotension, hyponatremia, and, ultimately, cardiovascular collapse during severe intercurrent stressful illness.
- *Gonadotrophin/gonadal deficiency* leads to loss of libido, loss of secondary sexual hair, amenorrhea, and erectile dysfunction.
- *Hyperprolactinemia* can cause galactorrhea and hypogonadism, including amenorrhea.
- *GH deficiency* causes growth failure in children and impaired wellbeing in some adults.
- *Weight increase* can be due to hypothyroidism.
- *Weight loss* can occur with severe combined deficiency (pituitary cachexia).
- *Panhypopituitarism* when long-standing gives the classic picture of pallor with hairlessness ("alabaster skin").

Treatment entails hormone replacement by synthetic equivalents. Steroid and thyroid hormones are essential for life. Both are given as oral replacement drugs, as in primary thyroid and adrenal deficiency, aiming to restore biochemical normality (see Table 22-5).

Table 22-5 Hypopituitarism: hormone replacement regimens.

Axis	Replacement Regimen
Adrenal	• Hydrocortisone 15–40 mg daily (starting dose 10 mg on rising/5 mg lunchtime/5 mg evening) Normally no need for mineralocorticoid replacement
Thyroid	• Levothyroxine 100–150 µg daily
Gonadal	
Male	• Testosterone—intramuscular, oral, transdermal, or implant
Female	• Estrogen/progesterone (cyclical)—orally or as patch
Fertility	• Human chorionic gonadotrophin *plus* Follicle-stimulating hormone (purified or recombinant) or gonadotropin-releasing hormone—for testicular development, spermatogenesis, or ovulation
Growth	• Children—recombinant growth hormone (GH); used to achieve normal growth in children • Adults—advocated for replacement therapy; GH has effects on muscle mass and wellbeing
Thirst	• Desmopressin 10–20 µg, 1–3 times daily by nasal spray or orally 100–200 µg 3 times daily • Carbamazepine, thiazides, and chlorpropamide—very occasionally used in mild diabetes insipidus
Lactation (breast)	• Dopamine agonist (e.g., cabergoline 500 µg weekly)

Source: Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(11):3888–3921.

ABNORMALITIES OF GROWTH AND STATURE

Growth Hormone

GH is the pituitary factor responsible for growth in humans. GH secretion is stimulated by growth hormone-releasing hormone (GHRH), released into the portal system from the hypothalamus (Figure 22-7). There is a separate GH-stimulating system that interacts with ghrelin, a hormone that is synthesized by the stomach. It is unknown how the two systems interact. GH binds to receptors mainly found on liver cells, which results in turn in the release of IGF-1, for which there are multiple binding proteins (IGF-BP) in the plasma. Of these, IGF-BP3 can be measured to assess GH status. The metabolic actions of this system are increased collagen and protein synthesis; retention of

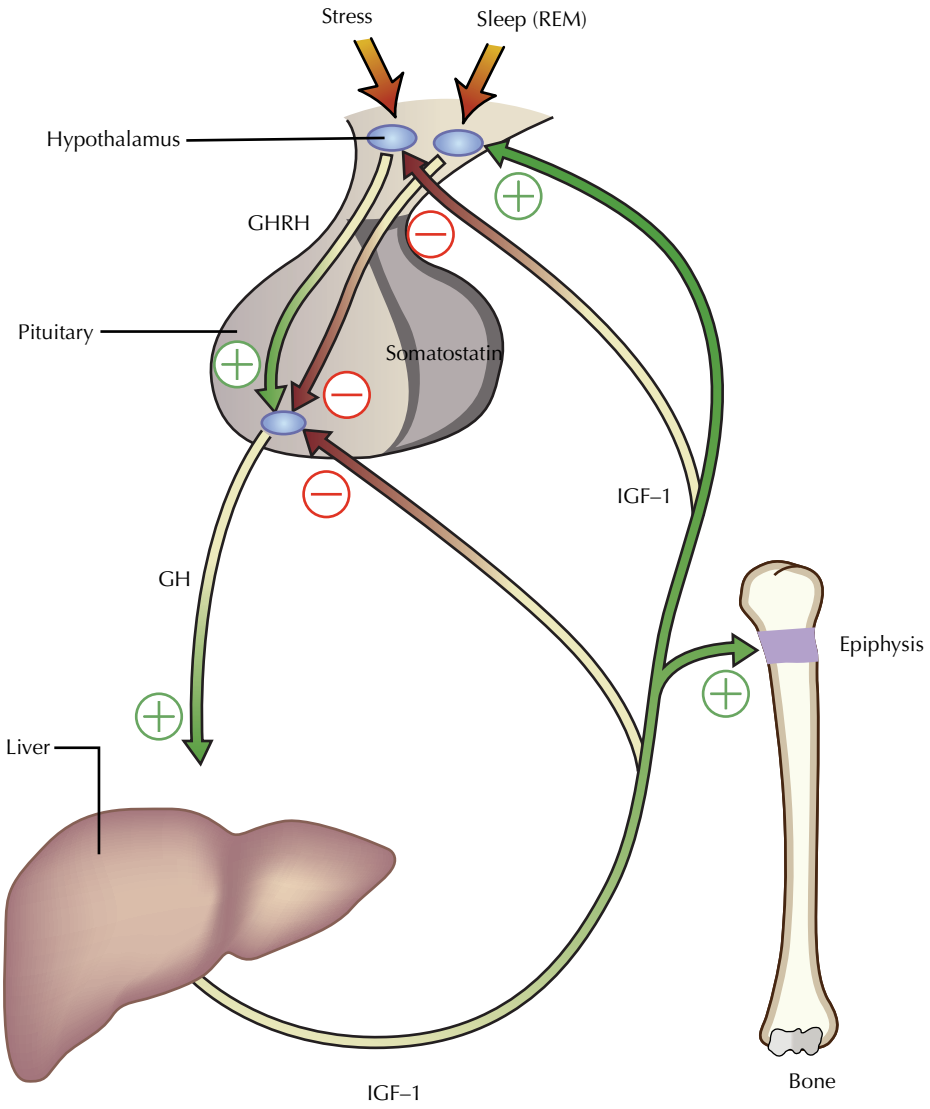


Figure 22-7 Growth hormone (GH): release and action. Pituitary GH is secreted under dual control of growth hormone-releasing hormone (GHRH) and somatostatin, and stimulates release of insulin-like growth factor 1 (IGF-1) in the liver and elsewhere. IGF-1 has peripheral actions, including bone growth by acting on the epiphyseal plate (epiphysis). *Source:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Reproduced with permission.

calcium, phosphorus, and nitrogen (necessary for anabolism; i.e., the building of molecules); and opposing the actions of insulin. GH release is intermittent, mainly nocturnal during REM sleep, and is significantly increased during adolescence, but afterward declines.

Apart from GH, the following factors play a role in the normal linear growth of humans:

- *Genetics*: children of short parents will probably be short and vice versa.
- *Nutrition*: inadequate nutrients result in impaired growth, either from inadequate dietary intake or small bowel disease, for example coeliac disease.
- *General health*: serious systemic disease, such as chronic infection, will impair growth.
- *Intrauterine growth retardation*: this will result in poor long-term growth, whereas premature infants tend to catch up.
- *Emotional deprivation and psychologic factors*: these play a role in growth and development, although the mechanisms are complex and not fully understood.

Growth Assessment and Treatment

Growth charts and associated computer programs are now available for national and specific ethnic groups to monitor

and predict a child's final height. The Centers for Disease Control and Prevention (CDC) have readily available (downloadable) growth charts consisting of a series of percentile curves that illustrate the distribution of selected body measurements in US children (Figures 22-8 and 22-9).[23,24] These growth charts are also essential for predicting the treatment and prognosis of orthodontic and/or orthognathic treatment.[25]

Growth Failure (Short Stature)

This is usually noted by the child's parents. Height velocity is more helpful than current height. This requires at least two measurements some months apart and, ideally, multiple serial measurements. Height velocity is the rate of current growth (centimeters per year), while the current attained height is largely dependent upon previous growth. Computer programs are available to calculate the key indices, which include standard deviation scores based on the degree of deviation from age/sex norms.[26]

Further investigations include dynamic assessment of GH levels, IGF and IGF-BP3 blood levels, thyroid function tests, and assessment of bone age, by radiographs of the nondominant wrist and karyotyping in females for Turner's syndrome.[27]

Risk Factors for Short Stature

Risk factors for short stature include:[28]

- Intrauterine growth retardation, and weight and gestation at birth.
- Systemic disorders, especially small bowel disease.
- Congenital abnormalities (i.e., skeletal, chromosomal, or other).
- Endocrine status, particularly thyroid.
- Dietary intake.
- Drugs, especially steroids for asthma.
- Emotional, psychological, family, and school problems.

A child with normal growth velocity is unlikely to have significant endocrine disease and the most common cause of short stature in this situation is pubertal or "constitutional" delay. However, low growth velocity without an apparent systemic cause requires investigation (Table 22-6), as does sudden cessation of growth, since this suggests major physical disease, and in the absence of findings of systemic disease then a cerebral tumor or hypothyroidism is most likely.

Tall Stature

Tall stature (as opposed to gigantism/acromegaly) is most commonly hereditary, because of having tall parents. However, if the child's stature is usually tall and not consistent with the stature of the parents, chromosomal abnormalities such as Klinefelter syndrome or Marfan syndrome, or metabolic abnormalities, need to be considered. GH excess is a very rare cause and is usually clinically evident.

Acromegaly and Gigantism (Growth Hormone Excess)

GH is released from the somatotropic cells within the lateral wings of the anterior pituitary gland and is the primary trophic hormone responsible for postnatal growth and development. GH excess causes what is more formally termed *pituitary gigantism* in children if this occurs before fusion of the epiphyseal plate (growth). Gigantism is a nonspecific term that denotes excessive growth in a pediatric patient.[29] GH excess results in *acromegaly* if it occurs after the bony growth plates have fused. In almost all cases this is due to GH-secreting pituitary adenoma.

GH's major trophic effect is the release of IGFs from the liver. IGFs, as their name suggest, are proteins with significant homology to insulin, with a wide range of functions, but principally act to increase bone growth (specifically bone length). Although many cells have GH receptors and may respond to GH, the vast majority of the growth-stimulating effects of GH are mediated by IGF-1. GH release is under positive regulation by the hypothalamic peptide GH-releasing hormone. The amount and pattern of GH production and IGF release change markedly across the life cycle, with maximal release during the intense growth periods of late childhood and adolescence and low levels with advanced age. GH is released from the pituitary in a pulsatile fashion, with peak secretion at night. Thus, serum GH values vary considerable over the course of a 24-hour period, so a random sample may not reliably indicate true GH levels. In contrast, IGF-1 serum levels are relatively constant over the course of the day, so an IGF-1 sample can be taken at any time of the day and is indicative of GH levels.

Gigantism is very rare, with 0.6% reported in a large pediatric cohort.[30] Acromegaly is rare, with an overall prevalence of estimated prevalence in Europe of 30–70 individuals per million, affecting men and women equally.[31] The rapid growth seen with gigantism can be distinguished from that of precocious puberty. In gigantism, growth occurs in the absence of early secondary sexual characteristics, as the pituitary tumors (somatotroph adenomas) that lead to GH excess result in the loss of production of other pituitary hormones, particularly the gonadal trophic hormones, FSH, and LH, which are responsible for sexual development. Mild to moderate obesity is also commonly seen in these patients.

The mean age at diagnosis of acromegaly is usually 40–45 years, but as the progression of disease is so slow, the interval from the onset of symptoms until diagnosis can be as much as 12 years. Manifestations include the classic facial appearance of coarse facies, macrognathia, macroglossia,

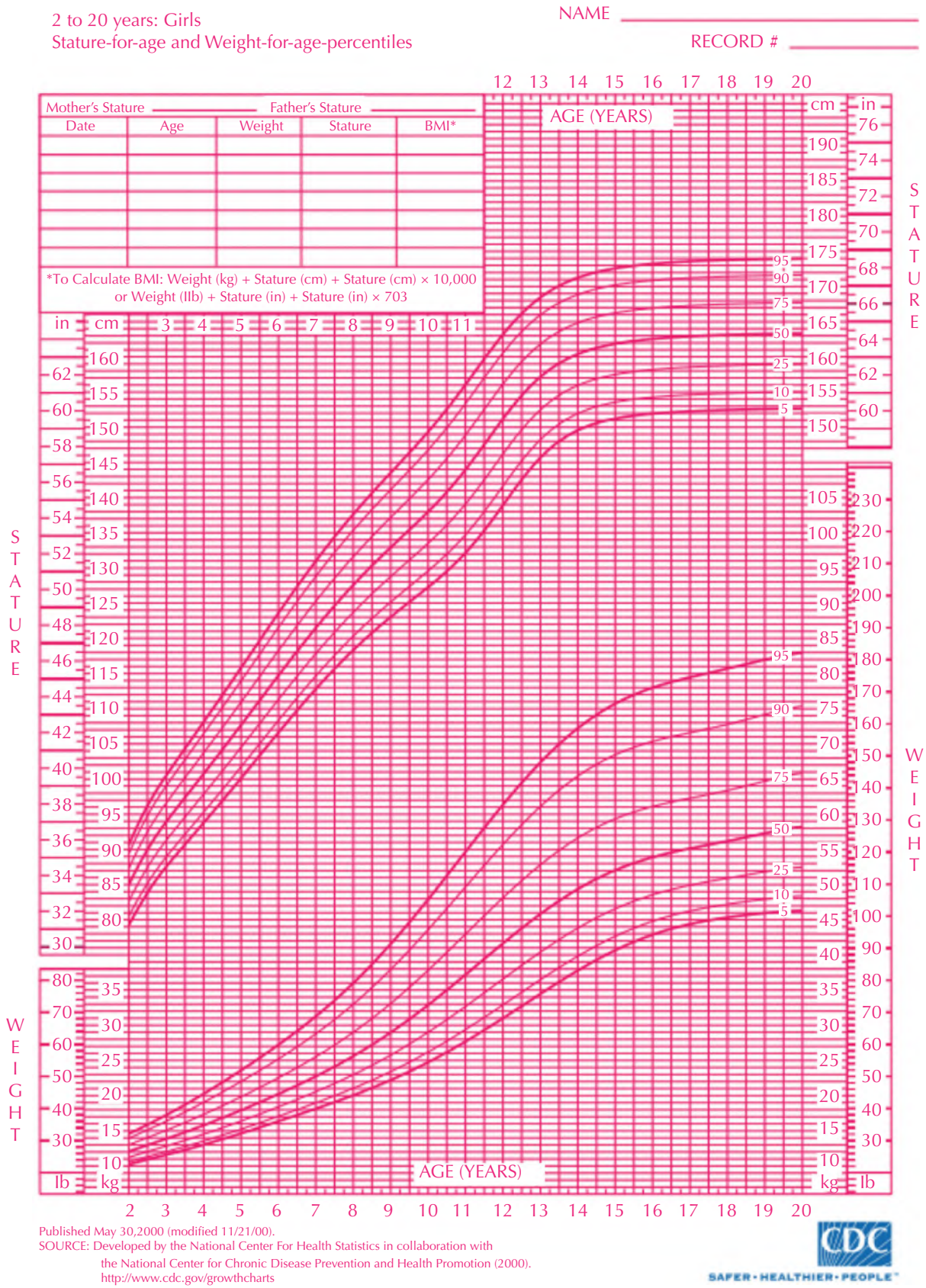


Figure 22-8 Height chart for girls.

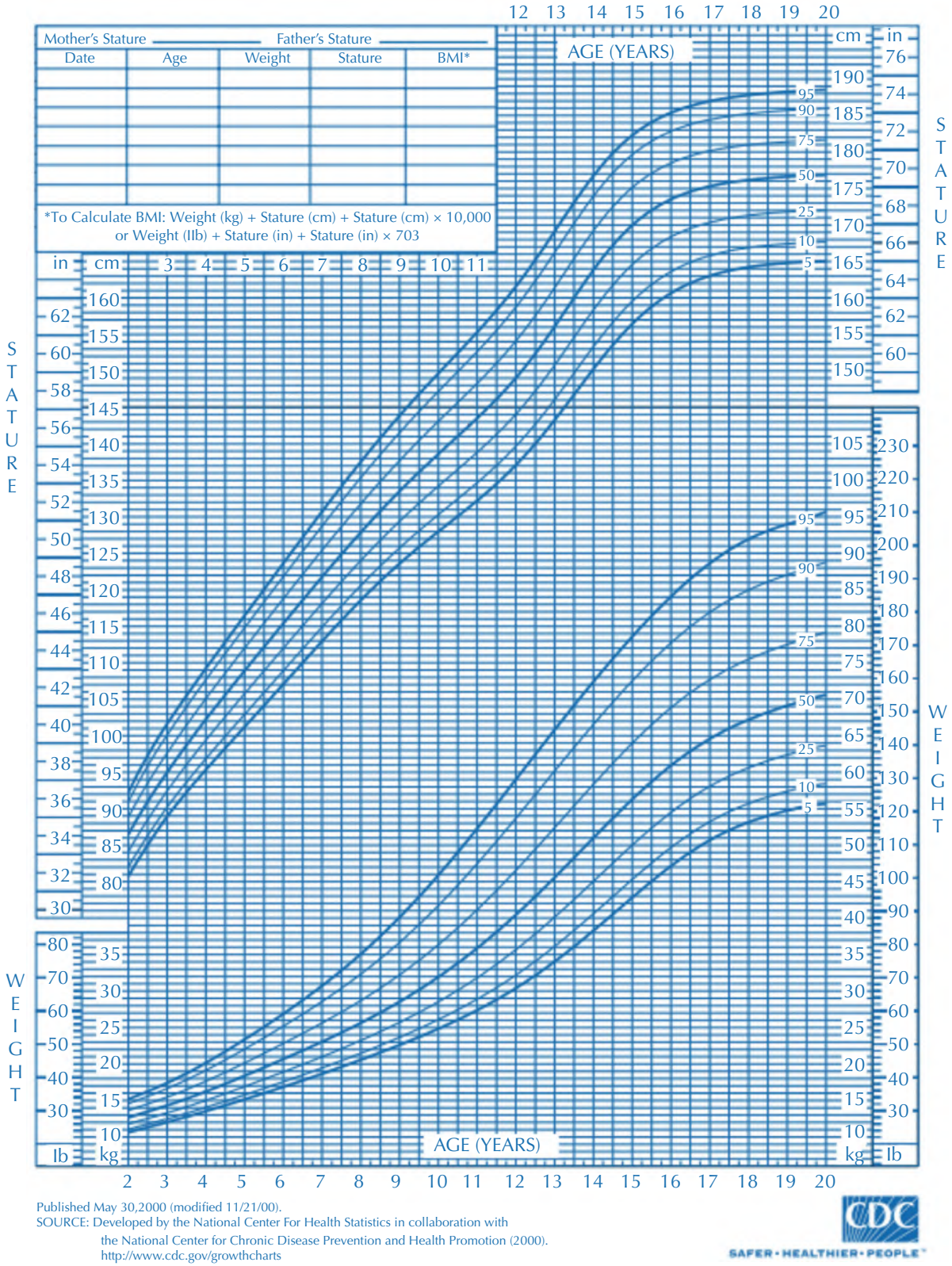


Figure 22-9 Height chart for boys.

Table 22-6 Clinical features of common causes of short stature.

Cause	Family History	Growth Pattern	Bone Age	Comments
Constitutional delay	Positive	• From birth: slow • Growth: delayed • Puberty: late but spontaneous	Moderate delay	• Difficult to differentiate from GH deficiency • Growth velocity assessment essential
Familial short stature	Positive	• From birth: slow • Growth: normal • Puberty: normal onset and growth	Normal	• Check height of parents/family members • Growth velocity: normal
Growth hormone (GH) deficiency	Rare	• From birth: slow • Overweight • Puberty: delayed	Moderate delay Worsens over time	• Need high level of clinical suspicion • Investigate early
Primary hypothyroidism	Rare	• From birth: slow • Puberty: delayed	Marked delay	• Check thyroid-stimulating hormone and T4
Small bowel disease • Celiac disease • Crohn's disease • Ulcerative colitis	Possibly	• From birth: slow • Growth: slow • Thin for height • Puberty: delayed	Delayed	• Check for irregular bowel habit, colic • Oral manifestations of celiac disease/ inflammatory bowel disease (IBD) • Check for anemia • Serology: celiac and IBD

large diastemas, and enlargement of the nose and frontal bones (frontal bossing) (Figure 22-10). Soft tissue edema, due to a direct effect of GH on sodium retention, leads to a "doughy" feel to the hands and feet, as well as an increase in shoe, hat, glove, and ring sizes. Patients can also have increased sweating, deepening of the voice due to enlargement of the thyroid cartilage and vocal cords, enlargement of the synovium and cartilages with hypertrophic arthropathy (knees, ankles, hips, spine, and other joints), skin tags, nerve compression (causing paresthesia of the hands, as in carpal tunnel syndrome), enlargement of the soft tissues of the pharynx and larynx (which can lead to obstructive sleep apnea), increased risk of uterine leiomyomata, colonic polyps, and organomegaly (including the thyroid, heart, liver, kidneys, and prostate). Some 50% of patients with GH excess develop hypertension, 10% develop cardiomegaly with heart failure, which accounts for much of the increased mortality associated with acromegaly and 30% develop insulin resistance or T2DM. Surprisingly, patients seldom independently seek care as the changes are so insidious, and treatment is often initiated when a relative or friend, who has not seen the patient for some time, notes the typical changes as described here.[17]

Diagnosis

Diagnosis is often made on the clinical presentation, with a third diagnosed by the changes in appearance, a quarter because of the visual field defects and/or headache, and the reminder by an astute clinician, including the patient's family physician (investigating potential causes for hypertension), dermatologist, and in particular the dentist.[32] Key investigations are serum GH levels, IGF-1 levels, MRI, which will reveal a pituitary adenoma, visual field examination, and glucose challenge test.

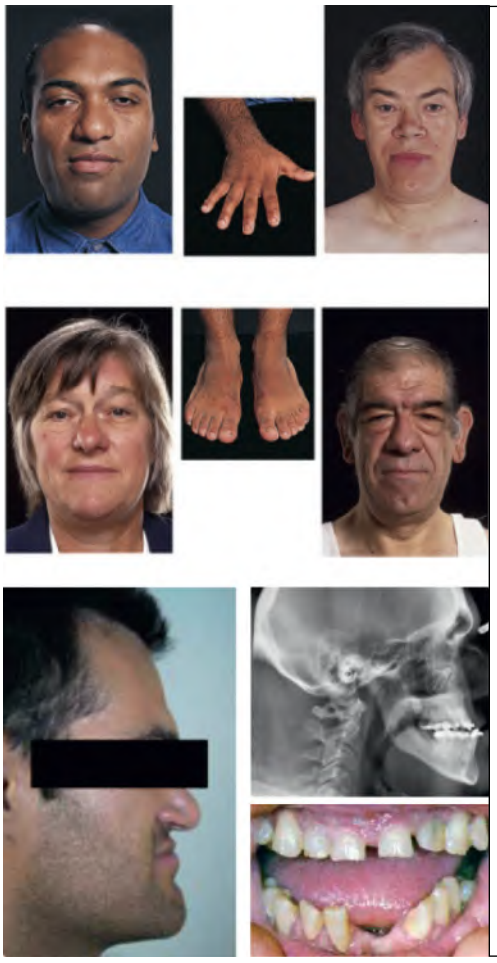
Treatment

Untreated acromegaly results in significant morbidity and increased rate of premature death. The aims of treatment are to establish a "safe" GH level and a normal IGF-1 level. If present, hypopituitarism also needs to be addressed. Concurrent hypertension and/or diabetes should be treated with conventional agents, but usually resolve with treatment of the acromegaly.

Treatment is usually surgical, most commonly by a transsphenoidal approach, or transfrontal for large adenomas, with radiotherapy reserved for situations in which GH levels fail to normalize. There are three potential targets for medical therapy: (1) somatostatin receptor agonists, either octreotide or lanreotide, which are given as monthly depot injections—these are generally effective, but do increase the risk for the development of gallstones; (2) dopamine agonists, either bromocriptine or cabergoline, which are best for patients with mild residual disease; and (3) growth hormone receptor antagonist, that is pegvisomant, a genetically modified analogue of GH that is reserved for patients who otherwise fail all other interventions.[33]

Symptoms

- Hypertension
- Dyslipidemia
- Obstructive sleep apnea (OSA)
- Headaches
- Deepening voice
- Visual changes (bitemporal hemianopsia)
- Gastroesophageal reflux disease (GERD)
- Colon polyps
- Insulin resistance
- Renal failure
- Osteopenia
- Arthritis
- Carpal tunnel syndrome
- Hypogonadism
- Amenorrhoea
- Erectile dysfunction



Signs

- Cardiomegaly
- Heart Failure
- Valvopathy
- Visual deterioration
- Deepening voice
- Diabetes mellitus
- Hyperhidrosis (excessive perspiration
- Changed appearance
- Enlarged hand and feet

Stomatognathic

- Prognathism
- Macroglossia
- Frontal bossing
- Class III malocclusion
- Anterior open bite
- Increasing interdental spacing and diastemas
- Thickened lips

Figure 22-10 Symptoms and signs of acromegaly. *Sources:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017. Prognathic jaw clinical photo and radiograph from Ivry G, Felsenfeld AL. Acromegaly: a dental disease? *J Calif Dent Assoc*. 2016;44(9):577–580. Reproduced with permission.

Stomatognathic Manifestations and Complications of Acromegaly

The predominant clinical findings in acromegaly—prognathism with evolving or established class III malocclusion; the development of significant diastemas, especially of the mandibular dentition; and radiographic findings of enlarged sella and frontal bossing (on lateral cephalogram)—mean that hygienists, dentists, and dental-related specialists are key in making the initial diagnosis of acromegaly. Following diagnosis and appropriate treatment, oral health professionals can facilitate oral rehabilitation. However, even patients with treated acromegaly can still have ongoing disease-related morbidities, which need to be identified on taking a comprehensive medical history. The key concerns in particular are treatment-refractory hypertension, valvopathy, and obstructive sleep apnea (OSA). The sleep apnea seen in association with acromegaly is predominantly obstructive and is related to thickening of walls of the upper airway, including the soft palate. However, the patient with acromegaly and sleep apnea presents special problems, as retropositioning the mandible to treat the prognathism is inconsistent with the principles involved in the management of OSA, necessitating alteration in conventional treatment planning.[34,35]

HYPERPROLACTINEMIA

Hyperprolactinemia can be caused by hyperplasia of the so-called lactotroph cells (prolactinomas) or decreased tonic dopaminergic inhibition of prolactin secretion (e.g., compression by a central nervous system tumor).[36] Prolactinomas can cause hypogonadism by suppressing gonadotropin secretion. In women, hypogonadism results in low serum estrogen levels that can present as oligomenorrhea, amenorrhea, infertility, and osteoporosis. In men, hypogonadism causes low serum testosterone concentrations that result in decreased libido and energy, decreased facial hair growth, loss of muscle mass, and osteoporosis. Hyperprolactinemia in men may also

be associated with impotence even when the serum testosterone concentration is normal. It can cause galactorrhea (leakage of milk from the breast other than during lactation) in women, but this only occurs very rarely in men.

Prolactinomas are relatively common, accounting for 30–40% of all clinically recognized pituitary adenomas. The diagnosis is made more frequently in women than in men, especially between the ages of 20 and 40 years, presumably because the hyperprolactinemia disrupts their menstrual cycle.[37] Such tumors can be identified by the enlargement of sella turcica incidentally observed on lateral cephalograms.[38]

Prolactinomas can be treated with dopamine agonists, such as cabergoline or bromocriptine. These drugs have the dual effect of decreasing hormone secretion and tumor size. If the adenoma does not respond to increasing doses of these medications or there is imminent visual loss, transsphenoidal surgery is required for removal of the tumor.[39]

DISORDERS OF ANTIDIURETIC HORMONE

Thirst Axis

Thirst and the symptoms of thirst, xerostomia and the signs of dehydration, namely hyposalivation and dry mucous membranes of the mouth, are of course of great relevance to the clinical practice of oral healthcare providers. Thirst and water regulation are largely controlled by vasopressin, also known as antidiuretic hormone (ADH). ADH is synthesized in the hypothalamus and then migrates in neurosecretory granules via axonal pathways to the posterior pituitary. Pituitary diseases that spare the hypothalamus do not lead to ADH deficiency, as the hormone still can "leak," even from the end of a damaged axon.

The kidney is the predominant site of action of ADH at normal concentrations. ADH stimulation of the vasopressin-2 (V2) receptors allows the collecting ducts to become permeable to water, via the migration of aquaporin-2 water channels, resulting in the reabsorption of hypotonic luminal fluid. ADH acts to reduce diuresis (i.e., less urine) and results in retention of water. At high concentrations, ADH can also cause vasoconstriction, via the V1 receptors present in the vascular tissues, thus limiting blood supply to the kidneys, resulting in further water retention and less urine output.

ADH is regulated by osmoreceptors in the anterior hypothalamus that can sense plasma osmolality. ADH secretion is suppressed at levels below 280 mOsm/kg, thus allowing maximal urine formation (diuresis). Above this level, plasma vasopressin increases in direct proportion to plasma osmolality. At the upper limit of normal (295 mOsm/kg), maximum antidiuresis is achieved (little if any urine production), with thirst being experienced at about 298 mOsm/kg.

DIABETES INSIPIDUS

Disorders of ADH are in essence disorders of water balance. ADH deficiency is termed diabetes insipidus (DI) and is a syndrome characterized by the inability for the kidneys to retain water.[40] It can be caused by inadequate pituitary production of ADH (termed *central DI*), or resistance to the actions of ADH on the kidneys (termed *nephrogenic DI*). DI can also be gestational, or present as an iatrogenic artefact of alcohol or some types of drug abuse. The primary presenting symptom is polyuria (>3 L/d), and resultant hypernatremia, nocturia, and compensatory polydipsia (excessive thirst/water intake). Daily urine output may reach as much as 10–15 L, leading to dehydration that may be very severe if the thirst mechanism or consciousness is impaired or if the patient is denied fluid. Diagnosis of DI is made by a water deprivation test, requiring medical supervision.[41]

Treatment is with the synthetic vasopressin (ADH) analogue desmopressin (also known as DDAVP, 1-desamino-8-d-arginine vasopressin, desamino cys-1-d-arginine-8 vasopressin), which has the advantages of a longer duration of action than vasopressin and no vasoconstrictive effects. It is reliably given by an intranasal spray 10–40 μg once or twice daily, but can also be given orally (100–200 μg three times daily or intramuscularly 2–4 μg daily). For patients with DI, a reversible underlying cause (e.g., a hypothalamic tumor) should be investigated for and treated, if found. Other causes of polyuria and polydipsia include diabetes mellitus (DM), hypokalemia, and hypercalcemia, which should be excluded. In the case of DM, the cause is an osmotic diuresis secondary to glycosuria, which leads to dehydration and increased thirst, owing to the hypertonicity of the extracellular fluid.[42]

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE

Excessive ADH (syndrome of inappropriate antidiuretic hormone, SIADH) is a syndrome of too much total body water and consequent hyponatremia, of which the electrolyte disturbance is the main concern and the cause of the presenting clinical features.[43] Major causes of SIADH include central nervous system (CNS) disturbances such as stroke, infection, trauma, and hemorrhage. Other causes are medications, serious illness (especially in the elderly), and some types of cancer. The clinical presentation tends to be slow, with the patient exhibiting confusion, nausea, irritability, and, later, fits and coma, but with no edema. Mild symptoms usually occur with plasma sodium levels below 125 mmol/L and serious manifestations occurring below 115 mmol/L.[44] The elderly may show symptoms with milder abnormalities. SIADH needs to be differentiated from dilutional hyponatremia

Table 22-7 Physiologic effects of the thyroid hormones.

Target Organs/Tissues	
Cardiovascular system	↑ Heart rate ↑ Cardiac output
Respiratory center	Maintains normal • Hypoxic drive • Hypercapnic drive (response to CO_2 concentration in the blood)
Neuromuscular function	↑ Muscle contraction and relaxation ↑ Muscle protein turnover
Sympathetic nervous system	↑ Catecholamine sensitivity ↑ β-adrenergic receptor numbers on: heart, skeletal muscle, adipose cells, and lymphocytes ↓ Cardiac α-adrenergic receptors
Gastrointestinal system	↑ Gut motility
Metabolism Carbohydrate	↑ Hepatic gluconeogenesis/glycolysis ↑ Intestinal glucose absorption
Lipid	↑ Lipolysis ↑ Cholesterol synthesis and degradation
Bone	• Bone turnover and resorption
Hematologic system	• Oxygen release by red blood cells to tissues

due to excess infusion of glucose/water solutions or diuretic administration (thiazides or amiloride). ACTH deficiency can give a very similar biochemical picture to SIADH; therefore, it is necessary to ensure that the HPA axis is intact, particularly in neurosurgical patients, in whom consequently ACTH deficiency is relatively common.

Management entails identifying the underlying cause and correcting this, when possible. Symptomatic relief includes fluid restriction, with an intake of only 500–1000 mL water daily; if complied with, this will usually correct the biochemical abnormalities. Such fluid restriction can result in salivary hypofunction and so directly contribute to higher rates of dental decay, and candidiasis.[45,46] Newly available, ADH (V2) antagonists (e.g., tolvaptan, sold as Samsca® in the United States; Otsuka America Pharmaceutical, Rockville, MD, USA) are being used with good effect.[47]

THYROID DISEASE

Thyroid disease occurs frequently and is the most common endocrine disease. The thyroid gland synthesizes three hormones: (1) thyroxine (T4), which is a prohormone; (2) triiodothyronine (T3), the active hormone that is critical in regulating the body's metabolic rate; and (3) calcitonin, which regulates bone metabolism. Adequate levels of thyroid hormone are essential in infants for normal CNS development, in children for normal skeletal growth and maturation, and in adults for the normal function of multiple organ systems (Table 22-7). In general, there are five main types of thyroid disease, and disease can be intercurrent in the same patient:

- Hypothyroidism (termed "myxedema" when it occurs in adults and "cretinism" when it occurs in infants and children), caused by a deficiency of thyroid hormones.
- Hyperthyroidism (thyrotoxicosis), due to an excess of thyroid hormones with consequent significant clinical issues, especially of the cardiovascular system.
- Abnormal thyroid function tests (TFTs), in an otherwise euthyroid (the state of having normal thyroid gland function) patient.
- Structural abnormalities, mainly goiter, which may be seen as diffuse enlargement of the thyroid gland, or single or multiple nodules, due to focal enlargement of only a portion of the gland,
- Neoplasms.

Epidemiology

Thyroid disease has prevalence of 6% as of 2019 and it is estimated that over 12% of Americans will develop some form of thyroid disease over the course of their lifetime.[48] Of these, some 60% are unaware of their condition. Thyroid diseases

are far more common in women. The management for most thyroid disorders is life-long and well tolerated. In the United States, autoimmune inflammation is the most common cause of thyroid disease whilst worldwide hypothyroidism and goiter due to iodine deficiency is much more common.[49] Although thyroid nodules are common, thyroid cancer is rare. Thyroid cancer accounts for less than 1% of all cancer in the US,[50] although it is the most common endocrine tumor and makes up greater than 90% of all cancers of the endocrine glands.[51]

Thyroid Gland: Anatomy and Physiology

The thyroid gland consists of two lateral lobes connected by an isthmus, closely attached to the thyroid cartilage and to the upper end of the trachea, and thus moves on swallowing. Embryologically, it originates from the base of the tongue and descends to the middle of the neck. Remnants of thyroid tissue can sometimes be found at the base of the tongue (lingual thyroid) and along the line of its descent.

Internally, the thyroid gland consists of follicles lined by cuboidal epithelioid cells within which is colloid (iodinated glycoprotein thyroglobulin), synthesized by the follicular cells. Each follicle is surrounded by basement membrane, and between them are parafollicular cells containing the C cells that secrete calcitonin. The thyroid also synthesizes triiodothyronine (T3), which acts at the cellular level, and L-thyroxine (T4), which is the prohormone. Inorganic iodine is essential for the synthesis of the two thyroid hormones and the precursor molecule, thyroglobulin (Figure 22-11). Globally, dietary iodine deficiency is a major cause of thyroid disease. Dietary supplementation of salt and bread has reduced the number of areas where "endemic goiter" still occurs. Surprisingly, in Western countries iodine deficiency is now a concern, given the decline in adventitious iodine in dairy products with use of noniodoform disinfectants in milk production and "food fads," with the use of noniodized rock salt in place of iodized salt in cooking. In the United States iodine intakes have fallen, and it is uncertain whether the iodine status for most pregnant woman is satisfactory, leading to calls for systematic iodine supplementation.[52]

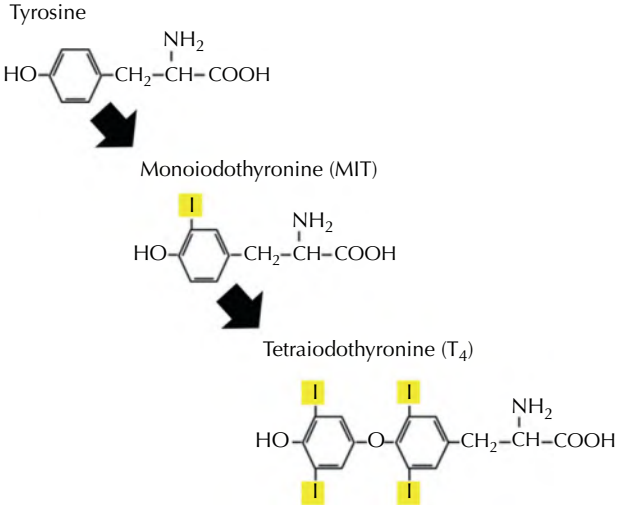


Figure 22-11 The conversion of the amino acid tyrosine, with the addition of iodine (yellow) atoms.

In plasma, more than 99% of all T4 and T3 is bound to hormone-binding proteins: TBG, thyroid-binding prealbumin, and albumin. Only unbound—that is, free—hormone is biologically active. Circulating T4 is peripherally deiodinated to T3, which has a far greater affinity for its receptors than T4. T3 binds to the two thyroid hormone nuclear receptors (TR-α and TR-β) of the target cells to cause gene transcription.

Control of the hypothalamic-pituitary-thyroid axis is, as is universal throughout the endocrine system, by negative feedback control. Thyrotropin-releasing hormone (TRH) is a peptide produced in the hypothalamus, which stimulates the pituitary to secrete TSH (Table 22-8). TSH, in turn, stimulates growth and activity of the thyroid follicular cells, which consequently secrete T3 and T4 into the circulation. T3 and T4 both exert negative feedback on the hypothalamus, leading to a decrease in the secretion of TRH and so a decrease in TSH and in turn a decrease in T3 and T4. The decrease in circulating T3 and T4 prompts increased release of TRH and, again, in turn an increase in TSH and then T3 and T4.

Hypothyroidism

Hypothyroidism, defined as the inadequate release of the two thyroid hormones T3 and T4, is usually primary; that is, due to disease of the thyroid gland, However, it may be secondary, due to disease of hypothalamic or pituitary, with consequent reduction in TSH, and so a decline in T3 and T4 release by an otherwise intact thyroid gland.

Hypothyroidism is one of the most common endocrine conditions, with a prevalence rate of 4.6% for the US population. Approximately 0.3% present with clinically overt disease and the remaining 4.3% with subclinical disease (decreased T3 and T4 levels but no clinical evidence of disease).[53] Of those with subclinical hypothyroidism, 2% per annum develop clinically evident hypothyroidism, hence the lifetime prevalence for an individual is higher—perhaps as high as 9% for women and 1% for men, with mean age at diagnosis around 60 years.[54]

Causes

Autoimmune

- *Atrophic (autoimmune) thyroiditis.* This is associated with the development of antithyroid autoantibodies with

Table 22-8 Thyroid function tests and role in clinical practice.

Normal Hypothalamic-Pituitary Function

Indication	Serum TSH*	Serum T4	Serum T3
Euthyroid	Normal	Normal	Normal
Primary hypothyroidism	High	Low	Normal or low
Subclinical hypothyroidism	High	Normal	Normal
Hyperthyroidism	Low	High or normal	High
Subclinical hyperthyroidism	Low	Normal	Normal

- If serum TSH is normal—no further testing indicated or required.
- If serum **TSH is HIGH**—the lab will add free T4 to determine degree of ***hypo***thyroidism.
- If serum TSH is LOW—both free T4 and T3 are added to the patient's sample to determine degree of ***hyper***thyroidism.

Clinical indications for additional testing:

- **Pituitary/hypothalamic disease suspected,** e.g., a young woman with amenorrhea and fatigue: test TSH.
- **Patient has symptoms of hyper- or hypothyroidism and normal TSH result:** test T4.

* With central hypothyroidism, serum TSH may be low, normal, or slightly high.
T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

consequent lymphoid infiltration of the thyroid glands, and eventual atrophy and fibrosis. It is associated with other autoimmune conditions including pernicious anemia, vitiligo, and other endocrinopathies.[55,56]

- *Hashimoto's thyroiditis.* This is most common in middle-aged women. High levels of autoantibodies are developed and directed against thyroid peroxidase (the enzyme that coverts T4 to T3).Atrophic changes are followed by regeneration, with this cycle leading to clinically evident generalized goiter, which is firm and hard on palpation.
- *Postpartum thyroiditis.* A destructive form of thyroiditis associated with the immune changes of pregnancy, this can occur up to year post parturition. It confers, as seen with most pregnancy-associated endocrine disease, a lifetime risk for the development of permanent hypothyroidism, necessitating ongoing screening for affected women.[57]

Defective Hormone Synthesis

- *Iodine deficiency.* This can result in endemic goiter, which can be massive, due to borderline iodine deficiency with consequent TSH stimulation, and therefore hyperplasia and hypertrophy of the thyroid gland. At a global scale, approximately 2 billion people suffer from iodine deficiency, of which approximately 50 million people present clinical features of hypothyroidism. The effect of chronic iodine deficiency and related hypothyroidism leads to cretinism in children, which causes growth delay, short stature, and severe cognitive impairment.[58]

Clinical Features

Hypothyroidism produces many symptoms and signs, but these can be subtle and difficult to distinguish from other causes of tiredness and fatigue. The alternate term "myxedema" refers to the typical appearance of patients with long-standing significant hypothyroidism, due to the accumulation of mucopolysaccharides in the subcutaneous tissues, presenting with mucinous, nonpitting edema, particularly of the hands, feet, and eyelids. The clinical presentation includes dry hair, thick skin, deepening of the voice, weight gain, complaints of cold intolerance, and bradycardia. Diagnosis is difficult in children, young women, and the elderly and TSH and serum T3 and T4 should be undertaken to exclude hypothyroidism in these subjects, even if only suspected. If hypothyroidism is proven (low T3 and T4), investigations are required to differentiate primary disease from diseases affecting the hypothalamus-pituitary-thyroid axis.[59]

Treatment

The commonest treatment for hypothyroidism is synthetic T4 (thyroxine), levothyroxine (sold in the United States as Synthroid®, AbbVie, North Chicago, IL, USA; Levoxyl®, Pfizer Medical, New York, USA; Tirosint®, IBSA Pharma, Parsippany, NJ, USA; and Euthyrox®, Provell Pharmaceuticals, Honey Brook, PA, USA).[60] The goals of treatment are amelioration of the patient's symptoms, normalization of the serum TSH levels, reduction in the size of goiter (if present), and, of most concern, avoidance of overtreatment (iatrogenic thyrotoxicosis). Both the initial and maintenance doses of levothyroxine are titrated

to effect, based on the serum T4 and TSH and serial electrocardiograms, to exclude the development of atrial fibrillation, a known complication of hyperthyroidism.[61] The starting dose is 100 μg/daily for the young and fit with no cardiovascular disease; 50 μg/daily for the small, frail, and elderly; and even lower (i.e., 25 μg/daily) in patients with severe, long-standing hypothyroidism or with a history of ischemic heart disease. The usual maintenance dose is 100–150 μg daily.

Myxedema Coma and "Madness"

This can occur as the culmination of severe, long-standing hypothyroidism or can be precipitated by an acute event in a poorly controlled hypothyroid patient, such as infection, myocardial infarction, cold exposure, surgery, or the administration of sedative drugs, especially opioids. The presenting features frequently do not result in a coma, but rather with variable degrees of altered consciousness, such as confusion and lethargy. However, in rare instances, the initial presentation is with prominent psychotic features, termed "myxedema madness." If this is unrecognized, patients will progress to coma. The other major clinical findings will be of hypothermia, which needs to be assessed by manually examining the patient, in particular the hands (peripheries), as many automatic thermometers do not record subnormal temperatures.[62] The patient's vital signs will demonstrate marked hypotension and bradycardia (slow pulse) and blood tests will reveal marked hypoglycemia and hyponatremia (decreased serum sodium levels). Myxedema coma is a medical emergency, with a poor prognosis, requiring prompt hospitalization. The key aspects of treatment are replacement T4 and T3. In addition, prophylactic hydrocortisone 100 mg is administered intravenously (every eight hours) until adrenal insufficiency is excluded, as well as intensive supportive measures, including mechanical ventilation, fluids, and vasopressor drugs to correct hypotension, passive rewarming), and intravenous dextrose. Empirical antibiotic treatment is usually also given. Ongoing cardiorespiratory monitoring for arrhythmias is also mandated. The mortality rate, even with the best inpatient care, is 30–50%.[63]

Hyperthyroidism

Hyperthyroidism (also termed thyrotoxicosis) is defined as thyroid overactivity with consequent increased release and greater circulating levels of T3 and T4. Hyperthyroidism is common. The reported overall prevalence is about 3%, with men and women over 65 years having the highest prevalence, of which 50% are taking levothyroxine. In the National Health and Nutrition Examination Survey, there was a bimodal distribution based on age, with prevalence highest in those subjects aged 20–39 years and those aged older than 79 years.[53]

Causes

Exogenous Causes

- The use of *supraphysiologic doses of levothyroxine* that may be intentional, e.g., in patients' post treatment for thyroid malignancy in order to maintain suppression of serum TSH.
- *Amiodarone-induced thyrotoxicosis*.[64] Amiodarone is a class III antiarrhythmic agent (Vaughan Williams' classification) that blocks the potassium channels of the atrial, nodal cardiac muscle cells and the ventricular tissues (which coordinate the heartbeat). Its main effect is to prolong repolarization of the cardiac muscle and is indicated for the treatment and prevention of ventricular fibrillation and ventricular tachycardia.[65,66] It causes both hypothyroidism and hyperthyroidism due to its high iodine content and its direct toxic effect on the thyroid.[67]

Endogenous Causes

- *Graves' disease*, a "classic" autoimmune condition, is the most common cause in young patients. It features the development of autoantigenic serum immunoglobulin (Ig) G antibodies that bind to the TSH receptors in the thyroid, thus stimulating thyroid hormone overproduction and secretion. Other autoimmune antibodies develop concurrently, similar to those seen in autoimmune hypothyroidism, including antibodies to thyroid peroxidase (TPO) and thyroglobulin antibodies. These can occur in up to 80% of cases and result perversely in hypothyroidism.
- *Toxic nodular goiter* (solitary or multinodular) with autonomous production and release of T3 and T4. Common in the elderly population.[68]
- *Subacute thyroiditis* (also known as subacute granulomatous thyroiditis, or de Quervain's thyroiditis) of likely viral etiology. Its main feature is painful goiter.
- *Postpartum thyroiditis* (see earlier).

Clinical Features

- *Eye signs*. Lid lag and "stare," which can occur with hyperthyroidism of any cause. However, there are other features that are distinct with Graves' orbitopathy (described later).
- *Skin*. Graves' dermopathy is rare and can occur on any extensor surface. Pretibial myxedema is the most commonly described and is an infiltration of the skin on the shin. Thyroid acropachy is very rare and consists of clubbing and new periosteal bone formation of the fingers, causing marked swelling.
- *Excessive growth rate/velocity*. Common in children together with weight gain or behavioral problems, such as hyperactivity.
- *Cardiovascular*. In the elderly, a frequent presentation is with atrial fibrillation, other types of tachycardias, and/or heart failure. TFTs are mandatory in patients with atrial fibrillation.

- *Apathetic thyrotoxicosis* in elderly patients presents with a clinical picture more like that of hypothyroidism.

Investigations

- *Serum TSH*, which will be reduced in hyperthyroidism (<0.05 mU/L).
- *Raised free T4 or T3* confirms the diagnosis; T4 is almost always raised, but T3 is a more sensitive indicator of hyperthyroidism.
- *TSH receptor–stimulating antibodies* (TSHR-Ab), which are 99% specific for Graves' disease.
- *Thyroid peroxidase (TPO) and thyroglobulin antibodies* are present in 80% of cases of Graves' disease.
- *Scintiscan ^{99}Tm* is useful if there is doubt as to the nature of the goiter.

Treatment

The hyperthyroidism of Graves' disease is treated by reducing thyroid hormone synthesis with an antithyroid drug, or by reducing the amount of thyroid tissue with radioiodine (^{131}iodine) treatment or thyroidectomy. Radioiodine is more often the first line of treatment in North America. Treatment approaches vary around the world, indicative that no single approach is ideal.

- *Radioactive ^{131}I* is given orally and, since iodine preferentially concentrates in the thyroid, the gland is then slowly destroyed over the course of months by the local radiotherapy effect. It is contradicted in pregnant and breastfeeding women.[69]
- *Antithyroid drugs*. The main drugs are the thionamides: propylthiouracil, carbimazole (not available in the United States), and the active metabolite of the latter, methimazole, which inhibits the function of TPO, reducing oxidation and organification of iodide. Remission rates are in the range of 30–60%. The major toxicity with these agents is a selective agranulocytosis, but this only occurs in less than 1% of patients.
- *Surgery*. Generally, this will be a total thyroidectomy. That is typically an option for patients who relapse after antithyroid drugs and who prefer this treatment to radioiodine.
- *Beta blockers*, in particular propranolol (20–40 mg every 6 h), or longer-acting selective β1 receptor blockers, such as atenolol, may be helpful to control the adrenergic symptoms, especially in the early stages before the antithyroid treatment is fully effective.
- *Surveillance*. 40–70% of patients may relapse following antithyroid drug therapy. Hypothyroidism occurs in most patients treated by drugs or radioiodine, and is inevitable after total thyroidectomy, hence these patients will need to be maintained on appropriately titrated, life-long replacement levothyroxine.

There is a small risk of increased overall mortality seen in patients with hyperthyroidism. The major long-term consequence of treatment for hyperthyroidism is an increased risk of osteoporosis. Marked TSH suppression leads to the development of atrial fibrillation, requiring cardiac rate-limiting drugs such as digoxin, with an attendant risk for thromboembolic stroke. Hence anticoagulant prophylaxis is required, either with either warfarin or increasingly with direct oral anticoagulants (DOACs; previously known as new oral anticoagulant agents or NOACs), which include apixaban (Eliquis®, Pfizer Medical), dabigatran (Pradaxa®, Boehringer Ingelheim, Ridgefield, CT, USA), rivaroxaban (Xarelto®, Janssen Pharmaceuticals, Titusville, NJ, USA), and edoxaban (Savaysa®, Daiichi Sankyo, Basking Ridge, NJ, USA).[70]

Graves' Orbitopathy

Graves' orbitopathy, also known as thyroid eye disease (TED), is an autoimmune inflammatory disorder of the orbit and periorbital tissues. It has distinctive clinical features, including the "stare," due to retraction of the upper eyelid with lid lag, and swelling of the orbit, causing an exophthalmos of variable severity. It occurs most commonly in association with Graves' disease, but can also be seen, albeit more rarely, with Hashimoto's thyroiditis, and even in patients who are otherwise euthyroid. The condition mostly affects the middle-aged (30–50 years of age) and predominantly women. Cigarette smoking raises the incidence eightfold. Annual incidence is 16 per 100,000 in women and 3 per 100,000 in men.[71] About 3–5% have severe disease with intense pain, and sight-threatening corneal ulceration or compression of the optic nerve. Unilateral orbitopathy can occur, but this is rare.

Initial treatment entails regulation of thyroid hormone levels and limitation of further damage to the eye, with the use of topical lubricants to prevent corneal damage. High-dose corticosteroids are effective in the initial reduction of the orbital inflammation. Radiotherapy has been trialed, but there is controversy as to its efficacy, as is the case with selenium, which is limited to the treatment of mild disease. As of January 2020, the US Food and Drug Administration (FDA) approved the use of the medication Tepezza® (teprotumumab-trbw; Horizon Therapeutics, Lake Forest, IL, USA) for the treatment of adults with TED.[72] Teprotumumab-trbw is a monoclonal antibody that binds IGF-1R. In TED pathogenic orbital disease, autoantibodies stimulate the orbital fibroblasts, resulting in the production of hyaluronan (a high molecular mass polysaccharide), causing the marked infiltration and so swelling of the eyelids and orbital tissues and resulting in the clinical features of TED. Teprotumumab blocks the stimulatory effects of pathogenic autoantibodies on the orbital fibroblasts.[73] Orbital decompression surgery is

indicated in severe eye disease to prevent blindness from optic nerve compression. Surgery is also indicated, after the incipient thyroid disease has been stable for six months, to improve function and to increase lubrication of the corneal surface to prevent corneal keratitis and for cosmesis.[74]

Thyroid Crisis

A thyroid crisis (or "thyroid storm") is a rare, life-threatening exacerbation of hyperthyroidism, which presents with fever, delirium, seizures, coma, vomiting, diarrhea, and jaundice. The mortality rate due to cardiac failure, arrhythmia, or hyperthermia is as high as 30%, even with treatment. Thyrotoxic crisis is usually precipitated by acute illness (e.g., stroke, infection, trauma, diabetic ketoacidosis), surgery (especially involving the thyroid), or radioiodine treatment of a patient with partially treated or untreated hyperthyroidism. In-hospital management is required, which includes intensive monitoring, supportive care, identification and treatment of the precipitating cause, and measures that reduce thyroid hormone synthesis; that is, large doses of antithyroid drugs, such as propylthiouracil. Propranolol is also given to reduce tachycardia and other adrenergic manifestations.

Thyroid Hormone Resistance

This occurs when the effectiveness of thyroid hormone is reduced and includes flaws in thyroid hormone action, transport, or metabolism. These are rare, in general have a genetic basis, and to date there is limited effective treatment. There are three main causes:

- Thyroid hormone cell membrane transport defect.
- Thyroid hormone metabolism defect.
- Thyroid hormone action defects.

Goiter (Thyroid Enlargement)

Goiter is a swelling of the anterior base of the neck resulting from an enlarged thyroid gland, which may be visible or only evident on palpation (see Table 22-9). In the United States where iodine deficiency is rare, up to 15% of the population have palpable goiter and as many as 50% microscopic nodules. In areas of the world where iodine deficiency is common and widespread, up to 90% of the population have significant goiter, termed "endemic goiter."[75,76]

The initial screening for thyroid dysfunction starts by examining and then palpating the thyroid gland for diffuse changes or nodules, which may be single or multiple. It is performed as part of a head and neck examination, which could be argued to be within the remit of dentists and

Table 22-9 Goiter: types and causes.

Diffuse
Simple
• Physiologic (puberty, pregnancy)
Autoimmune
viral (infective) thyroiditis
Large
• Endemic
Nodular
• Multinodular
• Solitary (single)
• Fibrotic (Riedel's thyroiditis)
Infiltration (miscellaneous)
• Sarcoidosis
Malignancy
• Adenomas
• Carcinoma
• Lymphoma

represents a comprehensive examination of the patient, with a focus on dental disease, but in the context of potential disease of the related regional anatomy. The thyroid gland is examined with the patient's head extended to one side and with the examiner using the fingers of both hands to palpate the thyroid gland. Next, the patient is instructed to swallow, during which time the examiner can evaluate the anatomic extent of the lobules using the last three fingers of one hand. Note that the right lobule is usually larger than the left and that on relaxation, the thyroid outline cannot be observed in a healthy patient. Any anatomic abnormality of the thyroid gland is defined by its consistency, size, tenderness, and growth. If an abnormal finding is discovered, hormone and function and imaging studies, particularly ultrasound, needs to follow, with consideration for ultrasound-guided fine needle aspiration (FNA) biopsy.[77]

Thyroid Malignancies

Thyroid carcinoma is the most common malignancy of the endocrine system. Thyroid neoplasms can arise in each of the cell types that populate the gland, including thyroid follicular cells, calcitonin-producing C cells, lymphocytes, and stromal and vascular elements, as well as metastases from other sites (Table 22-10). Over the last 30 years, the incidence of thyroid cancer has increased from 4.9 to 14.3 cases per 100,000 individuals in the United States, with over 65,000 cases diagnosed in 2015.[78]

The risk factors for thyroid malignancy are (1) exogenous, namely exposure to radiotherapy of the head and/or head

Table 22-10 Thyroid malignancies.

Malignant Carcinoma (Arising from Thyroid Epithelium)	Prevalence
Follicular epithelial cell	
Papillary carcinomas	80–85%
Follicular carcinomas	2.5–7%
Poorly differentiated carcinomas	3–5%
Anaplastic (undifferentiated) carcinoma	1%
Neuroendocrine Tumor (Arising from the C [Calcitonin-Producing] Cells)	
Medullary thyroid cancer	<10%
Sporadic	
Familial	
Multiple endocrine neoplasia 2	
Lymphomas	1%
Metastases	
Breast, melanoma, lung, kidney	

Source: Data from Clayman, G. Thyroid cancer: thyroid cancer symptoms, diagnosis, and treatments. https://www.endocrineweb.com/conditions/thyroid-cancer/thyroid-cancer.

and neck region, which can include cranial radiotherapy, or from nuclear fallout following explosions of nuclear power plants, at Chernobyl (1986)[79] and more recently Fukushima (2011);[80] and (2) endogenous, specifically genetic abnormalities, patients who have a family history of papillary thyroid cancer in two or more first-degree relatives, multiple endocrine neoplasia type 2 (MEN 2), or other genetic syndromes associated with thyroid malignancy, such as Cowden's syndrome, familial polyposis, and Carney complex.[51]

Treatment

Papillary and Follicular Cancer

As most tumors are still TSH responsive, levothyroxine suppression of TSH is a mainstay of initial thyroid cancer treatment, followed by partial or near-total thyroidectomy (depending on the size of the tumor). This is followed by radioablation of the remnant thyroid gland (and tumor). Serum thyroglobulin is a sensitive marker of residual/recurrent thyroid cancer after initial treatment.

Anaplastic Thyroid Cancer

This is a poorly differentiated and aggressive cancer with a dismal prognosis, with most patients dying within six months of their diagnosis.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) can be sporadic or familial, and accounts for about 5% of thyroid cancers. There are three familial forms of MTC: MEN 2A, MEN 2B, and familial MTC without other features of MEN.[81] The management of MTC is primarily surgical, as these tumors, unlike papillary and follicular thyroid cancer, do not take up radioiodine. Targeted small molecule tyrosine kinase inhibitors (TKIs) have shown benefit in large or recurrent disease. Examples include cabozantinib (sold in the United States as Cabometyx® and Cometriq®, Exelixis, Alameda, CA, USA), which inhibits the tyrosine kinases c-Met and vascular endothelial growth factor receptor 2 (VEGFR-2), and vandetanib (Caprelsa®, Sanofi Genzyme, Cambridge, MA, USA) acts as a kinase inhibitor of a number of cell receptors, mainly VEGFR, epidermal growth factor receptor (EGFR), and RET-tyrosine kinase.[82] The TKIs that target vascular growth receptors that have a role in angiogenesis have been shown to increase the risk of medication-related osteonecrosis of the jaws (MRONJ), particularly if given concurrently (fivefold increased MRONJ risk) with either a bisphosphonate or denosumab.[83] External radiation treatment has also been shown to provide benefit.

Thyroid Lymphoma

Treatment follows the guidelines used for other forms of lymphoma.

Stomatognathic Manifestations and Complications of Thyroid Disease

Both hypothyroidism and hyperthyroidism can occur in the same patient, because patients with clinically significant hypothyroidism are on replacement levothyroxine, and there is the risk of overtreatment and iatrogenic thyrotoxicosis. Similarly, patients on treatment for their hypothyroidism can develop marked hypothyroidism if they omit a number of doses, or if they are on an insufficient dose. Therefore, dentists need to be familiar with the symptoms and signs of both hypothyroidism and hyperthyroidism.

Patients with a history of thyroid cancer have probably undergone surgery or radioactive iodine therapy that can affect the adjacent regional tissues. Salivary gland dysfunction is one of the most common side effects of high-dose ^{131}I therapy for thyroid cancer.[84,85] ^{131}I targets the salivary glands, where it is concentrated and secreted into saliva. Dose-related damage to the salivary parenchyma results from ^{131}I irradiation and causes salivary gland swelling, pain, and hypofunction.[86–89]

Dental Management of the Patient with Thyroid Gland Disorders

Patients with autoimmune thyroid diseases (Hashimoto's thyroiditis) may also be susceptible to other autoimmune connective tissue disorders, including Sjögren syndrome. Antinuclear antibodies (ANAs) are found in one-third of

patients with autoimmune thyroid disorders, and Sjögren syndrome is found in nearly one-tenth of ANA-positive patients with autoimmune thyroid disorders.[90] The most common additional autoimmune disease identified in patients with primary Sjögren syndrome has been hypothyroidism;[91] also, there is a 7–17% prevalence of detectable thyroid antibodies in patients with Sjögren syndrome and rheumatoid arthritis.[92] Therefore, the thyroid patient who presents with signs and symptoms of hyposalivation and xerophthalmia should be evaluated for Sjögren syndrome.[84,93–95]

Hypothyroidism

In hypothyroidism, the orofacial findings include myxedema of the skin, an enlarged tongue (macroglossia), compromised periodontal health, delayed tooth eruption, delayed wound healing, and a hoarse voice. Salivary gland enlargement, changes in taste, and burning mouth symptoms have also been reported.[96,97]

Patients with hypothyroidism are susceptible to cardiovascular diseases; therefore, consultation with the patient's medical provider is indicated. Patients who have atrial fibrillation may be taking anticoagulants, depending on the severity of the arrhythmia. The use of epinephrine-containing local anesthetics is not contraindicated if the patient's hypothyroidism is well controlled, but in patients who have cardiovascular disease (congestive heart failure, atrial fibrillation) or who have uncertain control of their thyroid disease, local anesthetic and retraction cord soaked with epinephrine can be used, but cautiously. Hypothyroidism, especially if uncontrolled, can also lead to respiratory depression, so that patient positioning should be carefully considered when treating such patients. Consideration should be given to treating patients in a semi-upright position, with oxygen supplementation via nasal prongs or by the mask used in providing nitrous oxide to patients.

Hypothyroid patients are sensitive to CNS depressants and so these medications should be used carefully, with input from the patient's physician. For postoperative pain control, narcotic use should be limited, since there is greater susceptibility to these agents in patients with hypothyroidism. Patients with long-standing hypothyroidism may experience increased bleeding after trauma or surgery. The presence of excess subcutaneous mucopolysaccharides (due to decreased degradation) may impair the ability of small vessels to constrict if severed or traumatized, and this may result in increased postoperative hemorrhage from such infiltrated tissues, including mucosa and skin. Delayed wound healing may also occur due to decreased metabolic activity of the fibroblasts. However, a study of well-controlled primary hypothyroid patients who had been provided with dental implants demonstrated no significantly increased risk for implant failure when compared with matched normal controls.[98]

Hyperthyroidism

Hyperthyroidism can exacerbate the patient's response to dental pain and anxiety. Routine examination of the head and neck may disclose signs of thyroid disease, including changes in oculomotor function, protrusion of the eyes, enlargement of the thyroid, and so difficulty in swallowing, or of the tongue. The patient may demonstrate excessive sweating. The greatest concern is the development of thyrotoxicosis or a "thyroid storm," which includes symptoms of extreme irritability and delirium, hypotension, vomiting, and diarrhea.[99] It can be triggered by surgery, sepsis, and trauma. Emergency medical treatment is required for this condition. Epinephrine is contraindicated, and elective dental care should be deferred for patients who have hyperthyroidism and exhibit signs or symptoms of thyrotoxicosis.

Increased susceptibility to infection may develop as an adverse side effect of antithyroid agents, which can cause agranulocytosis or leukopenia. Propylthiouracil can also cause sialolith formation and can increase the anticoagulant effects of warfarin. Certain analgesics must be used with caution in these patients. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) may cause increased levels of circulating T4, leading to thyrotoxicosis. NSAIDs can also decrease the effect of beta blockers.[50] The use of epinephrine requires special consideration when treating hyperthyroid patients and those taking nonselective beta blockers.

DISORDERS OF THE ADRENAL GLANDS (CORTEX)

The normal adrenal glands weigh 6–11 g each, are located above the kidneys, and have their own rich blood supply.[100] Within the glands is the adrenal cortex, which produces three classes of corticosteroid hormones:

- Glucocorticoids (e.g., cortisol).
- Mineralocorticoids (e.g., aldosterone). Glucocorticoids and mineralocorticoids act through specific nuclear receptors, regulating aspects of the response to physiologic stress, and controlling blood pressure as well as electrolyte and glucose homeostasis.
- Adrenal androgen precursor (dehydroepiandrosterone [DHEA]) prohormones that are converted in peripheral target cells, principally the gonads, to become the sex steroids that, in turn, act via nuclear androgen and estrogen receptors. The sex steroids interact with androgen receptors that stimulate or control the development and maintenance of male characteristics, that is testosterone, or with the estrogen receptors, so regulating both the menstrual and the reproductive cycles.

Adrenal steroidogenesis occurs in a zone-specific fashion, with mineralocorticoid synthesis occurring in the outer zona

glomerulosa, glucocorticoid synthesis in the zona fasciculata, and adrenal androgen synthesis in the inner zona reticularis (Figure 22-12).

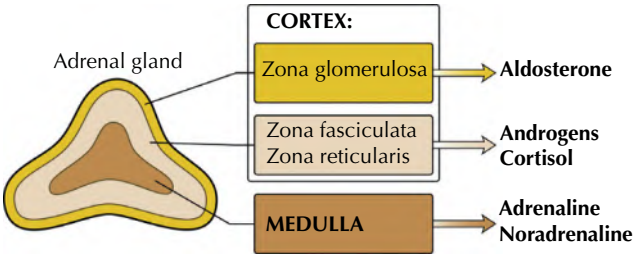


Figure 22-12 Adrenal steroidogenesis occurs in a zone-specific fashion. Mineralocorticoid synthesis (aldosterone) occurs in the outer zona glomerulosa. Glucocorticoid synthesis occurs in the zona fasciculate. Adrenal androgen synthesis occurs in the inner zona reticularis. The catecholamines (epinephrine and norepinephrine) are synthesized in the chromaffin cells of the adrenal medulla. *Source:* Kumar PJ, Clark ML (Eds.). *Kumar and Clark's Clinical Medicine*, 9th edn. Edinburgh: Saunders; 2017.

All the steroid hormones are derivatives of cholesterol (Figure 22-13). The steroidogenic pathway requires the import of cholesterol into the mitochondrion, a process initiated by the action of the steroidogenic acute regulatory (StAR) protein, which shuttles cholesterol from the outer to the inner mitochondrial membrane. Regulation of the production of glucocorticoids and adrenal androgens is under the control of the HPA axis (Figure 22-13).

Mineralocorticoids are regulated by the renin-angiotensin-aldosterone (RAA) system. Glucocorticoid synthesis is under inhibitory feedback control by the hypothalamus and the pituitary. Hypothalamic release of corticotrophin-releasing hormone (CRH) occurs in response to endogenous or exogenous stress. CRH in turn stimulates the release of ACTH by the cells of the anterior pituitary. ACTH is the pivotal regulator of cortisol synthesis, with additional short-term effects on mineralocorticoid and adrenal androgen synthesis. The release of CRH, and subsequently ACTH, occurs in a pulsatile fashion that follows a circadian rhythm, under the control of the hypothalamus. Reflecting this

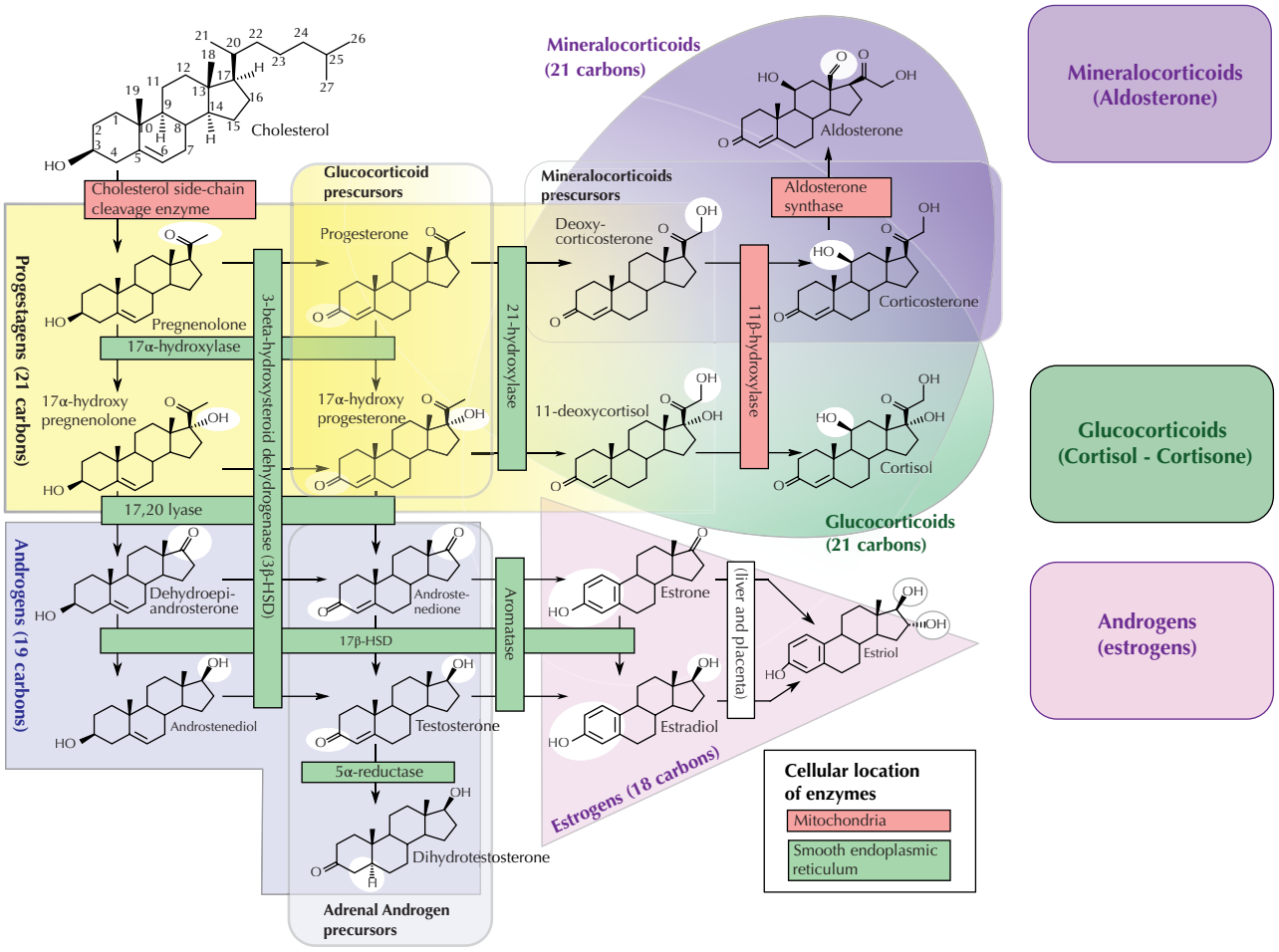


Figure 22-13 Adrenal steroidogenesis. Note how all the steroid hormones are derived from cholesterol. *Source:* https://commons.wikimedia.org/wiki/File:Steroidogenesis.svg. Creative Commons Attribution-Share Alike 3.0 Unported license.

pattern of ACTH secretion, adrenal cortisol secretion is also circadian, with peak levels in the morning and low levels in the evening

Diagnostic tests assessing the HPA axis makes use of the fact that it is regulated by negative feedback (Figure 22-1). Glucocorticoid excess is diagnosed by the dexamethasone suppression test. Dexamethasone, a potent glucocorticoid, suppresses CRH/ACTH and therefore lowers endogenous cortisol levels. If cortisol production is autonomous (e.g., from an adrenal adenoma), ACTH is already suppressed and the dexamethasone has little additional effect. If cortisol production is driven by an ACTH-producing pituitary adenoma, dexamethasone suppression is ineffective at low doses, but usually induces suppression at high doses. If cortisol production is driven by an ectopic source of ACTH, such as an ACTH-producing tumor, this is usually unaffected by dexamethasone suppression. Therefore, the dexamethasone suppression test is useful both in establishing the diagnosis of Cushing's syndrome (corticoid excess) and in differentiating the cause.[101] Conversely, to assess glucocorticoid deficiency, ACTH stimulation of cortisol production is used. The standard ACTH stimulation test involves administration of cosyntropin (Synacthen, a potent ACTH agonist) parenterally and the collection of blood samples at 0, 30, and 60 minutes to check the cortisol level.[102] A normal response is defined as a cortisol level >20 μg/dL or an increment of >10 μg/dL over baseline. Alternatively, an insulin tolerance test (ITT) can be used to assess adrenal insufficiency.

Mineralocorticoid production is controlled by the RAA regulatory cycle, which is initiated by the release of renin from the juxtaglomerular cells in the kidney, resulting in cleavage of angiotensinogen to angiotensin I in the liver. Angiotensin-converting enzyme (ACE) cleaves angiotensin I to angiotensin II, which binds and activates the angiotensin II receptor type 1 (AT1 receptor), resulting in increased aldosterone production and vasoconstriction. Aldosterone enhances sodium retention and potassium excretion, and increases renal arterial perfusion pressure, which in turn regulates renin release. As mineralocorticoid synthesis is primarily under the control of the RAA system, disorders of the hypothalamic-pituitary axis generally do not adversely affect adrenal gland synthesis of aldosterone.

Cushing's Syndrome (Glucocorticoid Excess)

Cushing's syndrome reflects a constellation of clinical features that result from the chronic effects of glucocorticoid excess, of any etiology and any source. Cushing's syndrome is rare, with an annual incidence of 1–2 per 100,000 population. The disorder can be ACTH dependent (e.g., pituitary corticotrope adenoma) or ACTH independent (e.g., adrenocortical tumor). Overwhelmingly, the medical use of glucocorticoids is the commonest cause of Cushing's syndrome. Only 10% of patients with Cushing's syndrome have a primary—that is, adrenal—cause of their disease.[103] The term "Cushing's disease" is specific to glucocorticoid excess caused by a pituitary adenoma secreting ACTH.

Ectopic ACTH production is predominantly caused by occult carcinoid tumors, most frequently in the lung, but also in the thymus or pancreas. Advanced small cell lung cancer can also cause ectopic ACTH production.[104]

Clinical Manifestations

Given that glucocorticoids (see Table 22-11) affect almost all cells of the body, the signs of cortisol excess impact multiple physiologic systems. In addition, excess glucocorticoid secretion overcomes the ability of a key kidney enzyme system (11 β-hydroxysteroid dehydrogenase type 2 or 11β-HSD2) to rapidly inactivate cortisol to cortisone. Cortisone has minimal mineralocorticoid activity, whereas cortisol has

Table 22-11 Major actions of glucocorticoids.

Organ/ Physiologic System	↑ Increased or Stimulated	↓ Decreased or Inhibited
Metabolic	↑ Gluconeogenesis ↑ Glycogen deposition ↑ Protein catabolism ↑ Fat deposition	↓ Protein synthesis
Renal (Kidneys) System	↑ Sodium retention ↑ Potassium loss ↑ Uric acid production	↓ Free water clearance
Hematologic System	↑ Circulating neutrophils	↓ Host response to infection, delayed hypersensitivity response ↓ Lymphocyte transformation, circulating lymphocytes, circulating eosinophils

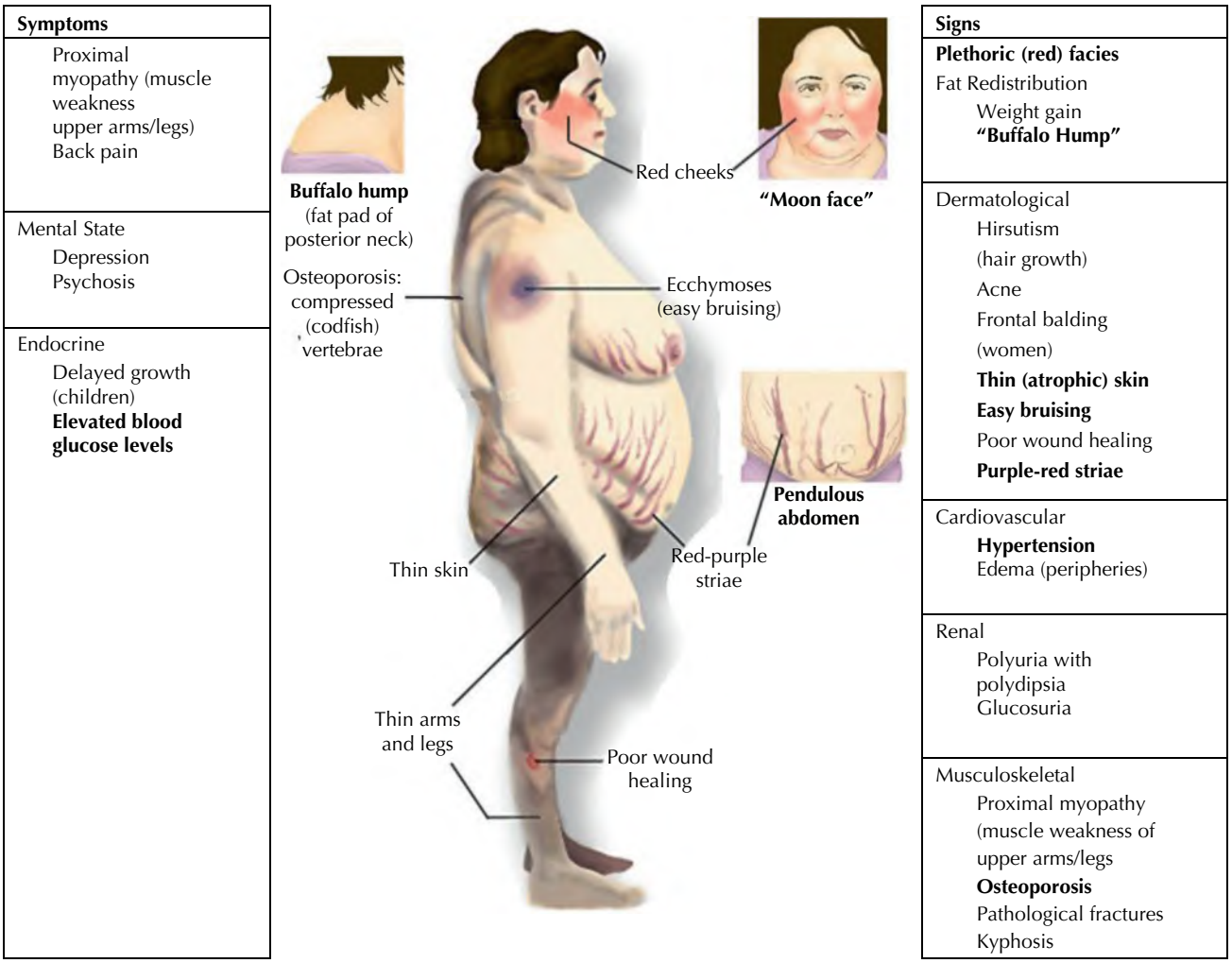


Figure 22-14 Hypercortisolism—Cushing's syndrome. Bold type indicates symptoms or signs of greater diagnostic significance.

some degree of mineralocorticoid action, which manifest as diastolic hypertension, hypokalemia, and edema. Excess glucocorticoids also interfere with central regulatory systems, leading to suppression of gonadotropins with subsequent hypogonadism and amenorrhea, and suppression of the hypothalamic-pituitary-thyroid axis, resulting in decreased TSH secretion.

The diagnosis of Cushing's syndrome should be considered when the following key clinical features are evident in the patient (see Figure 22-14): fragility of the skin, with easy bruising and broad (>1 cm), purplish striae, and signs of proximal myopathy, with the patient struggling to stand up from a chair (without the use of hands). Patients with Cushing's syndrome may develop marked hypercoagulopathy, so are at acutely increased risk of deep vein thrombosis and subsequent pulmonary embolism. Psychiatric symptoms of marked anxiety and/or depression are also common, but acute paranoia or frank psychosis may also occur.[101]

Overt untreated Cushing's syndrome is associated with a poor prognosis. In ACTH-independent disease, treatment consists of surgical removal of the adrenal tumor. In Cushing's syndrome, the treatment of choice is selective removal of the pituitary corticotrophic-producing tumor, usually via a transsphenoidal approach.

Conn's Syndrome (Mineralocorticoid Excess)

Hyperaldosteronism, the excessive release of the principal mineralocorticoid, aldosterone, typically presents as hypertension, given the adverse effects on the renin-angiotensin system that so powerfully controls renal perfusion and homeostasis, and blood pressure. The commonest cause is primary hyperaldosteronism, excess production of aldosterone by the adrenal zona glomerulosa, typically occurring with bilateral micronodular adrenal hyperplasia. Infrequently, Conn's syndrome occurs due to an adrenocortical carcinoma.

The clinical hallmark of mineralocorticoid excess is hypokalemic hypertension, but not hypernatremia, with the serum sodium tending to be normal due to the concurrent fluid retention, which in some cases can lead to marked peripheral edema. Severe hypokalemia can be associated with muscle weakness, overt proximal myopathy, or, in severe cases, hypokalemic paralysis, or tetany.[105] Diagnostic screening for mineralocorticoid excess is not currently recommended for all patients with hypertension, but should be considered in hypertensive patients younger than 40 years, treatment-refractory hypertension, hypokalemia, or the finding of an adrenal mass. The accepted screening test is concurrent measurement of plasma renin and aldosterone with subsequent calculation of the aldosterone–renin ratio, but the serum potassium needs to be normalized prior to testing.

With the diagnosis of hyperaldosteronism, CT imaging of the adrenal glands is needed. The treatment provided is dependent on the patient's age and fitness for surgery. Laparoscopic adrenalectomy is the preferred approach. Medical treatment, which can also be considered prior to surgery to avoid postsurgical hypoaldosteronism, is usually with the mineralocorticoid receptor antagonist spironolactone.[106]

Addison's Disease (Adrenal Insufficiency)

The US prevalence of adrenal insufficiency (Table 22-12) is 5 in 10,000 in the general population. Disorders of the hypothalamic-pituitary axis are more frequent, with a prevalence of 3 in 10,000, whereas primary adrenal insufficiency has a prevalence of 2 in 10,000, with about half of cases due to genetic causes (e.g., congenital adrenal hyperplasia). Primary adrenal insufficiency is most commonly caused by autoimmune destruction of the adrenal gland, with some 60–70% developing adrenal insufficiency as part of an autoimmune polyglandular syndrome (APS). APS1, an autosomal recessive disorder also termed APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), is the underlying cause in 10% of patients affected by APS.[107] These patients invariably develop chronic mucocutaneous candidiasis, which usually manifests in childhood and precedes adrenal insufficiency by years or decades. Coincident autoimmune-induced endocrinopathies most frequently include thyroid autoimmune disease, vitiligo, and premature ovarian failure. Less commonly, T1DM and pernicious anemia (with consequent vitamin B_{12} deficiency) may occur. Rare causes of adrenal insufficiency involve destruction of the adrenal glands as a consequence of infection, with tuberculous adrenalitis still a frequent cause of disease in developing countries. Hemorrhage, or more rarely bilateral bulky metastatic infiltration with replacement of the adrenal glands, can also result in hypoadrenalism.

The commonest cause of adrenal insufficiency is iatrogenic, arising from suppression of the HPA axis as a consequence of exogenous glucocorticoid treatment (see Tables 22-13 and 22-14).[108] This has a reported prevalence of some 0.5–2% of the population in developed countries. Secondary adrenal insufficiency is the consequence of dysfunction of the hypothalamic-pituitary component of the HPA axis. Excluding iatrogenic impairment of the HPA axis (exogenous corticosteroid use), the majority of cases are caused by pituitary or hypothalamic tumors, or their treatment by surgery or radiotherapy.

In principle, the clinical features of primary adrenal insufficiency (Figure 22-15) are characterized by the loss of both glucocorticoid and mineralocorticoid secretion. In contrast, in secondary adrenal insufficiency only glucocorticoid deficiency is evident, as the adrenal itself is intact and can still be regulated by the RAA system. Adrenal androgen secretion is disrupted in both primary and

Table 22-12 Adrenal insufficiency (hypoadrenalism): classification.

1. **Primary Adrenal Insufficiency (Addison's Disease)**	2. **Secondary Adrenal Insufficiency**
a. **Destruction of adrenal gland** Immune (autoimmune) "Idiopathic" Surgical removal Infection (tuberculosis, *Mycobacterium avium*–intercellular complex, fungal, viral) Hemorrhage (anticoagulants)	a. **Hypopituitarism** Due to hypothalamic-pituitary disease (intracranial brain tumors)
b. **Metabolic failure of hormone production** Congenital adrenal hyperplasia Enzyme inhibition (ketoconazole) Cytotoxic agents (Mitotane)	b. **Suppression of the hypothalamic-pituitary-adrenal (HPA) axis** Exogenous glucocorticosteroids Endogenous adrenocorticotropic hormone/steroid from a tumor
	c. **Endogenous glucocorticosteroid resistance** Severe acute illness (shock/ICU admission)

Table 22-13 Therapeutic use of corticosteroids.

Nervous system	• Cerebral edema • Raised intracranial pressure
Respiratory	• Angioedema • Anaphylaxis • Asthma • Sarcoidosis • Obstructive airway disease
Endocrine	• Replacement therapy (Addison's, pituitary disease, adrenal hypoplasia) • Graves' ophthalmopathy
Gastrointestinal	• Inflammatory bowel disease (ulcerative colitis, Crohn's disease) • Orofacial granulomatosis
Liver	• Chronic active hepatitis • Transplantation (antirejection)
Renal	• Nephrotic syndrome • Vasculitides • Transplantation (antirejection)
Rheumatology	• Systemic lupus erythematosus • Polyarteritis • Temporal arteritis • Rheumatoid arthritis
Musculoskeletal	• Polymyalgia rheumatica • Myasthenia gravis
Skin/oral medicine	• Dermatitis • Pemphigus • Oral dermatoses
Hematology	• Malignancy • Hemolytic anemia • Idiopathic thrombocytopenic purpura • Chemotherapy-related nausea

Table 22-14 Glucocorticoid equivalencies.

Glucocorticoid	Equivalent Dose (mg)	Potency	Biologic Half-life (h)
Short-Acting Corticosteroids			
Cortisol	20.0	1.0	8–12
Cortisone	25.0	0.8	8–12
Intermediate-Acting			
Prednisone	5.0	4.0	18–36
Prednisolone	5.0	5.0	18–36
Triamcinolone	4.0	5.0	18–36
Methylprednisolone	4.0	5.0	18–36
Long-Acting			
Dexamethasone	0.75	30	36–54

Source: Data from Nicolaides NC, Pavlaki AN, Maria Alexandra MA, et al. Glucocorticoid therapy and adrenal suppression. Updated 2018. In: Feingold KR, Anawalt B, Boyce A, et al. (Eds.), *Endotext*. South Dartmouth, MA: MDText.com. https://www.ncbi.nlm.nih.gov/books/NBK279156/.

secondary adrenal insufficiency. Hypothalamic-pituitary disease can lead to additional clinical manifestations due to the involvement of other endocrine axes, or visual impairment with bitemporal hemianopia caused by compression of the optic chiasma. Iatrogenic adrenal insufficiency caused by exogenous glucocorticoid suppression of the HPA axis and its abrupt cessation can cause all of the symptoms associated with glucocorticoid deficiency, but the patient will appear cushingoid from the preceding "overexposure" to glucocorticoids.

Acute adrenal insufficiency usually occurs after a prolonged period of nonspecific complaints and is more frequently observed in patients with primary adrenal insufficiency, due to the loss of both glucocorticoid and mineralocorticoid secretion. The associated postural hypotension is a "red flag," as the patient may then progress to hypovolemic shock. Adrenal insufficiency may also mimic the features of an acute abdomen with abdominal tenderness, nausea, vomiting, and fever. An adrenal crisis can be triggered by an intercurrent illness, surgery, or other stress.[109]

The diagnosis of adrenal insufficiency is established by the short cosyntropin test (Synacthen), a safe and reliable tool with excellent diagnostic sensitivity. The ITT is an alternate, but can be hazardous to the patient, and requires supervision by a specialist physician.

Acute adrenal insufficiency requires immediate rehydration (1 L/hour of saline infusion) with cardiac monitoring and glucocorticoid replacement by bolus injection of 100 mg hydrocortisone, followed by further hydrocortisone supplementation (100–200 mg hydrocortisone over the course of 24 h). Mineralocorticoid replacement can wait until the daily hydrocortisone dose has been reduced to <50 mg, because at higher doses the hydrocortisone provides sufficient stimulation of the mineralocorticoid receptors.

Glucocorticoid replacement (Table 22-15) for the treatment of chronic adrenal insufficiency should be administered at a dose that replaces the physiologic daily cortisol production, typically orally administered hydrocortisone at a dose of 15–25 mg, in two divided doses: 10–20 mg in the mornings and 5 mg in the evenings, mimicking the natural circadian levels of cortisol.

Mineralocorticoid replacement in primary adrenal insufficiency is achieved by the use of 100–150 μg of fludrocortisone. Its efficacy is assessed by measuring the blood pressure, while both sitting and standing, to detect a postural drop indicative of hypovolemia, and assessing serum sodium, potassium, and plasma renin levels. Adrenal androgen replacement is an option for patients with a lack of energy, or with features of androgen deficiency, such as loss of libido.

Symptoms

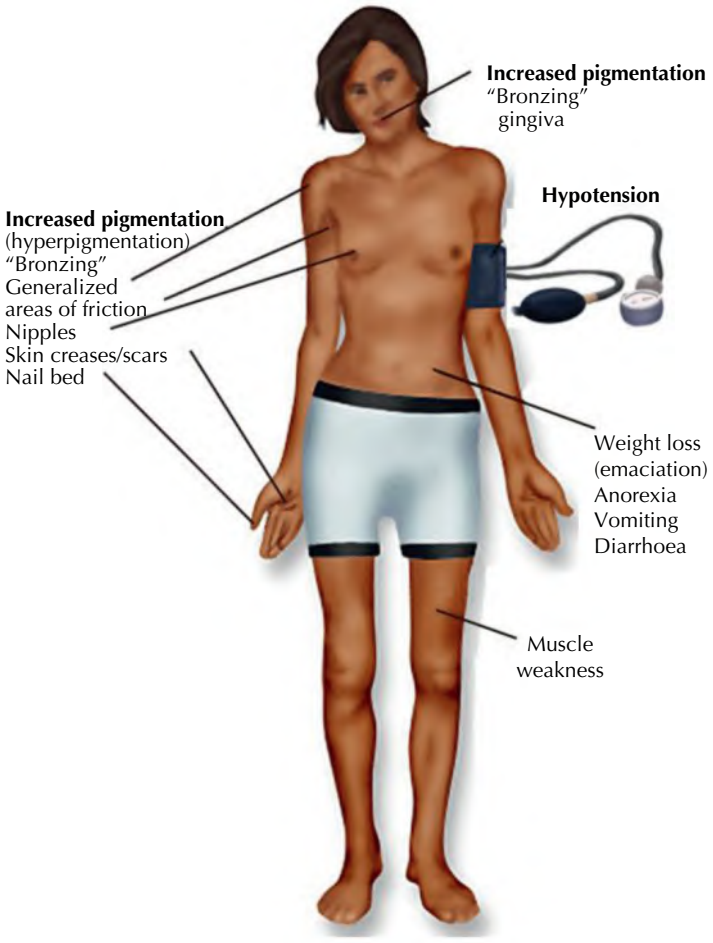
Weight loss
Anorexia
Weakness/fatigue

Mental State
Depression
Confusion
Seizures

Cardiovascular
Syncope
from postural
Hypertension

Gastrointestinal
Emesis
Nausea/vomiting
Constipation

Musculoskeletal
Myalgia
Joint pain



Signs

Dermatological
Hyperpigmentation
-generalised
"Bronzing"
gingiva
Skin creases/scars
Nail bed
Loss of body hair

Figure 22-15 Hypoadrenalism—Addison's disease. Bold type indicates symptoms or signs of greater diagnostic significance. *Source:* Letters to the Editor. Medical mystery—the answer revealed. *N Engl J Med.* 1998;338(4):266–268.

Table 22-15 Indications for corticosteroid use.

Therapeutic Uses	Supplementation for Hypoadrenalism
Anti-inflammatory/immune suppression • Topical • Intralesional • Inhaled • Intra-articular • Systemic (PO/parenteral) • Prevention of surgical edema (wisdom teeth removal)	Hydrocortisone (corticosteroid): dose dependent on patient's weight and age • 20 mg am/10 mg pm (or dexamethasone 5 mg/day) + fludrocortisone (mineralocorticoid) 0.05–0.20 mg/day +/– presence of stressors: illness, infection, surgery, and/or pregnancy
Antineoplastic (hematologic malignancy)	**3. Replacement ("Stress") Corticosteroids**
Antiemetic (chemotherapy)	HPA axis impairment (exogenous corticosteroid use): • Primary hypoadrenalism
Palliative care	

po; per oral

Pheochromocytoma

This is an adrenal tumor that produces epinephrine, norepinephrine, or both catecholamines. Patients are hypertensive, with headache, sweating, tachycardia, palpitations, and pallor. Occasionally, these can be syndromic, as part of Multiple Endocrine Neoplasia Syndrome Type 2B (MEN2B) presenting with a marfanoid habitus, high arched palate, neuromas (of the tongue, buccal mucosa, lips, conjunctivae, and eyelids), and corneal nerve thickening. The diagnosis of pheochromocytoma is confirmed by measuring urinary and plasma catecholamine levels.[110]

Stomatognathic Manifestations and Complications of Disorders of the Adrenal Gland

Hyperadrenocorticism (Glucocorticoid Excess or Cushing's Syndrome)

The primary orofacial feature of Cushing's syndrome is a round, moon face due to muscle wasting and accumulation of fat. Surface capillaries in the face and other skin regions become fragile, rendering them readily susceptible to hematomas after mild trauma. The facial skin has a ruddy color that simulates "glowing health"; acne and excessive facial hair (hirsutism) are also commonly seen. Long-standing Cushing's syndrome in children produces delayed growth and development, including of the skeletal and dental structures. Many of the systemic findings of Cushing's syndrome are similar to those seen in patients on moderate- to high-dose glucocorticoid therapy, and these patients are considered to be immunosuppressed. Therefore, oral signs and symptoms of immunosuppression can be seen, including oral candidiasis, recurrent herpes labialis and herpes zoster infections, gingival and periodontal diseases, and impaired wound healing.

Hypoadrenocorticism (Glucocorticoid Deficiency or Addison's Disease)

The primary orofacial feature of Addison's disease is unusual skin pigmentation, most intensely of the sun-exposed areas due to ACTH stimulation of the melanocytes. Facial freckles and moles appear darker, in addition to the development of a tan-like complexion ("bronzing" of the skin and sometimes of the oral mucosa), which does not fade on cessation of sunlight exposure. The mucocutaneous junctions undergo increased pigmentation, including the lips, but hyperpigmentation can also involve the intraoral mucosal surfaces, such as the gingival margins, buccal mucosa, palate, and lingual surface of the tongue. The oral pigmentations appear as irregular spots that range from pale brown to gray or black.[111]

Dental Management of Patients with Adrenal Gland Disorders

Hyperadrenocorticism (Glucocorticoid Excess or Cushing's Syndrome)

Dental management of the patient with Cushing's syndrome must take into consideration concomitant medical conditions that can include hypertension and heart failure, depression or psychosis, as well as DM and osteoporosis. Patients will present with easy bruising of the skin, impaired wound healing, and the infective consequences of immunosuppression. Prophylactic antibiotic coverage should be considered prior to surgery (extractions) for active dentoalveolar infections.

Assessment of the ability to withstand stress is an essential component of treatment planning for patients with Cushing's syndrome and other patients who have been on long-term moderate- to high-dose glucocorticoid therapy (see Table 22-12). Stress may be induced by an invasive surgical procedure, the onset of infection, an exacerbation of an underlying disease, or a serious life event, such as the death of a family member.[112] When normal individuals undergo stress, the plasma cortisol levels can double, due to the inherent ability of the adrenal glands to significantly increase cortisol production. But, in a patient with adrenal insufficiency, adrenal function is inadequate to produce sufficient cortisol in response to stress. Consequently, the patient may experience severe hypotension, with cardiovascular events such as stroke, coma, and death. Patients with established severe adrenal insufficiency usually require premedication with oral or intramuscular glucocorticoids before an invasive procedure. Dosages must be agreed upon with the patient's physician; a frequent regimen is to double the daily dose of oral glucocorticoids the day before the surgery and on the day of surgery.[113]

Hypoadrenocorticism (Glucocorticoid Deficiency or Addison's Disease)

Dental management is similar to that for the patient who has taken long-term moderate to high doses of glucocorticoids (see earlier), since Addison's disease is frequently treated with exogenous glucocorticoids. The oral health practitioner must be able to recognize and provide initial management of an acute adrenal crisis (intramuscular or intravenous hydrocortisone) when treating these patients.[114]

Use of Replacement Corticosteroid Therapy ("Stress Steroids" or "Steroid Cover")

Cortisol (hydrocortisone) is essential to maintain vasomotor tone, and so normal blood pressure, by sensitizing the alpha-adrenergic receptors (alpha 1A, 1B, and 1D receptors) of the vasculature to circulating epinephrine and norepinephrine

Table 22-16 Dental procedures and recommended replacement corticosteroids.

Risk Category	Dental Procedure	Hydrocortisone	Prednisone	Dexamethasone
Negligible	• Nonsurgical & in chair +/- local anesthetic	Nil	Nil	
Mild	• Minor oral surgery • Minor periodontal surgery } in the dental chair			Nil
Moderate to severe	• Major oral or periodontal surgery—multiple extractions/implants • Procedure >60 mins • Significant blood loss • general anesthetic/intubation	50–100 mg day of surgery *and 24 hours* afterward	10–20 mg within 2 hours of procedure	~2–4 mg (long-acting) >48 hours
Monitoring	• BP (100/60) systolic >100; diastolic >60 ➔ if *lower* give fluids (5% dextrose saline)			

and increasing catecholamine release from the adrenal cortex. If insufficient cortisol is produced at times of marked physiologic stress, this can result in vasodilation, reduced cardiac return, and potential hypotensive cardiac shock, leading to collapse and death. Significant physiologic stressors include severe infection and/or injury; that is, surgery and intubation associated with general anesthesia.[115–117]

Iatrogenic adrenal insufficiency is caused by suppression of the HPA axis due to exogenous glucocorticoid therapy. The mean cortisol production rate is 5.7 mg/m^2/day, or about 10 mg/day (equal to 2.5 mg of prednisone or 0.5 mg of dexamethasone) (see Table 22-15).[118] Body surface area (BSA) is used to calculate the dose of a drug relative to the patient's "ideal" body weight, resulting in a dose per meter squared (m^2). The BSA is a better indicator of the patient's "ideal" body weight because it is less affected by abnormal adipose mass, and this is useful when giving drugs with a narrow therapeutic safety index, such as chemotherapy agents. Of the various formulations, the Mosteller equation is simpler and considered more accurate:

$$\mathrm{BSA}\left(\mathrm{m2}\right)=\frac{\sqrt{height\left(cm\right)\times weight\left(kg\right)}}{3600}$$

Therefore, exogenous glucocorticoids that exceed the mean level of cortisol production can result in suppression of the HPA axis, as well as atrophy of the adrenal glands. Consequently, at times of acute physiologic (and possibly psychologic stress), the now atrophied adrenal gland is unable to produce sufficient cortisol for the affected patient to respond appropriately to stress. Historically this resulted in the so-called Rule of Twos, in which a patient was thought to be susceptible to an impaired response to physiologic stress, due to adrenocorticoid suppression from exogenous corticosteroids used for the medical treatment of predominantly immune-related or inflammatory conditions. The Rule stated that if a patient had taken glucocorticoids in excess of 20 mg of cortisone, continuously for 2 weeks (or more), within 2 years of the date/day of their dental treatment, this patient needed supplementary steroids prior to their dental treatment.[119] What is now very clear is that the published evidence has concluded that supplementary steroids ("steroid cover") are not indicated for dental procedures done in the dental chair and facilitated by means of local anesthesia, for patients using therapeutic corticosteroids. The evidence for using such "stress steroids" is at best equivocal for more major dental (surgical) procedures. For patients who have recently (within 2 years) ceased supraphysiologic corticosteroid therapy, the evidence is again considered to be equivocal.

Thus, in assessing the need for a patient with hypoadrenalism to receive preprocedural supplemental corticosteroids (Table 22-16), the essentials still need to be applied: careful patient assessment and evaluation, including taking a detailed medical history, with particular attention to recent surgery and how the patient coped with the procedure.[120–122] However, for patients undertaking dental procedures utilizing oral or intravenous sedation with potent short-acting benzodiazepines (e.g., midazolam) to abrogate the psychologic stresses associated with invasive dental treatment, this intended blunting of the emotional stress response may blunt the physiologic stress response. Therefore, for those patients with primary hypoadrenalism or on long-term supraphysiologic doses of corticosteroids having dental treatment aided by means of oral or intravenous sedation, supplementary pre- or periprocedural "stress steroids" should be considered and possibly provided.[123]

GONADS AND GONADAL DYSFUNCTION

The gonads, like most other endocrine organs, are incorporated into an endocrine axis: the hypothalamic-pituitary-gonadal (HPG) axis. The physiologic function and regulation of the HPG axis, especially in women, is complex and

changes dramatically over a lifetime. The hypothalamic hormone in the HPG axis is gonadotropin-releasing hormone (GnRH). GnRH is released in a complicated pulsatile fashion that varies widely in a person's lifetime and is significantly different between men and women. The general principles of stimulation and feedback inhibition apply to the HPG axis (see Figures 22-4 and 22-5); however, this axis is complicated by two issues: GnRH is pulsatile, and the pituitary makes two hormones, LH and FSH. In the male, LH stimulates testosterone production from the Leydig cells of the testicles, and FSH stimulates sperm production by the Sertoli cells. In females, FSH stimulates maturation of the ovarian follicle, and LH causes "luteinization," or maturation of the follicle into a corpus luteum, as well as the production of ovarian estradiol.

For both males and females, the HPG axis is relatively dormant before the onset of puberty. The onset of puberty in girls occurs approximately 2 years before that of boys. In girls, the average age at which breast development starts is 10.5 years, and menses starts at about 12 years. In boys, the peak growth rate and beginning of voice change are about the age of 14 years, whereas facial hair appears on average at the age of 15 years. In men, from late puberty until about age 60 years, the serum testosterone levels are relatively constant and begin to decline gradually thereafter. In women, serum estradiol levels vary widely over the course of the menstrual cycle, but after the onset of menopause (which occurs on average at the age of 50 years), serum estradiol levels become very low and gonadotropin (LH and FSH) levels are elevated.

Precocious Puberty, Delayed Puberty, Hypogonadism, and Menopause

In both males and females, precocious puberty, delayed puberty, and hypogonadism are clinical diagnoses, made by early or late signs of secondary sexual differentiation or loss of sexual characteristics.[124] Pubertal development is measured clinically by a staging system developed by Tanner.[125] Puberty is generally considered precocious in boys if it starts before age 10 years and in girls before age 8.5 years, or delayed if there are no signs of sexual development by the age of 13 years in girls and 14 years in boys.[126]

Once a clinical diagnosis of gonadal dysfunction is established, the next step is to determine whether the pathophysiologic process is of the gonads (primary/end-organ disorder), pituitary (secondary endocrinopathy), hypothalamus (tertiary endocrinopathy), or, alternatively as in the case of precocious puberty, due to an ectopic (or exogenous) source of the hormone. Gonadal testing usually involves measuring the appropriate sex steroid (testosterone or estradiol) and the pituitary gonadotropins LH and FSH. The most common cause of precocious puberty in boys and girls is early onset of pituitary hormone production, termed "central precocious puberty." If the end-organ hormones are elevated and the gonadotropins are suppressed (gonadotropin-independent precocious puberty), this suggests primary (autonomous) gonadal dysfunction. Finally, the adrenal gland also produces androgens that can lead to early puberty in boys and masculinization in girls.

Premature ovarian failure heralded by the onset of menopause before the age of 40 years presents as "hot flushes." The most common associated problem is cessation or marked irregularity of the menstrual cycle. Hypogonadism in men presents with a loss of libido and decreased growth rate of facial hair, and can lead to osteoporosis and fractures; it is diagnosed by a low serum testosterone level. Premature ovarian failure is diagnosed by the early loss of menstrual cycles in the setting of an elevated serum FSH. Replacement of the primary gonadal steroid, testosterone or estradiol or one of its analogues, in men and women is straightforward. However, replacement of the missing hormone will not return fertility, which is often the major concern. If the gonad is still functional but disorder or loss of the relevant pituitary hormones leads to a loss of function, the pituitary hormones can then be replaced.

Oral Manifestations of Gonadal Disorders

Hypersecretion of female sex hormones commonly occurs in pregnancy. High levels of female sex hormones cause increased capillary permeability, increased susceptibility to the development of gingivitis (pregnancy gingivitis), gingival hyperplasia, and pyogenic granulomas (pregnancy tumor).[127] These factors may complicate preexisting periodontal disease. A decrease in gonadal hormones at menopause is associated with a decrease in salivary flow and salivary composition.[128] Postmenopausal women also have increased susceptibility to osteoporosis, so dental radiographs may demonstrate hypocalcified bone.[129]

Dental Management of Patients with Gonadal Disorders

Elective and stressful dental procedures should be avoided during the first trimester of pregnancy and the last half of the third trimester. The second trimester is the safest period to provide dental care during pregnancy. During this time, emphasis should be on prevention, maintenance of optimal oral health, and treatment of dental concerns that may lead to complications in late stages of pregnancy.[130] Injudicious use of medications should be avoided in pregnancy; choice of medication should be guided by FDA pregnancy classifications for prescription drugs to avoid those with possible teratogenic effects.[131]

Table 22-17 Type 1 versus type 2 diabetes mellitus (DM) characteristics.

	Type 1 DM	Type 2 DM
Prevalence (DM—all types)	<5–10%	>90–95%
Age (of onset)	Younger (<30 years of age)	Older (>30 years of age)
Weight	Lean	Overweight/obese
Symptom duration	weeks	Months/years/decades
Risk factors		
Ethnicity	Northern European	Asian, African, American Indian, Australian Aboriginal, Polynesian
Social/lifestyle	(?) uncertain	Obesity, sedentary lifestyle
Heredity	HLA-DR3 or DR4 (>90%)	No HLA linkage
Pathogenesis	Autoimmune disease	?
Ketonuria	Yes	No
Clinical	Insulin deficiency	Partial insulin deficiency, initially then increasing insulin resistance
	± ketoacidosis	± hyperosmolar state
	Insulin dependent	Need insulin with time as beta pancreatic cells fail
	Increased risk of hypoglycemia	Lower risk of hypoglycemia

DIABETES MELLITUS

DM encompasses a group of heterogeneous metabolic disorders with a common phenotype of persistent, abnormally elevated blood glucose levels (hyperglycemia) in association with dysregulation of carbohydrate, protein, and lipid metabolism (see Table 22-17). This persistent hyperglycemia (disordered glucose homeostasis) results from either a defect in the secretion of insulin from the pancreas, or resistance to the action of insulin by the body's cells, or both.[132] Hyperglycemia has been shown to affect almost all tissues in the body and is associated with significant complications of multiple organ systems, including the eyes, nerves, kidneys, and blood vessels. These complications are responsible for the high degree of morbidity and mortality seen in the diabetic population. In the United States (as in other Westernized countries), DM is the leading cause of end-stage renal disease (ESRD);[133] nontraumatic toe, foot, and lower limb amputation;[134] and adult blindness.[135]

Epidemiology

Worldwide, DM, in particular T2DM given that it accounts for 90–95% of all patients with DM, is now one of the most common noncommunicable diseases. It is the ninth leading cause of death in most high-income countries and there is substantial evidence that it is now also becoming epidemic in many low- and middle-income countries.[136] The main risk factor for DM, specifically T2DM, is obesity. Obesity is defined as a condition in which excess body fat has accumulated to the extent that it may have a negative effect on health, leading to reduced life expectancy and/or morbidity.[137–139] The incidence of DM rises as the population ages and the prevalence of obesity increases.[140,141] In the United States, for the period 2007–2010, the crude total prevalence of DM was estimated at 11.4% of the population over 20 years of age (data obtained by self-report of physician-diagnosed diabetes and exclude women who reported having diabetes during pregnancy).

Hormonal Control of Blood Glucose[142]

Plasma glucose levels are normally tightly regulated in health, confined to a range of 3.5–8.0 mmol/L (63–144 mg/dL), despite physiologic stressors of food, fasting, and exercise. The principal organ of glucose homeostasis is the liver, which absorbs and stores glucose (in the form of glycogen) in the postabsorptive state (after the intake of food), and releases glucose into the circulation between meals to meet the rate of glucose utilization (cellular respiration) by the peripheral tissues. The liver is also the site of gluconeogenesis ("new sugar formation"), whereby 3-carbon molecules

derived from the breakdown of fat (glycerol), muscle glycogen (lactate), and protein (e.g., alanine) are synthesized into the 6-carbon glucose molecule. About 200 g of glucose is produced and used each day. More than 90% of this is derived from the glycogen stores in the liver and from gluconeogenesis. The remaining 10% is derived from gluconeogenesis undertaken by the kidneys.

The brain is the major consumer of glucose, requiring up to 1 mg/kg bodyweight per minute (i.e., 100 g/daily in a 70 kg patient). Glucose uptake by the brain is obligatory and not dependent on insulin, with the glucose used for energy (cellular respiration) or oxidized to form carbon dioxide and water. Other tissues, namely the fat and muscle cells, are facultative consumers of glucose, which otherwise rely on fatty acid oxidation for their energy needs. Glucose taken up by muscle cells is stored as glycogen or broken down to lactate, which enters the circulation to become a major substrate for hepatic gluconeogenesis. Glucose is used by fat cells as a source of energy and as a substrate for triglyceride synthesis. Lipolysis is the breakdown of lipids by the hydrolysis of triglycerides into free fatty acids and glycerol. The resulting glycerol also serves as a substrate for hepatic gluconeogenesis.

Cell membranes, because of their polar lipid bilayer, are not readily permeable to glucose. Glucose transporters (GLUT) are a family of four, ubiquitous, specialized cell membrane proteins that facilitate the transport of glucose (and related hexoses) through the plasma membrane.[143] The glucose transporter responsible for the majority of glucose uptake by cells of the body is GLUT 4, which operates solely at the bidding of insulin. GLUT 4 is found on the cells of adipose tissue as well as skeletal and cardiac muscle, and glucose cannot enter these cells without the presence of insulin.

Insulin

Insulin is the key hormone involved in the storage and controlled release of the energy available from food. Insulin is a peptide hormone produced by the beta (islet) cells of the endocrine pancreas. After secretion, insulin enters the portal circulation and is transported to the liver, its prime target organ. Half of this insulin is taken up from the circulation and degraded by the liver, with the residue broken down in the kidneys.

Insulin is a major regulator of intermediate metabolism. Although its actions are modified by many other hormones, its importance lies in its differing actions in the fasting and postprandial states. In the fasting state insulin functions to regulate the release of glucose by the liver, and in the postprandial state it facilitates the uptake of glucose by fat and muscle. The effect of counter-regulatory hormones (namely glucagon, epinephrine, cortisol, and GH) is to cause a greater release of glucose from the liver and decrease the utilization of glucose by the fat and muscle cells, for a given level of insulin.

Glucagon

Glucagon is a peptide hormone synthesized and secreted from alpha cells of the islets of Langerhans, of the endocrine portion of the pancreas (Box 22-2). Glucagon acts to raise blood glucose levels (Figure 22-16), so the effect of glucagon is opposite to that of insulin (which lowers blood glucose levels). The pancreas releases glucagon when blood glucose concentrations fall critically low (Table 22-18). Glucagon generally elevates blood glucose levels by promoting gluconeogenesis and glycogenolysis in the liver. High blood glucose levels stimulate the release of insulin, which then allows glucose to be taken up and used by insulin-dependent tissues. Thus, glucagon and insulin are part of a feedback system that maintains blood glucose levels at a stable level. Glucagon also regulates the rate of glucose production through lipolysis.

Amylin

Amylin, or islet amyloid polypeptide (IAPP), is a 37-residue peptide hormone. It is co-secreted with insulin from the pancreatic beta cells at a ratio of approximately 100:1. Amylin functions as a synergistic partner to insulin. The overall effect is to slow the rate of appearance of glucose in the blood. After eating, amylin causes a coordinated slowing of gastric emptying, the inhibition of digestive secretions (gastric acid, pancreatic enzymes, and bile), and the induction of satiety that results in a reduction in food intake. Blood glucose levels are also reduced by inhibiting secretion of the gluconeogenic hormone glucagon. Collectively, these actions reduce the total demand for insulin. These actions are largely mediated by the glucose-sensitive part of the brain stem, the *area postrema*,

Box 22-2 Glucagon (Peptide Hormone) versus Glycogen (Polysaccharide)

Glucagon is secreted by the pancreas, is a peptide hormone that raises blood glucose levels, and its effect is *opposite that of insulin* (insulin lowers blood glucose levels).

Glycogen is a multibranched polysaccharide of glucose that serves as secondary energy storage (the primary energy stores being fats held in adipose tissue). Glycogen is made and stored primarily in the hepatocytes and the muscles.

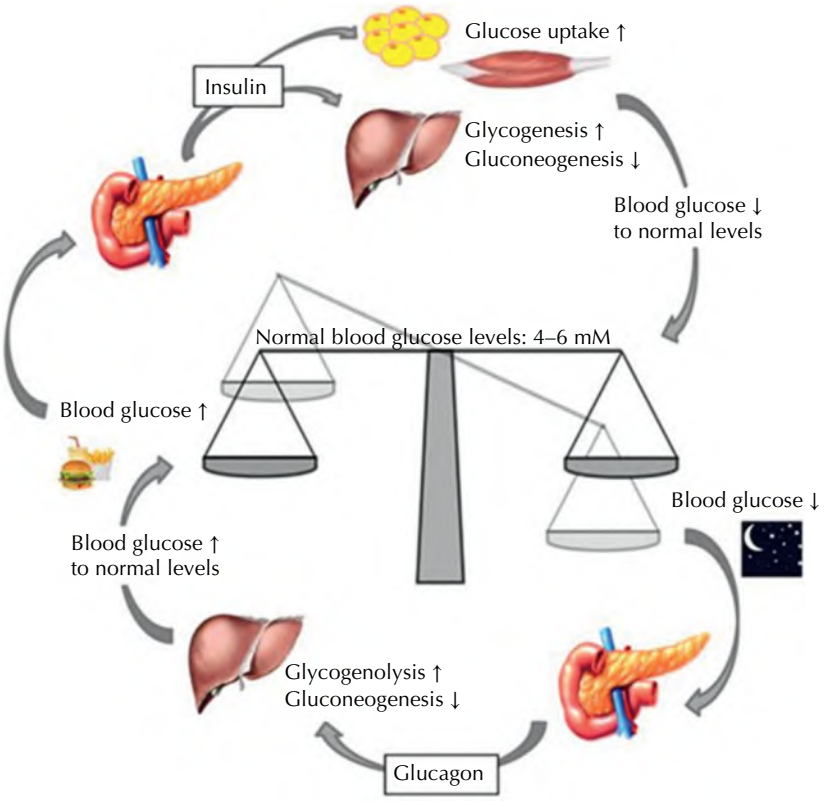


Figure 22-16 Maintenance of blood glucose levels by glucagon and insulin. When blood glucose levels are low, the pancreas secretes glucagon, which increases endogenous blood glucose levels through glycogenolysis. After a meal, when exogenous blood glucose levels are high, insulin is released to trigger glucose uptake into insulin-dependent muscle and adipose tissues as well as to promote glycogenesis. *Source:* Röder PV, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. *Exp Mol Med*. 2016;48(3):e219. Reproduced with permission.

Table 22-18 Regulation of glucagon.

↑ **Glucagon** secretion of glucagon is **stimulated by:**	• **Hypoglycemia** • Epinephrine • Arginine • Alanine (muscle-derived pyruvate/glutamate transamination • Acetylcholine • Cholecystokinin
↓ **Glucagon** secretion of glucagon is **inhibited** by:	• **Insulin (via GABA)** • Somatostatin • PPARγ/retinoid X receptor heterodimer • Increased free fatty acids and keto acids into the blood • Increased urea

but this control can be overridden during hypoglycemia. Both insulin and amylin are regulated by similar factors since they share a common regulatory promoter motif, with amylin being degraded in part by insulin-degrading enzymes and by peptidases in the kidney. A synthetic analogue of human amylin, pramlintide (Symlin®, AstraZeneca, Wilmington, DE, USA), is used in both T1DM and T2DM. Both insulin and pramlintide are injected separately, before a meal, to synergistically control the post-prandial glucose levels.[144]

Pathophysiology of Diabetes Mellitus

The pathophysiology of DM is mediated by alterations of carbohydrate metabolism and insulin action. After a meal, breakdown of carbohydrates leads to hyperglycemia, an elevation in blood glucose levels. Hyperglycemia stimulates insulin secretion from pancreatic beta cells because insulin is critical for glucose uptake by most cells (except in the brain). Insulin binds to specific cellular receptors and facilitates entry of glucose into the cell, which then uses the glucose for energy. The end result is a reduced blood glucose level and ultimately decreased insulin secretion. If insulin production and secretion are altered by disease, glucose entry into cells will be inhibited, resulting in sustained hyperglycemia.

Hyperglycemia can also ensue if insulin cannot function effectively, termed "insulin resistance." Following meals, the amount of glucose available often exceeds cellular demand for glucose. The excess glucose is stored in the liver in the form of glycogen, which serves as a ready reservoir of glucose for future use. When energy is required, glycogen stores in the liver are converted into glucose via glycogenolysis, elevating blood glucose levels and providing the needed cellular energy source. The liver also produces glucose from fat (fatty acids) and proteins (amino acids) through the process of gluconeogenesis. Glycogenolysis and gluconeogenesis

both serve to increase blood glucose levels. Thus, glycemia is controlled by a complex interaction between the gastrointestinal tract, the pancreas, and the liver. Insulin is the only hormone that lowers blood glucose levels. Counter-regulatory hormones such as glucagon, catecholamines, GH, thyroid hormone, and glucocorticoids all act to increase blood glucose levels, in addition to their other effects.

Type 1 Diabetes Mellitus

T1DM is characterized by idiopathic autoimmune destruction of pancreatic beta cells, usually leading to an absolute insulin deficiency (Tables 22-18 and 22-19).[4] It constitutes 5–10% of all DM cases. T1DM typically occurs before the age of 25 years in 95% of affected persons, but can occur at any age. It affects both sexes equally, and is more prevalent in Caucasians. The risk of developing T1DM is increased by a family history of T1DM, having gluten enteropathy (celiac disease), or other endocrine diseases. There are two distinct subclasses:

- *Immune-mediated form of T1DM*. This has a slow onset, with a subclinical prodromal period, characterized by cellular-mediated autoimmune destruction of the insulin-producing beta cell in the pancreatic islets. This may be triggered by a viral infection, but it is also associated with other autoimmune disorders, such as Hashimoto's thyroiditis, Addison's disease, vitiligo, or pernicious anemia.
- *Idiopathic T1DM*. This is acute in onset, and the cause of beta cell destruction is still unclear. It is prevalent among people of African or Asian origin and has a strong pattern of familial inheritance.[145]

Since the pancreas no longer produces insulin, a T1DM patient is completely dependent on exogenously administered insulin for survival. People with T1DM are highly susceptible to diabetic ketoacidosis. Although glucose is present, it is trapped in the circulation, but without insulin the cells are unable to take up the glucose. To meet cellular energy needs, fat is broken down through lipolysis, releasing glycerol and free fatty acids. Glycerol is converted to glucose for use by the cells. Fatty acids are converted to ketones, with an increase in the ketone levels in body fluids, which thus become increasingly alkaline (increased pH). Ketones are excreted in the urine, accompanied by large amounts of water. This accumulation of ketones in body fluids, increased pH, electrolyte loss, and dehydration from excessive urination, in addition to alterations in the bicarbonate buffering system, result in diabetic ketoacidosis. Untreated diabetic ketoacidosis can result in coma or even death. Many patients with T1DM are initially diagnosed following an episode of diabetic ketoacidosis.[146]

Table 22-19 American diabetes association diagnosis and classification of diabetes mellitus (DM).

1 Type 1 (Type 1 DM)	Formerly termed "juvenile diabetes" or "insulin-dependent diabetes"
2 Type 2 (Type 2 DM)	Formerly termed "adult-onset diabetes" or "non-insulin-dependent diabetes"
3 "Other"	A group of other types of DM caused by specific genetic defects of beta cell function or insulin action, diseases of the pancreas, or drugs or chemicals
4 Gestational diabetes	

Note: Arabic numbers are used instead of Roman numerals, thereby eliminating the confusion of type II, for example, as the number 11.

Type 2 Diabetes Mellitus

T2DM is the most common type of DM, constituting 90–95% of DM cases (Tables 22-18 and 22-19). It is characterized by insulin resistance in the peripheral tissues and/or defective insulin secretion by the pancreatic beta cells.[147] The etiology of T2DM is multifactorial, including genetic predilection, advancing age, obesity, and lack of exercise (Table 22-20).[10] Most T2DM patients are overweight, and most are diagnosed as adults.

Table 22-20 Risk factors for type 2 diabetes mellitus.

Diabetes-Related Risk Factors
Previously identified with: • impaired fasting glucose; or • impaired glucose tolerance; or • HbA1c of 5.7–6.4%
History of gestational diabetes or delivery of a baby >4 kg (9 lb)
Cardiovascular Risk Factors
History of cardiovascular disease
Hypertension (blood pressure ≥140/90 mmHg)
Dyslipidemia • high-density lipoprotein cholesterol level <35 mg/dL (0.90 mmol/L); and/or • triglyceride level >250 mg/dL (2.82 mmol/L)
Conditions/Diseases Associated with Development of Diabetes
Polycystic ovary syndrome
Acanthosis nigricans
Family History/Lifestyle Risk Factors
Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
Obesity (body mass index [BMI] ≥25 kg/m^2)
Physical inactivity

The underlying pathophysiologic defect in T2DM does not involve autoimmune beta cell destruction, and is characterized by the following three features:

- Peripheral resistance to insulin, especially by the muscle cells.
- Increased production of glucose by the liver.
- Defective insulin secretion by the pancreatic beta cells.[5]

Increased tissue resistance to insulin generally occurs first, followed by impaired insulin secretion. The pancreas produces insulin, yet insulin resistance prevents its proper use at the cellular level. Glucose cannot enter target cells and accumulates in the bloodstream, resulting in hyperglycemia. The high blood glucose levels often stimulate an increase in insulin production by the pancreas; thus, people with T2DM often have excessive insulin production (hyperinsulinemia), but then, over several years, this drops to below normal levels.

In addition to hyperglycemia, patients with T2DM often have a group of disorders called "metabolic syndrome" comprising hyperglycemia, hypertension, dyslipidemia, atherosclerosis, and central or abdominal obesity (Table 22-20).[148] Obesity contributes greatly to insulin resistance and may explain the dramatic increase in the incidence of T2DM in the United States and worldwide in the past 10–20 years. Other risk factors include advancing age, high caloric intake, sedentary lifestyle, and low birth weight. People with impaired glucose tolerance, impaired fasting glucose, and gestational DM have a high risk of developing T2DM later in life, with these conditions being considered the preclinical stages of T2DM.

T2DM has a slow onset and may remain undiagnosed for years, given that some 50% of affected people are unaware of their disease. By the time many T2DM patients are diagnosed, diabetic complications and the consequent morbidity are already established. T2DM patients do not require exogenous insulin for survival since they still produce insulin. However, insulin is often an integral part of medical management for T2DM. Unlike patients with T1DM, those with T2DM are generally resistant to diabetic ketoacidosis, because their pancreatic insulin production is often sufficient to prevent ketone formation, although severe physiologic stress can still induce diabetic ketoacidosis in those with T2DM. Long periods of severe hyperglycemia can result in hyperosmolar nonketotic acidosis. This occurs when hyperglycemia results in the urinary excretion of large amounts of glucose, with attendant water loss. If this fluid is not replaced, dehydration can result in electrolyte imbalance and acidosis.

Gestational DM includes the development of T1DM or the discovery of undiagnosed asymptomatic T2DM during pregnancy.[8] Approximately 2–5% of pregnant women in the United States develop a mild degree of fasting hyperglycemia or glucose intolerance during the third trimester, which significantly increases perinatal maternal morbidity and mortality. Some 30–50% of women with gestational DM will develop T2DM within 10 years.

Diagnosis and Monitoring

The diagnosis of DM is based on specific laboratory findings, as well as the presence of clinical signs and symptoms. Diagnostic guidelines include testing of the fasting and nonfasting glucose levels. Diagnosis is not made until the patient has exceeded threshold glucose levels on two separate occasions. The classic signs of DM vary in number and order, but are typically described as (1) polyuria (frequent urination); (2) polydipsia (increased thirst); (3) polyphagia (increased hunger); (4) weight loss; and (5) either disturbed (blurry) vision or peripheral neuropathy.

Glycosylated Hemoglobin Assay

The glycosylated hemoglobin assay (HbA1c) allows the determination of blood glucose status over the 30–90 days prior to collection of the blood sample. It has now been officially recommended as one of the tests for the definitive diagnosis of DM, for screening of individual patients suspected to have DM, and for population screening. As glucose circulates in the bloodstream, it becomes attached to a portion of the hemoglobin molecule on red blood cells (like barnacles on a ship). The higher the plasma glucose levels are over time, the greater the percentage of hemoglobin that becomes glycosylated. The American Diabetes Association recommends that individuals with DM attempt to achieve a target HbA1c value of less than 7%. An HbA1c value of more than 8% suggests that a change in patient management may be needed to improve glycemic control.[4] The HbA1c can provide false-positive and -negative values in rare situations, such as patients with severe iron deficiency and those with any form of hemoglobinopathy, for example sickle cell disease.

Glucometers

The development of small, accurate, handheld glucometers has allowed the diabetic individual to take much greater control of their disease. Glucometers use a small drop of capillary blood from a finger-stick sample to assess glucose levels within seconds.[149]

Screening

The American Diabetes Association recommends screening all individuals >45 years every 3 years, and screening individuals at an earlier age if they are overweight (body mass index [BMI] >25 kg/m^2) and have one additional risk factor

for diabetes, as listed in Table 22-19. Dental healthcare providers are well placed to undertake screening of their patients for diabetes.[150–152]

Management

The primary treatment goals for DM are to achieve blood glucose levels as close to normal as possible and to prevent diabetic complications.[13] Secondary goals are to maintain normal growth and development, normal body weight, the avoidance of sustained hyperglycemia or symptomatic hypoglycemia, and the prevention of diabetic ketoacidosis and nonketotic acidosis. The other major aim is the prevention and management of the long-term complications of diabetes. Diet, exercise, weight control, and medications (Table 22-21) are the mainstays of diabetic care. Weight reduction and exercise improve tissue sensitivity to insulin and allow its proper use by target tissues.

Medications

Drugs used to treat DM lower glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide, and pramlintide, all are administered orally and are therefore also called oral hypoglycemic agents or oral antihyperglycemic *agents* (see Table 22-22).[153,154]

Gastric Banding and Gastric Bypass Surgery

These surgical treatments are indicated for patients with severe, morbid obesity who are unresponsive to 6 months' intensive attempts at dieting and graded exercise. FDA-recommended BMI thresholds for surgery range from 30–40 kg/m^2, with one or more obesity-related medical conditions: hypertension, heart disease, DM, or sleep apnea. The surgical risks and postoperative complications are frequent and potentially severe. Also, long-term intensive specialist care and follow-up are needed, including psychologic support and nutritional supplements (subsequent to bowel resection procedures). About one-third of DM patients have complete resolution of their disease, becoming medication free.[155,156] However, DM can still recur.

Insulin

All patients with T1DM use exogenous insulin, as do many with T2DM. Insulin is given via subcutaneous injection. Insulin infusion pumps deliver insulin through a subcutaneous catheter. Ideally, the use of exogenous insulin provides an insulin profile similar to that seen in a nondiabetic individual, with a continuous basal level of insulin availability augmented by increased availability following each meal (see Tables 22-21, 22-22, and 22-23).

Human insulin is only absorbed slowly, reaching a peak 60–90 minutes after subcutaneous injection, and its action tends to persist after meals, predisposing to hypoglycemia. Rapid-acting insulins (insulin lispro, insulin aspart, and insulin glulisine) enter the circulation more rapidly than human soluble insulin, but also disappear more rapidly and are of limited effectiveness.[157]

The action of human insulin can be prolonged by the addition of zinc or by the addition of protamine. The most widely used form is neutral protamine hagedorn (NPH or isophane insulin), which is a suspension of crystalline zinc insulin combined with protamine; this has an intermediate duration of action that is longer than that of regular insulin, but shorter than ultralente, glargine, or detemir. NPH has the advantage that it can be premixed with soluble insulin to form stable mixtures (biphasic insulins), of which the combination of 30% more readily soluble absorbable insulin with 70% NPH is most widely used. The intermediate-acting insulins (lente and NPH) take several hours after injection to begin having an effect. Peak activity varies among individuals and sites of injection, but generally occurs 4–10 hours after injection.

Long-acting insulins include insulin glargine. This form of insulin is soluble in the vial as a slightly acidic (pH 4) solution, but precipitates on subcutaneous injection, which prolongs its duration of action. Ultralente insulin is the longest-acting insulin. Commonly called "peakless" insulin, ultralente has a very slow onset of action, minimal peak activity, and a long duration of action. It is usually taken to mimic the basal metabolic rate of insulin secreted from a normally functioning pancreas (see Table 22-22).

Insulin Complications

The most common complication of insulin therapy is hypoglycemia, a potentially life-threatening emergency.[10] Intensified treatment of DM to achieve a tightly regulated blood sugar level increases the risk of hypoglycemia. One-third of severe hypoglycemic episodes result in seizure or loss of consciousness and 36% of episodes occur with no warning symptoms for the diabetic patient. The phenomenon known as "hypoglycemia unawareness" is more common in diabetic patients with good glycemic control than in those with poor control. Signs and symptoms of hypoglycemia are most common when blood glucose levels fall to <60 mg/dL, but they may occur at higher levels in diabetic patients with chronic poor metabolic control.[13] In people with hypoglycemia unawareness, glucose levels can fall to 40 mg/dL or lower before an individual feels or reports being unwell.[158]

Pancreas or Beta-Islet Cell Transplantation

Transplantation of the whole pancreas or just the pancreatic islet cells is an option for T1DM, particularly for patients with severe or poorly controlled disease.[159]

Table 22-21 Drug therapies used for diabetes mellitus.

Oral Agents

Insulin Sensitizers

Class	Actions	Generic Name	Trade Name(s)[a]	Advantages	Disadvantages/ Warnings
Biguanides	↓ Hepatic glucose production ↓ Intestinal absorption of glucose Improves insulin sensitivity by increasing peripheral glucose uptake and utilization	Metformin	Diabex Fortamet Glucophage Glumetza Riomet	Weight neutral No hypoglycemia	Lactic acidosis with metformin: risk increases with degree of renal impairment, patient's age, unstable/ acute congestive heart failure
Thiazolidinediones ("glitazones")	↑ Tissue sensitivity to insulin ↓ Hepatic gluconeogenesis ↓ Glucose use ↓ Blood glucose levels.	Rosiglitazone Pioglitazone	Avandia Actos	Lower insulin requirements No hypoglycemia	May increase risk of congestive heart failure and myocardial infarction
Insulin Secretagogues (Increase Insulin Release)					
Sulfonylureas (1st generation)	↓ Lowers blood glucose acutely	Tolazamide Tolbutamide	Tolazamide Orinase	?	Significant adverse side effects (relative to 2nd-generation sulfonylureas)
Sulfonylureas (2nd generation)	↑ Insulin by stimulating its release from pancreas	Gliclazide[b] Glimepiride Glipizide Glyburide	Diamicron[b] Amaryl Glucotrol DiaBeta Glynase	More potent, but fewer side effects or drug interactions	Hypoglycemia Increased risk of cardiovascular mortality
Nonsulfonylurea Insulin Secretagogues					
Meglitinides	↓ Lowers blood glucose ↑ Insulin by stimulating its release from pancreas	Nateglinide Repaglinide	Starlix Prandin	Acts similar to sulfonylureas but much shorter half-life	Hypoglycemia
Alpha-Glucosidase Inhibitors (Have No Effect on Insulin)					
α-Glucosidase Inhibitors	↓ Digestion and ingestion of glucose (in the form of starch) from the gastrointestinal tract	Acarbose Miglitol	Precose Glyset	Reduce postprandial hyperglycemia	Flatulence Inhibits hydrolysis of sucrose to glucose and fructose; use oral glucose (dextrose) instead of sucrose in treatment of mild–moderate hypoglycemia

(*Continued*)

Table 22-21 (Continued)

Oral Agents

Insulin Sensitizers

Class	Actions	Generic Name	Trade Name(s)[a]	Advantages	Disadvantages/ Warnings
Glycosuric Agents					
Sodium/glucose cotransporter 2 (SGLT2) Inhibitors	↓ Reabsorption of renally filtered glucose ↓ Lowers renal threshold for glucose, thereby increases urinary glucose excretion ↓ Glucose blood levels	Canagliflozin Dapagliflozin[b] Empagliflozin	Invokana Forxiga[b] Jardiance	Weight reduction Reduced blood pressure	Hypotension Hyperkalemia Genital mycotic infections, urinary tract infection, increased urination
Dipeptidyl Peptidase-4 Inhibitors					
Dipeptidyl peptidase-4 inhibitors	↓ Enzymic inactivation of incretin hormones, thereby increasing serum concentrations ↓ Fasting and postprandial glucose blood levels	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin[b]	Nesina Tradjenta Onglyza Januvia Galvus[b]	No hypoglycemia	Angioedema
Parenteral Agents					
Insulin					
Short-acting Long-acting Combination (short- and long-acting)	↑ Glucose utilization (and absorption) ↓ Hepatic gluconeogenesis	Various (see Table 22-11)		Known and predictable safety profile	Parenteral: injection needed Weight gain (increases hunger) Hypoglycemia
Incretin Mimetics					
Gastric inhibitory peptide (GLP-1) agonists	↑ Insulin ↓ Glucagon	Exenatide	Bydureon (XR) Byetta	Slow gastric emptying and so increase satiety, leading to weight loss	Injection Hypoglycemia Nausea Pancreatitis
		Liraglutide	Victoza		
Amylin analogues	Modulation of gastric emptying ↓ Postprandial rise in plasma glucagon ↑ Satiety	Pramlintide	Symlin	Satiety ↓ Caloric intake → Potential weight loss Regulates food intake	Parenteral: injection needed Increased risk of insulin-induced severe hypoglycemia (especially in patients with type 1 diabetes mellitus)

↓, decreases; ↑, increases; →, leads to; ?, uncertain; XR, extended release

[a] Table entry refers to the single agent. Oral antidiabetic agents are often prescribed and supplied in combination with other antidiabetic agents.

[b] Not marketed in the United States.

Source: Data from MIMS Australia (http://www.mims.com.au/index.php/about-mims/mims-australia) and Rx List (https://www.rxlist.com/script/main/hp.asp).

Table 22-22 Types of insulin.

Type	Class	Onset of Activity (h)	Peak Activity (h)	Duration of Activity (h)
Lispro	Rapid-acting	0.25	0.5–1.5	<5
Insulin aspart (Novorapid)	Rapid-acting	0.25	0.67–1.5	3–5
Insulin glulisine (Apidra)	Rapid-acting	0.2	0.67–1.5	3–5
Regular	Short-acting	0.5–1.0	2–3	4–12
Lente	Intermediate-acting	3–4	4–12	16–20
Neutral protamine hagedorn	Intermediate-acting	2–4	4–10	14–18
Insulin detemir	Long-acting	Onset 2 h	No peak	6–24
Insulin glargine	Long-acting	Onset 2 h	No peak	20 to >24
Ultralente	Long-acting	6–10	12–16	20–30

Table 22-23 Common insulin regimens.

Insulin(s) Description	Frequency of Injection	Timing of Injection	Characteristics
intermediate-acting	Single (1×) daily	Morning early	• Peak insulin activity at midday • Can provide enough insulin for midday meal only • Hyperglycemia common upon rising, following breakfast and dinner
Mixture of intermediate-acting and regular or rapid-acting	Single (1×) daily	Morning early	• Peak insulin activity at both mid-morning (from regular or lispro insulin) and midday (from intermediate-acting insulin) can provide enough insulin for breakfast and midday meals Hyperglycemia common on rising and late afternoon to next morning
Intermediate-acting	Twice (2×) daily	Prior to breakfast Prior to dinner	• Peak insulin activity at both midday (from morning injection) and evening (from dinner injection) • Can provide enough insulin for lunch and sometimes dinner to prevent early-morning high blood glucose levels • Hyperglycemia common after breakfast and shortly after dinner
Mixture of intermediate-acting and regular or rapid-acting	Twice (2×) daily	Prior to breakfast Prior to dinner	• Peak insulin activity after breakfast (from morning regular or lispro insulin), after lunch (from morning intermediate-acting insulin), after dinner (from dinnertime regular or lispro insulin), and late evening or early morning (from dinnertime intermediate-acting insulin) • Can provide enough insulin for all meals • Prevents early-morning high blood glucose levels
Regular or rapid-acting and one injection of intermediate-acting	Three (3×) daily	Prior to each main meal	• Peak insulin activity after breakfast, lunch, and dinner (from regular or lispro insulin before each meal) and late evening or early morning (from dinnertime intermediate-acting insulin) • Can provide enough insulin for all meals • Prevents early-morning high blood glucose levels
	Single (1× daily)	Bedtime	• Provides better glycemic control than once- or twice-daily injection regimens
Ultralente and regular or rapid-acting	Once (morning)	Morning	• Peak insulin activity after breakfast, lunch, and dinner (from regular or lispro insulin before each meal), insulin activity in late evening or early morning (from morning Ultralente insulin)
	Three (3×) daily	Prior to each main meal	• Can provide enough insulin for all meals • Prevents early-morning high blood glucose levels • Provides better glycemic control than once- or twice-daily injection regimens
Infusion* regular or rapid-acting	Continuous with bolus (before meals)	See note	• Provides on-demand insulin with meals • Basal metabolic rate most closely mimics normal pancreatic function • Often (not always) provides best glycemic control

* Rate set to provide continuous low dose with bolus programmed to be given prior to each meal.

Complications of Diabetes Mellitus

Life expectancy is considerably reduced in patients with DM (Table 22-24). The major causes of death are cardiovascular complications, renal failure, and infection(s).[160,161] The pathophysiology is related to (1) nonenzymatic glycosylation of proteins such as hemoglobin, collagen, and tubulin in peripheral nerves, thus impairing their function and also leading to an accumulation of advanced glycosylated end-products, causing injury and inflammation;[162] and (2) disruption of the polyol pathway[163] of the vascular endothelium, with the metabolism of glucose being increased by intracellular aldose reductase, which leads to the accumulation of sorbitol and fructose that causes changes in vascular permeability, cell proliferation, and capillary structure.

Table 22-24 Complications of diabetes mellitus.

System/Organ	Presentation
Cardiovascular system	Macrovascular disease (accelerated atherosclerosis) leading to peripheral vascular disease, coronary artery disease and cerebrovascular disease, ischemic ulcers, andgangrenous feet
Nervous system	Sensory: peripheral neuropathy, cranial neuropathy affecting cranial nerves III, IV, VI, VII Autonomic: gastroparesis; changes in cardiac rate, rhythm, and dysfunction; postural hypotension; gastrointestinal neuropathy; urinary bladder atony; impotence
Kidney	Nephropathy, renal failure
Skin and oral mucosa Periodontium	Unusual infections, delayed wound healing Gingivitis and periodontal diseases
Eyes	Retinopathy, cataracts, blindness

Macrovascular Complications

Diabetes is a risk factor for the development of atherosclerosis (Table 22-25). Consequently, myocardial infarction is 3–5 times more likely for both diabetic men and women. Similarly, stroke is two times higher and foot amputation for gangrene is 50 times more likely to occur.

Microvascular Complications

Small blood vessels throughout the body are affected, but the disease process is of particular concern in three sites: retina, renal glomerulus, and nerves (specifically the nerve sheath), the latter resulting in a variety of sensory and autonomic neuropathies.

Infectious Complications

Infections in diabetics tend to be more frequent and generally more severe (Table 22-26), due to abnormalities of cell-mediated immunity and impaired polymorphonuclear leucocytes (neutrophil) function. Neutrophil chemotaxis and phagocytosis are diminished, because at high blood

Table 22-25 Macrovascular complications of diabetes and their management.

Risk Factor	Aim	Treatment/Intervention
Duration of diabetes mellitus	Maintenance of optimal glycemic control	Frequent monitoring, by patient and health professionals
Hypertension	Aggressive maintenance of target blood pressure	Usually requires a combination of antihypertensive agents: angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor antagonists
Myocardial infarction/stroke		Aspirin (low dose): reduces macrovascular risk, but is associated with complications from bleeding
Proteinuria (including microalbuminuria)	Regular urinary analysis	Urine to be checked regularly (at least annually) for proteinuria Screening of younger patients for microalbuminuria
Dyslipidemia/ hyperlipidemia	Aggressive control of hypercholesterolemia	Statins: there is no "safe" cut-off for serum cholesterol, so the lowest achievable level seems best practice
Other factors (as per the general population): Aging Smoking Excessive alcohol intake Poor diet	Avoidable/modifiable	Consistent efforts should always be made to address modifiable risk factors

Table 22-26 Infectious complications in diabetic patients.

Site/Organ	Infectious Organism(s)	Clinical Entity
Skin	*Staphylococcal* spp.	Boils Abscesses Carbuncles
Mucosa	*Candida* spp.	Mucocutaneous candidiasis Vulvo-vaginal candidiasis
Oral cavity	Mixed bacterial infection	Periodontal disease
Bone	*Staphylococcal* spp.	Spontaneous spinal osteomyelitis
Lung	*Staphylococcal* spp. *Pneumococcus* spp. Gram-negative bacteria Tuberculosis	Pneumonia Pulmonary tuberculosis
Gastrointestinal tract	Mixed bacterial infection	Rectal and ischiorectal abscesses
Urinary tract	Mixed bacterial infection	Urinary tract infections (in women) Pyelonephritis Perinephric abscess

glucose concentrations neutrophil superoxide generation is impaired, and there is reduced tissue vascularity (reduced microcirculation/number of vessels and capillaries in the tissues). Reduced tissue vascularity results in hypoxia and ischemia that limit the access of neutrophils and any antibiotic given to the patient to sites of infection. Hyperglycemia also aids in the colonization and growth of *Candida* and other fungi, and of select bacterial species. Conversely, all types of infections may lead to impaired glycemic control and are a common cause of ketoacidosis. Insulin-treated patients need to increase their insulin dose(s) by up to 25% when infection occurs, and non-insulin-dependent diabetics may need insulin to be instituted during the course of the infection.[164] Apart from increased frequency and severity of common infections, there are district rare infections of diabetic populations: malignant, invasive otitis externa, usually secondary to *Pseudomonas aeruginosa*, which can lead to osteomyelitis and even meningitis; emphysematous (gas-forming) bacterial infections of the gall bladder and urinary tract; and rhinocerebral mucormyositis of the sinuses.[165]

Stomatognathic Manifestations and Complications of Diabetes Mellitus

Dentists also must be prepared to provide, sometimes highly invasive, surgical treatment for patients with DM, which may include the use of general anesthesia (Table 22-27). Good oral health, especially the prevention and treatment of infections, such as the various forms of candidiasis, periodontal disease, and odontogenic-related soft tissue infections and cellulitis, is essential for the maintenance of glycemic control, and the diabetic patient's overall wellbeing and health.[166]

Medical History and Review of Physiologic Systems

The focus of a thorough medical history and review of systems is to determine both the severity and stability of the medical condition(s). Stability of DM is the more critical concern. It can be readily assessed by reviewing the patient's ongoing glycemic control, such as their self-assessment of fasting and nonfasting blood glucose levels using a home glucometer, or arranging testing of HbA1c, which serves as a useful assessment of glycemic control for the last three months. Other important clues to glycemic control are the number and severity of the known complications of DM. These include the state of their cardiovascular health, which is critical to safe dental treatment, the frequency of hypoglycemic episodes, or the length of time since the patient's last hypoglycemic episode. For T2DM patients, the number of medications they use, recent adjustments in the dose or frequency of their medications, and whether they require insulin as part of their management regimen are also highly informative in determining the level of their glycemic control. A favorable outcome of recent dental extractions and surgery within the past 3–6 months is also indicative of a favorable outcome for any dental surgery needed in the immediate future.

The most likely and serious complication is inadvertent hypoglycemia, in a patient taking their normal medication, especially insulin, but failing to eat, either because of a dental problem associated with discomfort and pain, or the

Table 22-27 Oral and dental findings with diabetes mellitus.

Clinical Finding (Sign)	Description	Etiology/Pathophysiology
Extraoral Findings		
Sialosis	Bilateral diffuse swelling of the parotid glands, in the absence of any other identifiable cause of bilateral parotid sialoadenopathy	Autonomic neuropathy
Angular cheilitis	Unilateral, but typically bilateral moist fissuring of the corners of the lips/mouth (commissures)	Infection (secondary to impaired immunity): *Candidal* spp. with coinfection from staphylococcal bacterial species resident on the perioral skin.
Intraoral Findings		
Hyposalivation	Clinical evident decrease in total volume of unstimulated and stimulated salivary flow Smooth surface dental caries Atrophy and desiccation of mucosal surfaces Atrophy of papillae of dorsal tongue	Autonomic neuropathy Dehydration secondary to polyuria
Candidiasis		Infection (secondary to impaired immunity) with contributory factors including hyposalivation, and increased presence in saliva of glucose
Oropharyngeal candidiasis	White, adherent, small plaques that on removal leave a red, superficially bleeding area scattered over the oral and oropharyngeal mucosa	
Atrophic candidiasis	Erythematous, atrophic oral mucosa, particularly of the hard palate	
Denture stomatitis	Markedly erythematous, atrophic oral mucosa of the denture-fitting surfaces of the oral mucosa (particularly the palate)	
Medium rhomboid glossitis	Erythematous, well-demarcated, somewhat rhomboid-shaped area of mucosa of the central dorsal surface of the tongue	
Periodontal disease(s)	Localized or generalized periodontal changes, with gingival erythema, presence of increased tooth mobility, and bleeding on periodontal probing, with associated alveolar bone loss, evident radiographically	Infection secondary to impaired immunity, due to accumulation of dental plaque and impaired neutrophil response (deficient chemotaxis and bacterial killing)
Poor oral hygiene	Bacterial plaque deposits and/or calculus readily evident on tooth surfaces, with gingivitis and easy bleeding of gingiva	Impaired manual dexterity, secondary to sensory and autonomic neuropathy affecting hands/fingers
Oral lichen planus/ lichenoid mucositis	Striae: fine white-gray lines on erythematous background, typically bilateral, involving buccal or latero-ventral surfaces of tongue, with similar-colored discrete plaques and/or mucosal ulceration and/or desquamative gingivitis	Lichenoid drug reaction to oral hypoglycemic agents (e.g., chlorpropamide)

mistaken belief in the need to fast prior to a dental procedure. Odontogenic-related infections (periapical periodontitis) that result in either in a collection in the adjacent soft tissues or cellulitis can trigger ketoacidosis. Therefore, a simple precaution before undertaking highly invasive dental surgical procedures is to check the patient's blood glucose level by means of an inexpensive, compact, point-of-care glucometer. A hypoglycemic patient can be provided with replacement sugar. For a conscious patient, this can be in the form of a glucose drink of 150 mL carbonated lemonade, two teaspoons of table sugar (sucrose), or preferably glucose (dextrose) in water. The clinician should check for patient recovery and recheck their blood glucose level.

For patients with a deteriorating level of consciousness, this represents an evolving medical emergency, requiring the prompt institution of first aid, and if necessary intramuscular administration of 1 mg glucagon (see later).

Oral Candidiasis

When DM patients present with candidiasis in any of its clinical forms, it is indicative of impaired glycemic control. Therefore, patients' random blood glucose and hemoglobin HbA1c should be checked. The treatment of oral fungal infections in DM patients is similar to that for standard patients, with the added consideration that topical antifungal medications need to be sugar free.

Periodontal Disease

Periodontal disease has been referred to as the sixth sign[167] or complication of DM, and the longer the duration of DM, the greater the likelihood of developing severe periodontal disease.[168,169] Severe periodontitis has also been suggested to be a risk factor for poor glycemic control.[170,171] Since glycemic control is connected to periodontal disease and progressive alveolar bone loss,[172] periodontal treatment must be in parallel with DM treatment.[173–177] There is firm evidence of improvement in glycemic control in diabetic patients that receive treatment of their periodontal disease. There is a modest, but significant, improvement in glycemic control, reflected by a 0.4% reduction in glycated hemoglobin levels.[178] Importantly, this modest benefit in the glycated hemoglobin level, as a result of periodontal therapy, when combined with other interventions, such as diet modification and exercise, may be sufficient to prevent or at least limit the number of medications required for good diabetic control, thereby limiting the cost to the patient and/or the healthcare system.[179,180]

Edentulism

Rates of tooth loss in patients with DM are not only higher compared with nondiabetic patients, but also more rapid, resulting in higher rates of edentulism at a younger age.[181] The main causes of tooth loss are predominantly due to dental caries and periodontal disease. It appears that diabetes per se does not directly contribute to tooth loss, but the combined effects of hyposalivation and peripheral neuropathy that affect manual dexterity are significant contributing factors, because they promote the formation, persistence, and growth of dental plaque. It is also important to note that the same causal lifestyle factors for T2DM—poor levels of health education, personal neglect, poor lifestyle choices, reflected in poor dietary choices—are also contributing factors to dental disease, with poorer levels of oral hygiene seen in this same group of patients.[182]

Dental Implants

DM is not a contraindication for dental implants. Although there is concern that implant survival may be reduced, a long-term cohort study demonstrated that smoking was independently a more significant and adverse factor for implant survival than DM. The study also showed that excellent frequent and regular implant maintenance was a significant factor to ensure and improve long-term implant survival.[183] As in all patients irrespective of diabetic status, appropriate patient selection and eradication of comorbidities such as poor oral hygiene, cigarette smoking, and periodontitis are critical to implant success. For patients with DM, one study demonstrated that stabilization of glycemic control HbA1c at around 7% and prevention of infection increased the success of dental implants to a satisfactory rate of 85–95%. The use of antibiotics at the time of implant placement for patients with DM is still debatable, as there is limited evidence that it may provide some benefit.

Dental Treatment Planning Considerations

Appointment Scheduling

Generally, the best time for dental treatment is either before or after periods of peak insulin activity. This reduces the risk of perioperative hypoglycemic reactions, which occur most often during peak insulin activity. The greatest risk would occur in a patient who has taken the usual amount of insulin or oral hypoglycemic agent but has not eaten prior to dental treatment. Patients with poor long-term glycemic control and patients with a history of severe hypoglycemic episodes are at greater risk of future hypoglycemia. Often it may not be possible to plan dental treatment in a way that will avoid peak insulin activity. This is particularly true for patients who take frequent insulin injections; these patients have greater risks of developing perioperative hypoglycemia. Pretreatment blood glucose level can be measured with a glucometer, and there should be a readily available source of carbohydrates in the dental office.[173]

Treatment Aims

For patients with sub-optimally controlled DM, treatment should be focused on addressing any active infection, and likely sources or sites of infection in the immediate future, such as periodontally compromised teeth with questionable prognosis. Odontogenic infections should also be aggressively addressed, by extracting the offending tooth or with root canal therapy (if appropriate), with an emphasis on excellent postoperative analgesia by using long-acting local anesthetics and opiate-containing analgesics. This may require aggressive surgical management with drainage of collections in the adjacent soft tissues, and antibiotic coverage. Hospital admission to stabilize the patient's blood glucose levels, and manage infection by surgery and intravenous antibiotics, may be merited. Extensive, elective dental treatment should be delayed until the patient's diabetes is better controlled.

For diabetic patients, it is important to ensure that the patient is able to eat and/or drink to replenish their glucose levels. Hypoglycemia can occur as a consequence of fasting, and happens more easily and more rapidly, so is a more critical concern than hyperglycemia. This can be best addressed by rechecking the patient's postoperative blood glucose level, providing supplementary glucose in the form of a drink (lemonade, orange juice), and ensuring that the patient travels home by private transport and that someone is at home to care for them on discharge from the clinic.

As to the specifics of patient positioning in the dental chair, patients with long-standing DM may have developed some degree of autonomic neuropathy with associated orthostatic hypotension. Thus it is vital to slowly and carefully raise the patient from the supine to the upright or standing position.

Drug Use and Adverse Drug Interactions

There are few significant drug interactions in DM (Table 22-28). The exception is metformin with radiographic iodine contrast, in which case temporary cessation of the metformin to allow time for the contrast to be administered and the imaging completed is recommended.

Table 22-28 Diabetic drugs—interactions with drugs relevant to dentistry/oral medicine.

Insulin Sensitizers					
Class	**Generic Name**	**Trade Name(s)[a]**	**Drug Interaction***		**Comment**
Biguanides	Metformin	Diabex Fortamet Glucophage Glumetza Riomet	Iodinated radiographic contrast	**S**	Recommendation is for temporary discontinuation of metformin
Insulin Secretagogues (Increase Insulin Release)					
Sulfonylureas (1st generation)	Tolazamide	Tolazamide	Hypoglycemic effects potentiated by NSAIDs and miconazole	?	
	Tolbutamide	Orinase			**
Sulfonylureas (2nd generation)	Gliclazide[b]	Diamicron[b]			
	Glimepiride	Amaryl	Hypoglycemic effects potentiated by NSAIDs, some azoles (miconazole, fluconazole)	?	**
	Glipizide	Glucotrol			
	Glyburide	DiaBeta Glynase			
Nonsulfonylurea Insulin Secretagogues					
Meglitinides	Nateglinide	Starlix	NSAIDs and CYP2C9 inhibitors: fluconazole, miconazole, may potentiate hypoglycemia	?	
	Repaglinide	Prandin	CYP3A4 and/or CYP2C8 inducers: carbamazepine, CYP3A4 inhibitors: erythromycin and OATP1B1 inhibitors: itraconazole, ketoconazole, clarithromycin	?	
Insulin					
Short-acting Long-acting Combination (short- and long-acting)	Various (see Table 22-14)		Epinephrine Corticosteroids	? S	
Incretin Mimetics					
Amylin analogues	Pramlintide	Symlin	Do not administer with agents that alter gastrointestinal motility (e.g., anticholinergic agents such as atropine) and pilocarpine (cholinergic agonists)	**S**	

[a] Table entry refers to the single agent. Oral antidiabetic agents are often supplied combined with other agents.
[b] Not marketed in the United States
* Corticosteroids all cause loss of glycemic control, but generally not mediated by adverse interaction with drugs used for the management of diabetes mellitus, except for insulin.
** Only isolated case reports of severe hypoglycemia with coadministration of miconazole.
CYP, cytochrome (superfamily of proteins found in hepatocytes and responsible for metabolism of organic substances); NSAID, nonsteroidal anti-inflammatory drugs; OATP, organic anion-transporting polypeptide, membrane transport proteins that mediate the transport of mainly organic anions across cell membranes; S, serious; ?, theoretical risk with no or limited case reports documenting adverse interaction.

Epinephrine (in Local Anesthetics)

Epinephrine is not contraindicated in diabetic patients per se, because it helps promote better dental anesthesia and significantly lowers the amounts of endogenous epinephrine released in response to pain and stress. However, in a patient with concomitant cardiovascular or renal disease, the level of epinephrine may need to be reduced to two or fewer carpules of local anesthetic containing 1:100,000 epinephrine. Two small-scale studies compared DM patients to controls and found no significant alteration in blood glucose levels after dental treatment, such as extractions, which required administration of local anesthetic with epinephrine.[184,185]

Corticosteroids

Topical and systemic corticosteroids have established value in a range of oral dermatoses; however; because of their physiologic actions rather than their drug interactions, dysregulation of glycemic control may ensue. Corticosteroids profoundly affect carbohydrate and lipid metabolism, designed to protect the glucose-dependent tissues (and their cells) such as the heart (cardiac myocytes) and brain (neurons) from starvation. Corticosteroids increase blood glucose levels by stimulating the liver to form glucose from amino acids and glycerol, and to store glucose as glycogen. In the periphery, corticosteroids increase protein breakdown and activate lipolysis. All these contribute to increased blood glucose levels that worsen glycemic control in patients with overt diabetes and precipitate the onset of hyperglycemia in susceptible patients, potentially leading to frank DM. Corticosteroids should be used with caution in collaboration with the patient's physician. If systemic corticosteroids are required, an adjustment of DM drugs may be necessary. Regular monitoring of glucose levels will be paramount to ensure good glycemic control.

Major Surgery, General Anesthesia, and Hospital Admission

Type I Diabetes Mellitus

Recommendations for those with T1DM undergoing general anesthesia and surgery:

- Long-acting and/or intermediate insulin should be stopped the day before surgery, with soluble insulin substituted.
- Diabetic patients should be first on the morning appointment list.
- Infuse glucose, insulin, and potassium during surgery. The insulin can be mixed into the glucose solution or administered separately by syringe pump. (The standard combination is 16 U of soluble insulin with 10 mmol potassium chloride in 500 mL 10% glucose, infused at 100 mL/h.) Any other intravenous fluids needed must be given through a separate intravenous line so as not to interrupt the glucose/insulin/potassium infusion.
- Postoperatively the infusion is maintained until the patient is able to eat.
- Glucose levels are checked every 2–4 hours and potassium levels are monitored and, if necessary, adjusted by provision of replacement insulin, dextrose, and/or potassium.

Type 2 Diabetes Mellitus

Patients with mild hyperglycemia (fasting blood glucose below 8 mmol/L [144 mg/dL]) can be treated as nondiabetics. For patients reliant on oral antidiabetic agents for management of their DM, they should stop medication two days before surgery. Moreover, these oral agents are of concern if the patient is fasting (in particular the risk of hypoglycemia with sulfonylurea agents). Those type 2 diabetics with poorly controlled diabetes can be managed with an insulin infusion or subcutaneous long-acting insulin plus preprandial, short-acting insulin.

Managing the Diabetic Emergency in the Dental Office

Hypoglycemia is a potentially life-threatening situation that must be recognized and treated expeditiously. Signs and symptoms include confusion, sweating, tremors, agitation, anxiety, dizziness, tingling or numbness, and tachycardia. Severe hypoglycemia may result in seizures or loss of consciousness. Prevention starts with the practitioner being familiar with the general medical risks for hypoglycemic events (Table 22-29) and assessing the patient's risk for developing hypoglycemia (Table 22-30). Every dental office that treats DM patients (see Table 22-31) should have readily available sources of oral carbohydrates (e.g., fruit juice, nondiet soda, hard candy). As soon as a patient

Table 22-29 General management considerations for the patient with diabetes.

Assess level and stability of glycemic control
Refer patients with signs and symptoms suggestive of undiagnosed or uncontrolled diabetes to physician for diagnosis and treatment
Obtain medical consultation if systemic complications are present
Use a glucometer to help avoid emergencies related to diabetes
Treat acute oral infections aggressively
Place patients on frequent recall visits to monitor and treat oral complications and maintain optimal oral hygiene and diet

Source: Adapted from Vernillo AT. Dental considerations for the treatment of patients with diabetes mellitus. *J Am Dent Assoc.* 2003;134:24S–33S.

Table 22-30 Determining risk of hypoglycemia: questions for the dental patient.

1. Have you ever had severe hypoglycemia?
2. How often do you have hypoglycemic reactions?
3. What diabetic medication(s) do you take?
   Did you take them today?
   When did you take them?
   Is that the same time as usual?
   How much of each medication did you take?
   Is this the same amount you normally take?
4. What did you eat today before you came to the dental office?
   Is that when you normally eat?
   Did you eat the same amount you normally eat for that meal?
   Did you skip a meal?

Table 22-31 Treatment of hypoglycemia in the dental office.

Patient Condition	Treatment
Patient is awake and able to take food by mouth	• Give 15 g oral carbohydrate • 4–6 oz (125–175 mL) fruit juice or soda (nondiet) • 3–4 tsp (equal to 15–20 mL) Table sugar (hard candy, cake frosting)
Patient is unable to take food by mouth and intravenous line is in place	• Give 25–30 mL D50 (50% dextrose solution) or • 1 mg glucagon
Patient is unable to take food by mouth and intravenous line is not in place	• Give 1 mg glucagon subcutaneously or intramuscularly at almost any body site

experiences signs or symptoms of possible hypoglycemia, the dentist should check the blood glucose with a glucometer, which has a typical response time of less than 15 seconds. Rapidly absorbed oral carbohydrates are preferable, particularly if the dentist is not trained or equipped to administer intravenous, intramuscular, or subcutaneous glucagon or dextrose. Following treatment, the signs and symptoms of hypoglycemia should resolve in 10–15 minutes, and the patient should be carefully observed for 30–60 minutes after recovery. A second evaluation with a glucometer should be done to ensure that a normal blood glucose level has been achieved.

A medical emergency from hyperglycemia is less likely to occur in the dental office since it develops more slowly than hypoglycemia. Emergency care entails protecting the airway and administering oxygen. Circulation and vital signs should be monitored, and the patient should be transported to a hospital as soon as possible. However, under some instances, severe hyperglycemia may present with symptoms mimicking hypoglycemia. If it is an actual hyperglycemic event, the small amount of extra glucose delivered will not have any deleterious effect. Nevertheless, emergency measures that will elevate serum glucose should not be delayed or withheld from a DM patient even if hyperglycemia is wrongly suspected in a patient who is actually hypoglycemic. This delay may result in severe adverse outcomes.[186]

Table 22-32 World Health Organization (Who) classification of obesity.

WHO Classification	Body Mass Index (BMI; kg/m^2)	Risk of Comorbidities
Overweight	25–30	Mildly increased
Obese	>30	
Class I	30–35	Likely
Class II	35–40	Very likely
Class III	>40	Very likely and severe
$\text{BMI} = \frac{\text{Weight (in kilograms)}}{\text{Height (in meters)}^2}$		

OBESITY

Obesity is defined as an abnormal or excessive fat accumulation such that it impairs health. It is commonly measured by calculating an individual's BMI (Table 22-32).[187]

The prevalence of obesity and the associated comorbidities, particular T2DM, has dramatically increased and has been termed an "obesity epidemic."[188] In the United States, 17% of children and more than 33% of adults are obese, so the problem is common and on the rise (Table 22-33).[188] Although there is ongoing contention as to the etiology of obesity, which includes genetic factors and disturbances of the gut microbiotome, the main factor is an energy imbalance; that is, excessive food intake and insufficient energy expenditure. The comorbidities and complications, including premature death from obesity, are established, with higher rates of DM, coronary heart disease, and cerebrovascular disease.

Metabolic Syndrome

Metabolic syndrome (also known also as "syndrome X" and "insulin resistance"; Table 22-34), in a patient with established obesity, is defined by five factors for increased risk of atherosclerotic cardiovascular disease (which includes consequent coronary heart disease and stroke):

- Atherogenic dyslipidemia comprising elevations in plasma triglycerides and apolipoprotein B (apo B), and reductions in high-density lipoproteins (HDL).
- Hypertension.
- Prediabetes or frank diabetes.
- A prothrombotic state with abnormalities in coagulation factors and blood platelets.
- A proinflammatory state resulting from inflammatory mediators acting on a variety of tissues.

Table 22-33 US data on prevalence of being overweight and of obesity among adults and children.

Prevalence	Class	Body Mass Index (BMI) (kg/m^2)
33%	of adults are overweight	25 to ≤30
36%	of adults are obese	≥30
6%	of adults are morbidly obese	≥40
17%	of children are obese*	25 to ≤30
*BMI for age and sex 95th percentile		
Target BMI is 18.5 to ≤25.0 BMI ≥30.0 + a comorbidity = morbid obesity		
Comorbidities • Hypertension; coronary heart disease; stroke • Sleep apnea • Type 2 diabetes mellitus; dyslipidemia • Osteoarthritis • Reduced fertility • Select cancers		

The contribution of each of these components to cardiovascular risk undoubtedly varies among individuals, but in combination they double the risk for atherosclerotic-related cardiovascular disease and are associated with a fivefold increased risk for diabetes.[189]

Stomatognathic Manifestations and Complications of Obesity[190,191]

Obesity: Clinical Implications

There is a contention that obesity is associated with an increased risk of periodontal disease. The chronic proinflammatory state associated with obesity may increase a patient's susceptibility to periodontal disease, although the published evidence is somewhat contradictory. There is a probable association between obesity and periodontal disease, but not a clear causal relationship. As obesity is associated with a higher intake of sugar, it has been suggested that this may be associated with higher rates of dental caries. Again, the reported studies have yielded contradictory results. There are case reports of higher rates of caries in patients post bariatric surgery, given their need for small, more frequent meals.[192] Dental erosion is related to increased rates of gastroesophageal reflux disease seen in patients with obesity, which is also a known complication of bariatric surgery, but the evidence consists of case reports only.

Concurrent Medical Comorbidities

Obese patients in general and those with metabolic syndrome are known to have a far greater likelihood of hypertension, cardiovascular disease, and T2DM. If these conditions are not identified as being managed by a physician in the course of taking the patient's medical history, it

Table 22-34 Classification systems for metabolic syndrome.

Risk Factor	NCEP 3 of any 6 features		IDF large waist + 2 other features	
Waist Circumference				
Men	>102	cm	>94	cm
Women	>88	cm	>80	cm
Triglycerides	>1.7	mmol/L	≥1.7	mmol/L
HDL Cholesterol				
Men	<1.03	mmol/L	1.03	mmol/L
Women		mmol/L	1.29	mmol/L
Blood Pressure	>130/85	mm Hg	>130/85	mm Hg
Fasting Glucose	≥6.1	mmol/L	≥5.6	mmol/L

HDL, high-density lipoproteins; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program.
Source: Data from Udovcic M, Pena RH, Patham B, Tabatabai L, Kansara A. Hypothyroidism and the heart. *Methodist Debakey Cardiovasc J.* 2017;13(2):55–59.

Table 22-35 STOP-bang questionnaire: a practical approach to screen for Obstructive Sleep Apnea (OSA).

S	1	Snoring	Do you snore loudly?*	Yes/No
T	2	Tired	Do you often feel tired, fatigued, or sleepy during daytime?	Yes/No
O	3	Observed	Has anyone observed you stop breathing during your sleep?	Yes/No
P	4	Pressure—BP	Do you have or are you being treated for high blood pressure?	Yes/No
B	5	BMI	BMI >35 kg/m^2	Yes/No
A	6	Age	Age ≥50 years of age?	Yes/No
N	7	Neck circumference	Neck circumference ≥40 cm?	Yes/No
G	8	Gender	Male gender?	Yes/No
High risk of OSA: answering yes to 3 or more items				
Low risk of OSA: answering yes to fewer than 3 items				

* E.g., louder than talking or loud enough to be heard through closed doors?
BMI, body mass index; BP, blood pressure.

may be prudent to undertake screening for these conditions before considering highly invasive surgical procedures. Obesity is highly predictive for OSA. The exact interaction between obesity and OSA is unclear. The buildup of adipose tissue in the upper airway predisposes it to collapse and narrowing; however, OSA may itself predispose individuals to worsening obesity due to sleep deprivation, daytime somnolence, and disrupted metabolism. Regardless, OSA is a contraindication to dental sedation; for all patients for whom sedation is being considered, clinicians should employ the STOP-Bang questionnaire (Table 22-35),[193] but particularly so for obese patients.

Weight-Loss Drugs and Potential Drug Interactions

Increasing numbers of patients are using medication to facilitate their weight loss (see Table 22-36). Of these the most notable in the recent past was the advent of the fenfluramine–phentermine (fen–phen) combination, which was associated with valvular heart disease and required affected patients to take antibiotic prophylaxis to limit the risk of infective endocarditis following invasive dental procedures.[194,195]

Orlistat (trade name Xenical®, Roche, Nutley, NJ, USA) is a reversible inhibitor of gastric and pancreatic lipases, thus it inhibits the absorption of dietary fats by 30%.[196] Orlistat can interfere in the absorption and uptake of fat-soluble vitamins, including vitamin K, and consequently can potentiate the anticoagulant effect of warfarin. An update of the patient's international normalized ratio (INR) prior to invasive dental procedures should be considered. Supratherapeutic INR (>4.0) and subtherapeutic INR (<2.0) needs attention by the treating physician.[197]

Lorcaserin (Belviq®, Arena Pharmaceuticals, San Diego, CA, USA) appears to have no major adverse effects and no significant drug interactions. The phentermine–topiramate combination (Qsymia®, Vivus, Campbell, CA, USA) consists of an amphetamine derivative and an antiseizure agent, respectively. Concurrent use of benzodiazepines (and other CNS depressants) with the phentermine–topiramate combination may potentiate CNS depression and should be avoided without medical consultation. With naltrexone–bupropion (Contrave®, Currax Pharmaceuticals, Morristown, NJ, USA), due to the antagonistic effect of naltrexone on endogenous opioid receptors, the analgesic effect of opioid agents is reduced. If opioid analgesia is required in such patients, then temporary cessation of Contrave must be considered.

Issues with Service Delivery

All oral healthcare clinicians have a role in screening for systemic disease and lifestyle factors that are proven to be harmful to a patient's wellbeing, for example smoking and obesity. However, there is a reluctance by dentists to undertake screening and to offer advice regarding the need for and value of weight loss,[198] and so further training and education on how to offer appropriate and acceptable health advice about obesity, and the need for weight loss, may address this concern.

Obesity presents a number of practical challenges to service delivery. The first is the need for longer appointment times, and the consequent increased cost of service delivery. Increased appointment times are attributed to reduced patient mobility as well as increased difficulty for the dentist

Table 22-36 Weight loss medications: major side effects and drug interactions.

Generic Name	Trade Name	Site and Mechanism of Action	Major Side Effects	Drug Interactions
Orlistat	Xenical	• GIT • Lipase inhibitor • Inhibits uptake of dietary fats by 30%	• Steatorrhea • Flatulence	Warfarin
lorcaserin	Belviq	• CNS • Serotonin agonist (5-HT2C receptor agonist) • Increased satiety so reduced food intake	• Headache • Dizziness • Nausea	Benzodiazepams
Phentermine/ topiramate	Qsymia	• CNS • Stimulator of noradrenaline, dopamine, and serotonin release, augmenting the activity of γ-aminobutyrate • Appetite suppression	• Dry mouth • Paresthesia • Constipation • Insomnia • Dizziness	Carbamazepine (decreased topiramate levels)
Naltrexone/ bupropion	Contrave	• CNS • Naltrexone is an opioid antagonist • Bupropion, a relatively weak inhibitor of the neuronal reuptake of dopamine and norepinephrine. • Affects areas of the brain involved in the regulation of food intake: the hypothalamus (appetite regulatory center) and the mesolimbic dopamine circuit (reward system)	• Nausea • Headache • Constipation • Dizziness • Vomiting • Dry mouth • Dysgeusia	Opioid analgesics (less effective)
Liraglutide	Saxenda	• GIT and CNS • Daily subcutaneous injection • Acylated human GLP-1 analogue with 97% homology to human GLP-1 • Like human GLP-1 it increases satiety, decreases key hunger signals, with transient inhibition of gastric emptying	• Nausea • Hypoglycemia • Diarrhea • Constipation • Vomiting	

CNS, central nervous system; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide-1.
Source: Data from RxList. https://www.rxlist.com/script/main/hp.asp.

Figure 22-17 Image of Barico dental chair at Westmead Centre for Oral Health, suitable for all patient groups up to 454 kg. Note the width of the chair (black arrow), especially at the shoulders (white arrows), which makes access to the patient's oral cavity by the treating dentist more difficult. Malik Z. Special needs dental management of the class 3 obese patient. *Case Rep Dent.* 2019;2019:7976531. Reproduced with permission.

in accessing the oral cavity in the larger, obese patient. The other aspect is the need to have equipment that is safe for obese patients. Body weights in excess of 140 kg may exceed the weight limitations of motorized dental chairs.[199–201] Consequently, there are increased costs required to purchase special-purpose and safe bariatric dental chairs (Figure 22-17) and wheelchairs as well as supplementary equipment, including hoists.

DISORDERS OF BONE AND MINERAL METABOLISM

Bone is a specialized connective tissue serving three major functions:

- *Mechanical*: attachment for muscles for movement and structure.
- *Metabolic*: providing the body's primary store of calcium, including a highly active role in calcium homeostasis and also in phosphate levels, as well as serving as a reservoir for sodium, magnesium, and other critical ions.

- *Protective*: of the vital organs as well as enclosing the marrow, containing the essential hematopoietic stem cells that produce all the cells found circulating in the blood (red blood cells, leukocytes, and platelets).

Bone comprises cells and a matrix of organic protein and hydroxyapatite crystal. Type I collagen is the main protein, forming parallel lamellae of differing density, which impair the propagation of cracks with trauma. Noncollagen proteins that are also found in bone include osteopontin, osteocalcin, and fibronectin. In cortical bone, concentric lamellae form around a central blood supply, and this collectively is termed the Haversian system, with transverse branches (termed Volkmann's canals). The long bones (e.g., femur, tibia, humerus) and flat bones (e.g., skull, scapula) are variably composed of:

- *Compact or cortical bone*, which forms the shaft of long bones and the outer shell of flat bones. Formed of concentric rings of bone, it is strong and is particularly resistant to the mechanical strain associated with flexure.
- *Trabecular or cancellous bone*, found at the ends of long bones and inside flat bones, is constituted by a network of interconnecting rods and plates of bone that provides great strength against compressive forces. It is the main site of bone turnover needed for mineral homeostasis.
- *Woven bone* lacks an organized structure. It appears in the first few years of life and at the sites of fracture repair, as well as in bone disorders associated with high turnover, such as Paget's disease. Woven bone is eventually remodeled to be organized and structurally sound bone.
- *Lamellar bone*, in which the collagen fibers are arranged in parallel bundles, forms much of the bone found in adults.

Bone Cells

Osteoblasts are of mesenchymal origin and are initially found on the surface of newly forming bone. The osteoblast secretes an organic matrix, which then is mineralized, encasing the cell, which is then termed an *osteocyte*; however, the osteocytes remain connected with each other, as well as with their blood supply, through a fine network of canaliculi, distributed throughout the bone. The vast majority of the cells found in bone are osteocytes, which serve to regulate bone formation and resorption and also serve as mechanosensors, signaling the osteoblasts and their progenitors through the canalicular network. Mineralization of the matrix, both in trabecular bone and in the osteones (of the Haversian system) of compact cortical bone, begins soon after the matrix is secreted and is termed primary mineralization, but it is not completed for several weeks or even longer by the process of secondary mineralization. Mineralization is a carefully regulated process that is dependent on the activity of osteoblast-derived alkaline phosphatase, and importantly the very high, near-saturation concentrations of calcium and phosphate present in the serum. Hormones such as parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D (1,25(OH)2D) activate receptors expressed by osteoblasts so as to regulate mineral homeostasis.

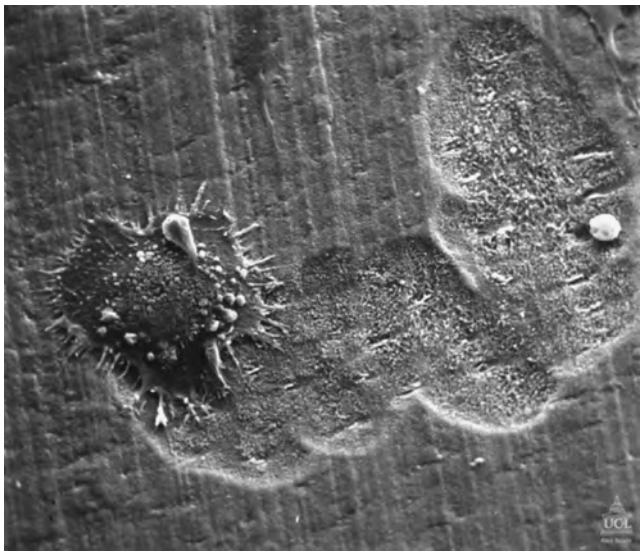


Figure 22-18 Osteoclast. *Source:* Bone Research Society, https://boneresearchsociety.org/resources/gallery/19/. Reproduced with permission.

Osteoclasts (Figure 22-18) serve to resorb bone, and are multinucleated cells that are formed by the fusion of cells derived from the same common precursor of macrophages. Multiple factors regulate osteoclast development and function. Macrophage colony-stimulating factor (M-CSF) plays a critical role during several steps in the pathway and ultimately leads to the fusion of osteoclast progenitor cells to form multinucleated, active osteoclasts. RANK (receptor activator of nuclear factor kappa-B) ligand is a member of the tumor necrosis factor (TNF) family, expressed on the surface of osteoblast progenitors and stromal fibroblasts. In a process involving cell–cell interactions, RANK ligand binds to the RANK receptor on the osteoclast progenitors, stimulating osteoclast differentiation and activation. Alternatively, a soluble decoy receptor, referred to as osteoprotegerin (OPG), can bind the RANK ligand and so inhibits osteoclast differentiation. OPG, also known as osteoclastogenesis inhibitory factor (OCIF), is a cytokine receptor and also a member of the TNF receptor superfamily. Several growth factors and cytokines can also modulate osteoclast differentiation and function (e.g., interleukins 1, 6, and 11, TNF, and interferon γ); they may also have role in the bone loss seen

in periodontal disease. Most hormones that influence osteoclast act indirectly, by influencing M-CSF and RANK ligand signaling of the osteoblasts. Both PTH and 1, 25(OH)2D increase osteoclast number and activity, whereas estrogen decreases osteoclast number and activity. Calcitonin, in contrast, binds directly to its receptor on the basal surface of osteoclasts and so inhibits osteoclast function. Osteoclast-mediated resorption of bone takes place in scalloped spaces (Howship's lacunae) where the osteoclasts are attached through a specific αvβ3 integrin to components of the bone matrix, such as osteopontin.[202]

Bone Growth and Remodeling

In the embryo and the growing child, bone develops by remodeling and replacing previously calcified cartilage, termed endochondral bone formation, or bone is formed without a cartilage matrix anlage, by means of intramembranous bone formation. Longitudinal growth occurs at the epiphyseal growth plate, a cartilaginous structure between the epiphysis and the metaphysis. Cartilage production is tightly regulated, with growth arrest and the subsequent mineralization occurring between the ages of 18 to 21 years, when the epiphysis and metaphysis plates fuse.

In adults, bone is constantly being remodeled, to repair microdamage and for the release of the calcium and phosphate needed for homeostasis. Signals regulating the initiation of remodeling include changes in osteocytes (apoptosis or altered signaling of sclerostin, prostaglandins, and other molecules), resulting in altered balance of RANK ligand and OPG expression by adjacent osteoblasts. Remodeling is carried out by the basic multicellular unit (BMU). Normal bone remodeling is a coupled process, with bone formation typically following resorption. New bone formation without resorption may, however, occur in the adult skeleton in response to anabolic therapy such as PTH peptides or estrogen (in both sexes), which is particularly involved by promoting the survival of osteocytes and inhibiting the formation of new osteoclasts.

Calcium Homeostasis

Over 99% of the 1–2 kg of calcium normally present in the adult human body resides in the skeleton, where it provides mechanical stability (in the form of hydroxyapatite) and also serves as a reservoir for maintenance of extracellular fluid (ECF) calcium concentration (Figures 22-19 and 22-20; Table 22-37). Only some 0.5–1% of the skeletal calcium is

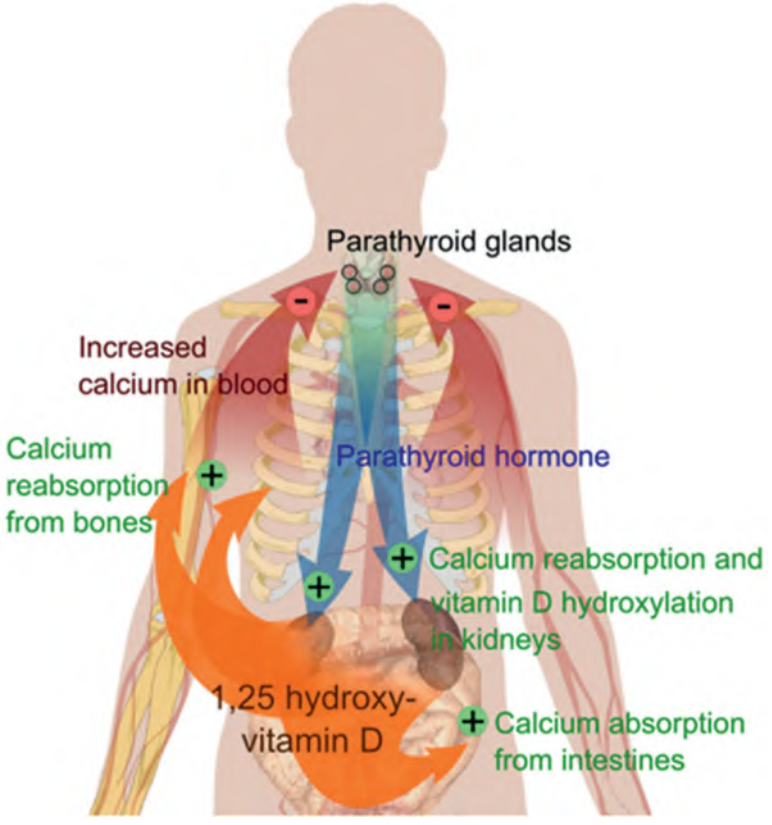


Figure 22-19 Calcium regulation and homeostasis. *Source:* https://commons.wikimedia.org/wiki/File:Calcium_regulation.png. Public domain.

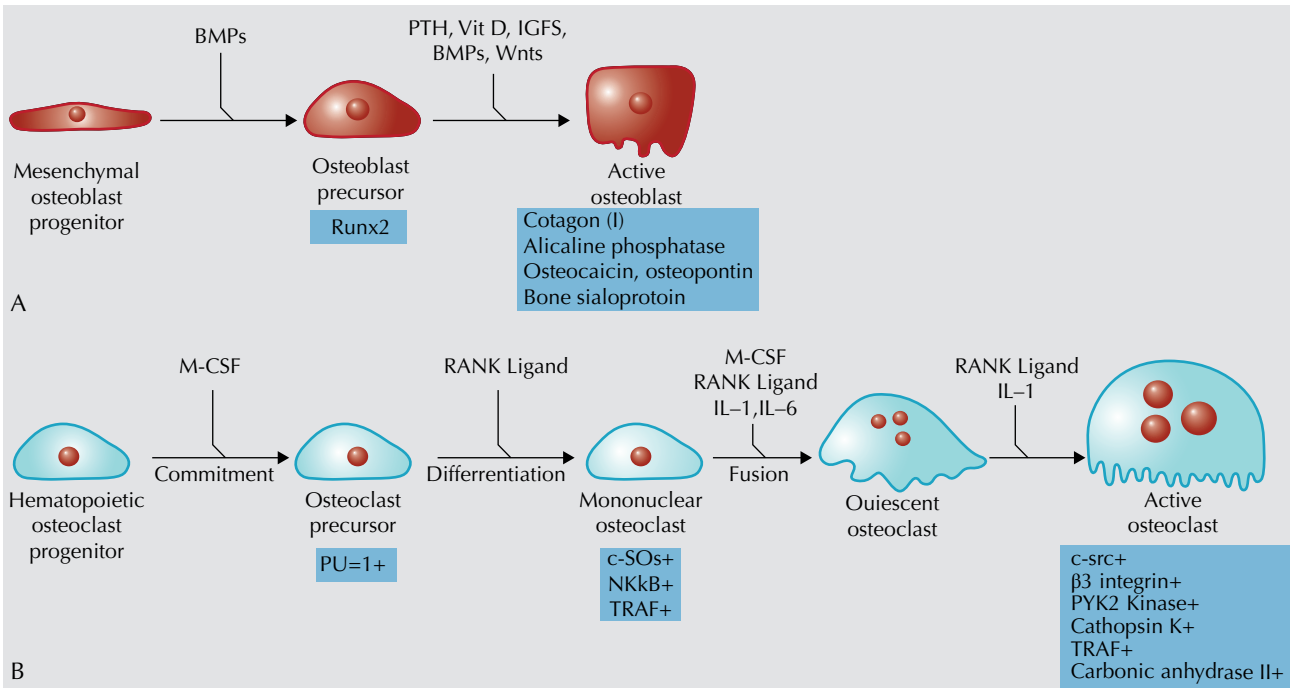


Figure 22-20 Pathways regulating development of (A) osteoblasts and (B) osteoclasts. Hormones, cytokines, and growth factors that control cell proliferation and differentiation are shown above the arrows. Transcription factors and other markers specific for various stages of development are depicted below the arrows. BMPs, bone morphogenic proteins; IGFs, insulin-like growth factors; IL-1, interleukin 1; IL-6, interleukin 6; M-CSF, macrophage colony-stimulating factor; NFκB, nuclear factor κB; PTH, parathyroid hormone; PU-1, a monocyte- and B lymphocyte–specific ETS family transcription factor; RANK ligand, receptor activator of NFκB ligand;Runx2, Runt-related transcription factor 2; TRAF, tumor necrosis factor receptor–associated factors; Vit D, vitamin D; wnts, wingless-type mouse mammary tumor virus integration site. *Source:* Adapted with permission from Suda T, Takahashi N, Udagawa N, Jimi E, Gillespie MT, Martin TJ. Modulation of osteoclast differentiation and function by the new members of the tumor necrosis factor receptor and ligand families. *Endocr Rev*. 1999;20:345.

freely exchangeable; that is, in chemical equilibrium with the calcium found in the ECF. The concentration of ionized calcium in the ECF is maintained within a strict narrow range, because of the critical role it plays in numerous critical cellular functions, particularly neuromuscular activity, secretion, and signal transduction. In the blood, total calcium concentration is normally 2.2–2.6 mM (8.5–10.5 mg/dL), of which some 40% is ionized and physiologically active. The remaining 60% is bound to negatively charged proteins (predominantly albumin and immunoglobulins) or loosely complexed with phosphate, citrate, sulfate, or other anions. Alterations in serum protein concentrations (e.g., hypoalbuminemia) directly affect the total blood calcium concentration, but the ionized calcium concentration tends to remain stable.

Control of the ionized calcium concentration in the ECF is regulated by the effects of PTH and 1,25(OH)2D3 acting on the gastrointestinal tract, kidney, and bone. Ionized calcium in the circulation both directly suppresses PTH secretion by stimulating the calcium-sensing receptors present in the parathyroid glands, and indirectly suppresses PTH secretion via effects on vitamin D_2 (1,25(OH)2D) production. Active calcium uptake from the gut by means of highly regulated, energy-dependent transportation across the gut epithelium accounts for up to 95% of the daily calcium intake needed. This occurs mainly in the proximal small bowel (duodenum and proximal jejunum). Calcium absorption may also be impaired in disease states such as pancreatic or biliary insufficiency, in which ingested calcium remains bound to unabsorbed fatty acids or food debris, conditions associated with gastrointestinal malabsorption, such as in celiac disease and in patients who have had an extensive bowel resection. At high levels of calcium intake, synthesis of 1,25(OH)2D is reduced and this then decreases the rate of active intestinal calcium absorption.[203]

Daily net calcium absorption is generally constant at 5–7.5 mmol/day (equal to 200–400 mg/day), regardless of variations in the daily dietary calcium intake. This daily load of absorbed calcium is excreted by the kidneys in a tightly regulated manner, with approximately 8–10 g/day of calcium being filtered by the glomeruli, of which only 2–3% appears in the urine. Most filtered calcium (65%) is reabsorbed in the proximal tubules via a nonregulated, passive, paracellular

Table 22-37 Investigation of bone and calcium disorders.

Test	Normal Values	Interpretation/Considerations
Total serum calcium (corrected) (Ca^{2+})	2.2–2.6 mmol/L	Total serum calcium (corrected) • 40% is ionized and physiologically active Note: ionized calcium is difficult to measure; in practice total calcium is measured and the value corrected to allow for protein binding (using established formula)
24-hour urinary calcium	F: 2.5–6.25 mmol/24 h M: 2.5–7.5 mmol/24 h	Indications: hypercalcemia ↑ Renal tubular reabsorption of Ca^{2+} is decreased ↑ Hypercalcemia: exception with familial hypocalciuric hypercalcemia—genetic defect leads to inappropriately reduced calcium excretion
Plasma phosphate (PO_4^{3-}) levels	0.8–1.4 mmol/L	↑ [PO_4^{3-}] • Renal failure and hypoparathyroidism ↓ [PO_4^{3-}] • Primary hyperparathyroidism • Hypophosphatemic rickets • Osteomalacia • Disorders of reduced renal tubular phosphate reabsorption
Serum alkaline phosphatase (ALP)	• Bone-specific isoenzyme of ALP can be measured (marker of bone formation), but there is overlap with the liver isoenzyme	↑ ALP • Bone growth • Fracture repair • High bone turnover states
Vitamin D	• Best assessed using serum 25-(OH)D3 Note: 1,25(OH)2D3 has a short half-life and does not reflect true vitamin D status	
Parathyroid hormone	• Measures intact hormone	
NTX or CTX—serum or urine levels	• N-terminal (NTX) and C-terminal (CTX) cross-linked telopeptides ➔ Reflect bone resorption activity	↓↑ Changes rapidly in response to antiresorptive drugs or in disease states
Bone mineral densitometry (BMD)	• Dual-energy X-ray absorptiometry (DXA): uses low-dose radiation to measure areal bone density—mineral per surface area (rather than true volumetric density) • Sites: lumbar spine, proximal femur	Note: Gold standard for the diagnosis of osteoporosis • Young adult mean value (T score) is the standard • Spinal values may be artefactually elevated with osteophytes, spinal deformity, and vertebral fractures (so interpret with caution in the elderly)

route that is coupled to concomitant sodium chloride (NaCl) transporter. The remaining 35% requires active reabsorption in the thick loop of Henle and distal tubule.

Vitamin D Metabolism

The primary source of vitamin D in humans is photoactivation in the skin of 7-dehydrocholesterol to cholecalciferol, which is then converted, first in the liver to 25-hydroxyvitamin D (25(OH)D3) and then subsequently in the kidney (by the enzyme 1α hydroxylase) to the active form, 1,25(OH)2D3. Regulation of the latter step is by PTH, phosphate, and feedback inhibition by 1,25(OH)2D3 itself.

The mounting concern about sun (ultraviolet, UV) exposure and the development of skin cancer has led to increased reliance on dietary sources of vitamin D. The third National Health and Nutrition Examination Survey (NHANES) revealed that vitamin D deficiency is widely prevalent in the United States. Vitamin D deficiency can be a result of deficient production of vitamin D in the skin (insufficient UV exposure), lack of dietary intake, accelerated losses of vitamin D, impaired vitamin D activation, or resistance to the biologic effects of 1,25(OH)2D. The elderly and nursing home residents are particularly at risk for vitamin D deficiency, since both the efficiency of vitamin D synthesis in the skin and the absorption of vitamin D from the intestine

decline with age. Long-standing vitamin D deficiency results in hypocalcemia accompanied by secondary hyperparathyroidism, impaired mineralization of the skeleton—termed osteopenia; that is, decreased bone mineral density (BMD)—with a resultant increased risk for progression to osteoporosis.

Parathyroid Hormone

PTH, an 84 amino acid hormone, is secreted from the chief cells of the parathyroid glands, which bear calcium-sensing and vitamin D receptors. PTH increases renal phosphate excretion and increases plasma calcium by four principal effects: increasing osteoclastic activity—a rapid response; increasing intestinal absorption of calcium—a slow response; increasing 1α-hydroxylation of vitamin D (the rate-limiting step); and increasing renal tubular reabsorption of calcium. Hypomagnesemia can suppress the normal PTH response to hypocalcemia.

Calcitonin

Calcitonin is produced by C cells in the thyroid gland. Although calcitonin inhibits osteoclastic bone resorption and increases the renal excretion of calcium and phosphate, neither excess calcitonin (e.g., from an MTC) nor its deficiency (following thyroidectomy) appears to have any significant effect on the skeleton or bone density. Calcitonin is a useful agent to suppress bone resorption in Paget's disease and osteoporosis and in the treatment of hypercalcemia of malignancy.

Sclerostin

Sclerostin is a glycoprotein secreted by osteocytes. Sclerostin has been shown to be a potent inhibitor of bone formation by means of a catabolic effect on bone, increasing osteoclast numbers and activity by augmented osteocyte expression of the RANK ligand. Significant research interest in this signaling pathway led to the evolution of antisclerostin agent; that is, inhibitory therapeutic antibody, romosozumab. Of note is that a decline in RANK ligand signaling could explain, in part, the sustained decreases in bone resorption markers observed in recent trials with antisclerostin therapies.[204]

The role of sclerostin in the modulation of the Wnt/β-catenin dependent pathway came from the study of sclerosteosis and van Buchem disease, two rare genetic disorders associated with abnormally high levels of bone density and consequently a significantly lower risk of bone fractures.[205] Both diseases were traced to mutations impacting a single gene, *SOST*, which is mainly expressed from osteocytes. The Wnt signaling pathway is a crucial, ancient, and evolutionarily conserved pathway that regulates key aspects of cell fate determination, cell migration, cell polarity, neural patterning and organogenesis during embryonic development. The Wnt signaling pathway has a significant interaction with a transmembrane lipoprotein receptor-related protein, LRP5. The *LRP5* gene was initially identified as a determinant of bone mass in the 1990s from studies into osteoporosis pseudoglioma syndrome, an autosomal recessive hereditary disorder (characterized by low bone mass and abnormal eye vasculature), due to an inactivation mutation of *LRP5*.[206] In contrast, gain-of-function *LRP5* mutations are linked to the autosomal dominant condition of high bone mass, excessive bone formation, bone thickening, and reduced risk of fracture.[207] These findings were confirmed in mouse models of defective Wnt signaling. *LRP5*-deficient mice manifested an osteoporotic phenotype with impaired bone formation, while bone resorption remained unaffected. In contrast, mice carrying an gain-of-function mutation within the *LRP5* gene developed thick abnormal bone (osteosclerosis).[208,209] Sclerostin production by osteocytes is inhibited by PTH, mechanical loading, and select cytokines, such as prostaglandin E2. Sclerostin production is increased by calcitonin. Thus, osteoblast activity is self-regulated by a negative feedback system involving sclerostin.[210,211]

Based on genetic and rat studies, a monoclonal antibody directed against sclerostin has been developed. Romosozumab (marketed as Evenity® in the United States; Amgen, Thousand Oaks, CA, USA) gained FDA approval in April 2019, albeit with black box warning of increased risk for myocardial infarction, stroke, and cardiovascular-related death and that the drug should not be taken by patients who had experienced a cardiovascular event within the previous year.[212] Romosozumab is given by monthly subcutaneous injection and has shown great promise, with one large trial indicating significant benefit in reducing vertebral fractures in osteoporotic women.[213] However, two cases of osteonecrosis of the jaws (ONJ) occurred in the romosozumab-treated cohort of 3321 women (0.06%) over the course of 12 months.[214]

PARATHYROID GLAND AND DISORDERS OF CALCIUM HOMEOSTASIS

PTH is secreted by four parathyroid glands found within the thyroid gland in the anterior neck. Secretion of the PTH is in response to the level of serum ionized calcium. Low serum ionized calcium stimulates PTH secretion, whereas high serum ionized calcium suppresses PTH secretion. Another major regulator of PTH is the active form of vitamin D_3 (1,25-dihydroxyvitamin D_3 or calcitriol). It suppresses PTH

synthesis by its ability to promote intestinal calcium absorption. PTH protects the body from chronic low serum calcium (hypocalcemia); therefore, an individual with chronic hypocalcemia and vitamin D deficiency may develop parathyroid gland hyperplasia.

Hyperparathyroidism

Hyperparathyroidism is chronic excessive secretion of the PTH by the parathyroid glands. It results in uncontrolled chronic high serum calcium (hypercalcemia). The condition occurs in 0.1% of adult patients, is more common in the third to fifth decades of life, and is three times more prevalent in women than in men. The vast majority (90%) of patients with hypercalcemia have either primary hyperparathyroidism or hypercalcemia of malignancy.

Primary hyperparathyroidism is the term that refers to excessive PTH secretion arising from one or more of the parathyroid glands. Commonly it is caused by a solitary adenoma (80% of cases), whereas 15% are due to parathyroid hyperplasia and 1% are due to carcinoma of the parathyroid glands. Postmenopausal women are more commonly affected by primary hyperparathyroidism.[215]

Secondary hyperparathyroidism occurs with compensatory parathyroid gland enlargement in response to persistent hypocalcemia induced by renal failure (see later), or metabolic disorders of deficiency of 1,25(OH)2D, or malabsorption of calcium found in rickets and some forms of osteomalacia. PTH secretion from enlarged parathyroid glands may become autonomous (secreting without control or response to feedback inhibition), leading to *tertiary hyperparathyroidism*.[216]

Many cases of hyperparathyroidism may be asymptomatic and only detected incidentally by serum analysis during routine serologic evaluation. Clinically, patients may have manifestations of skeletal and renal disorders and hypercalcemia. They complain of a classic quintet of complaints, namely "bones, stones, abdominal groans, psychic moans, and psychic overtones." Skeletal presentations include bone demineralization that manifests as a reduction in bone mass (osteopenia). Bone radiographs show well-circumscribed unilocular or multilocular radiolucent lesions, known as "brown tumors" of hyperparathyroidism, but brown tumors are now rare because of early detection of hyperparathyroidism. Due to routine screenings and early detection of hypercalcemia, skeletal presentation is now commonly just as osteopenia. Renal presentations include polyuria and polydipsia as a result of hypercalcemia-induced DI, and 10–15% of patients may develop kidney stones consisting of calcium phosphate or calcium oxalate. Nonspecific presentations of hypercalcemia include "abdominal groans" of constipation, indigestion, weight loss, nausea, vomiting, peptic ulceration, and pancreatitis, as well as "psychic moans" of lethargy, fatigue, depression, loss of memory, paranoia, neuroses, change in personality, confusion, stupor, and coma.

The most common laboratory finding is high alkaline phosphatase in patients with bone lesions. Serum calcium is elevated (>10.5 mg/dL), but phosphate may vary from low-normal (<3.5 mg/dL) to low (<2.5 mg/dL). Serum PTH is often elevated, and the level of 1,25(OH)2D may also be high due to the stimulatory effect of PTH on 1-α-hydroxylase. Imaging should be undertaken to assess for the presence of a parathyroid adenoma. For symptomatic primary hyperparathyroidism, definitive treatment is surgical parathyroidectomy, which has a 95% success rate. Medical management may involve use of vitamin D when associated with vitamin D deficiency, as well as bisphosphonates and calcimimetics and the calcium-sensing receptor agonist cinacalcet (Sensipar®, Amgen). As postmenopausal women are commonly affected by hyperparathyroidism, high-dose estrogen replacement therapy is often needed to treat bone lesions and reduce serum calcium, but it does not reduce the PTH level.

Hypoparathyroidism

Hypoparathyroidism is a deficiency in the production, secretion, or action of PTH and is the most common cause of hypocalcemia. It usually results when parathyroid glands are surgically removed to correct primary hyperparathyroidism or during thyroidectomy. Radiation to the neck, metastatic cancer, infection, and magnesium deficiency are other unusual causes of hypoparathyroidism. Damage to the parathyroid glands by heavy metals, for example copper in Wilson's disease or iron in hemochromatosis, and from transfusion hemosiderosis is also an unusual cause of hypoparathyroidism. The parathyroid glands may be underdeveloped or completely absent in DiGeorge syndrome (now more accurately known as 22q11.2 deletion syndrome), a developmental abnormality of the third and fourth pharyngeal pouches.[217] *Pseudohypoparathyroidism* is a term used to describe a group of disorders that cause hypocalcemia as a result of renal resistance to PTH despite high levels of PTH. Other causes of hypocalcemia in addition to hypoparathyroidism are vitamin D deficiency, hyperphosphatemia, malabsorption of calcium, and chronic renal failure.[218]

Hypocalcemia

Hypocalcemia is often asymptomatic; however, acute hypocalcemia produces symptoms that result from neuromuscular irritability or excitability. This leads to muscular and mental manifestations that include paresthesia of hands, feet, and

circumoral muscles; electroencephalographic abnormalities; anxiety; confusion; and depression. A positive Chvostek's sign may be elicited by tapping on the facial nerve in the preauricular region, which causes twitching of the facial muscles. Patients may develop tetany characterized by tonic–clonic seizures, carpopedal spasm, and severe laryngospasm. In DiGeorge syndrome, tetany is usually noticed in infancy, but may remain undetected until adulthood. Laboratory findings are low PTH and low serum calcium levels, but serum phosphate is elevated and alkaline phosphatase is normal. Most patients with hypocalcemia can be treated with oral calcium and vitamin D supplements, although acute cases may require intravenous calcium infusions.

Chronic Renal Failure

Impaired production of 1,25(OH)2D by the diseased kidneys is thought to be the principal factor that causes calcium deficiency, secondary hyperparathyroidism, and bone disease. Treatment entails dietary changes, with the restriction of phosphate in the diet, avoidance of aluminum-containing phosphate-binding antacids to prevent the problem of aluminum intoxication, adequate calcium intake orally, usually 1–2 g/day, and supraphysiologic amounts of vitamin D or calcitriol, despite the fact that the uremic state also causes impairment of intestinal absorption of vitamin D. The aim is to restore normal calcium balance to prevent osteomalacia and severe secondary hyperparathyroidism.

Stomatognathic Manifestations of Parathyroid Gland Disorders

Hyperparathyroidism

The primary clinical orofacial signs and symptoms of hyperparathyroidism are reflections of the systemic effects of hypercalcemia. Long-standing hypercalcemia causes generalized osteoporosis, which is visible on dental radiographs. Patients develop cortical resorption and rarefactions, loss of trabeculation presenting as "ground-glass" appearance, partial or total loss of lamina dura, lytic lesions, and metastatic calcifications.[219] The rarefactions occur secondary to generalized osteoporosis when fine trabeculae disappear later in the disease process, leaving a coarse pattern. Alveolar bone is particularly sensitive to increased levels of PTH from either primary or secondary hyperparathyroidism.[220] Thinning and eventual loss of the cortical bone of the maxilla and mandible may occur, especially on the lower border of the mandible. Severe cases may result in spontaneous mandibular fracture.[221]

Stomatognathic Manifestations and Dental Management

Children with rickets/osteomalacia may present with delayed tooth eruption, loss of lamina dura, and enamel and dentine hypoplasia that may progress to periapical infections. Malocclusion and hypoplastic teeth increase the risks of dental caries; therefore, regular oral health evaluation is necessary to monitor dental and periodontal health.

OSTEOPOROSIS

Osteoporosis is defined as "a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and an increase in fracture risk."[222] The World Health Organization (WHO) defines osteoporosis as a bone density of 2.5 standard deviations (SDs) below the young healthy adult mean value (T score ≤ -2.5) or lower. Values between -1 and -2.5 SDs below the young adult mean are termed "osteopenia."

Fractures due to osteoporosis are a major cause of morbidity and mortality in elderly populations and a major contributor to rising health costs. Osteoporotic fractures of the spine cause severe, acute pain or deformity and postural back pain. The risk of fracture increases exponentially with age, with 1 in 2 women and 1 in 5 men aged 50 years having an osteoporotic fracture during their remaining lifetime (Table 22-38). Caucasian and Asian races are particularly at risk.

Osteoporosis occurs from increased bone breakdown by osteoclasts and decreased bone formation by osteoblasts, leading to loss of bone mass. Bone mass decreases with age, but will depend on the "peak" mass attained in adult life (at about the age of 40–45 years) and on the rate of loss in later life. The main risk factor for osteoporosis is estrogen deficiency. In the elderly, vitamin D insufficiency and consequent hyperparathyroidism are of greater importance. Hyperparathyroidism, hyperthyroidism, and malabsorption all increase the lifetime risk of a person having a low bone mass and low BMD. Additional risk factors associated with increased bone loss, or with increased bone fragility, include

Table 22-38 Hip fractures per 1000 patient-years.

World Health Organization Category	50–64 Years of Age	>64 Years of Age	Overall
Normal	5.3	9.4	6.6
Osteopenia	11.4	19.6	15.7
Osteoporosis	22.4	46.6	40.6

Source: Cranney A, Jamal SA, Tsang JF, Josse RG, Leslie WD. Low bone mineral density and fracture burden in postmenopausal women. *Canadian Med Assoc J*. 2007;177(6):575–580.

glucocorticoid therapy and smoking. Falls increase the risk of fracture, on top of the risk associated with the particularly low bone mass. Osteoporosis is asymptomatic, except subsequent to a fracture. Bone density assessment by use of dual-energy X-ray absorptiometry (DXA) is the gold standard for the diagnosis of osteoporosis.

Prevention and Treatment of Osteoporosis (and Consequent Fractures)

Exercise

Life-long weight-bearing exercise, as little as 30 minutes, three times a week, may increase BMD. Gentle exercise in the elderly reduces the risk of falls and improves the protective reflexes needed with falling.

Smoking Cessation

This should be strongly encouraged, as smoking is associated with lower BMD and increased fracture risk.

Reduced Alcohol Intake

Alcohol intake of >3 units/day should be avoided.

Fall Reduction

This can be assisted with physiotherapy and assessment of home safety, with installation of hand rails and nonslip floor surfaces, especially in wet areas such as the bathroom and toilet.

Vitamin Supplementation

Calcium

Research has established that optimal calcium intake reduces bone loss and suppresses bone turnover. For men and women aged 19–50 years the recommended daily intake is 1000 mg/day, and for adults 51 years and older this should be increased to 1200 mg/daily. The best sources are dairy foods, but many patients require calcium supplementation.

Vitamin D

The US Institute of Medicine recommends 200 IU/daily for adults <50 years of age, 400 IU/daily for those 50–70 years, and 600 IU for those >70 years.

Pharmacologic Interventions

See Table 22-39.

Estrogen(s)/Hormone Replacement Therapy

Given the adverse effects of an increased risk for breast cancer and cardiovascular disease risk, hormone replacement therapy (HRT) is a second-line option for osteoporosis, except in younger postmenopausal women at high fracture risk.

Selective Estrogen-Receptor Modulators

Raloxifene 60 mg daily is a selective estrogen-receptor modulator (SERM) that has the advantage of having no stimulatory effect on the endometrium, but activates estrogen receptors in bone. It prevents BMD loss of bone from the spine and hip in postmenopausal women. It also reduces the incidence of estrogen-receptor-positive breast carcinoma in women treated for up to 4 years. Leg cramps and flushing may occur and the risk of thromboembolic complications is also increased, including stroke, to a degree similar to that seen with HRT.

Antiresorptive Agents

Bisphosphonates

These synthetic analogues of bone pyrophosphate adhere to hydroxyapatite and inhibit osteoclasts (Tables 22-40 and 22-41). Alendronate, risedronate, and ibandronate are approved for the prevention and treatment of postmenopausal osteoporosis in the United States. Aclasta® (zoledronic acid; Novartis Europharm, Frimley, UK) infusion is approved for use in the treatment and prevention of osteoporosis in the United Kingdom and Europe. Risedronate and alendronate are approved for the treatment of steroid-induced osteoporosis. Bisphosphonates are generally well tolerated, but the orally given agents are associated with upper gastrointestinal side effects, such as esophagitis. Bisphosphonates given as an infusion negate the gastrointestinal side effects and ensure patient compliance, thus they are increasingly popular for the management of osteoporosis, apart from their established role in malignancy-associated bone diseases (hypercalcemia, bony metastases, and multiple myeloma). The optimal duration of bisphosphonate therapy is unknown, with prolonged suppression of bone turnover having adverse effects, including atypical, low-impact, femoral fractures, and ONJ. Current recommendations are to reassess the need for ongoing bisphosphonate treatment after 3–5 years, although the benefits appear to exceed the risk of these complications.

Denosumab

Sold as Prolia® (Amgen) when used for osteoporosis (in contrast to Xgeva® [Amgen] when used in the setting of malignancy), this is a fully human monoclonal antibody to RANK ligand. It is given twice yearly by subcutaneous administration for osteoporosis. Randomized controlled trials in postmenopausal women with osteoporosis have shown it to increase BMD in the spine, hip, and forearm and reduce vertebral, hip, and nonvertebral fractures over a 3-year period by 70%, 40%, and 20%, respectively. Fracture risk reduction is equivalent to bisphosphonates. Interestingly, the risk for osteonecrosis is equivalent to that seen with the more potent bisphosphonates, comparable with the use of zoledronic acid, in the setting of malignancy.

Table 22-39 Drug therapies used for osteoporosis.

Oral Agents

Class	Actions	Generic Name	Trade Name(s)[a]	Indications	Disadvantages/ Warnings
Minerals and Vitamins					
Calcium	• Essential for bone mineral formation	Calcium carbonate Calcium citrate	Various (plus, various combinations with vitamin D)	Aids in prevention and treatment of osteoporosis	
Vitamin D3	• Maintenance of skeletal calcium • Promotes calcium absorption from gastrointestinal tract • Maintains calcium and phosphate levels for bone formation • Proper function of parathyroid hormone (PTH)	Cholecalciferol (vitamin D3) Calcitriol (1,25-dihydroxy-vitamin D3), active form of D3	Various (plus various combinations with calcium)	Aids in prevention and treatment of osteoporosis	• Hypervitaminosis D (daily allowance:15 µg/d (600 IU/d • Excess of vitamin D: → hypercalcemia → overcalcification of the bones, soft tissues, heart and kidneys → Damage to kidney → Kidney stones
Estrogen/Estrogen-Related Agents					
Hormone replacement therapy	• Effect of estrogen is to inhibit bone resorption • With estrogen deficiency, the osteoclasts live longer and are therefore able to resorb more bone	Conjugated estrogens	Premarin	Prevention of postmenopausal osteoporosis	Risks: ↑ Myocardial infarction ↑ Stroke ↑ Pulmonary embolism (PE) and deep vein thrombosis (DVT) ↑ Breast cancer ? Dementia
Selective estrogen-receptor modulators	• Acts as estrogen agonist in bone ↓ Decreases bone resorption ↓ Bone turnover ↓ Decreases fracture incidence ↑ Bone mineral density	Raloxifene	Evista	Treatment and prevention of osteoporosis in postmenopausal women Reduction in risk of invasive breast cancer	Risks: ↑ DVT, PE ↑ Stroke ↑ Major coronary event
Antiresorptive Agents					
Bisphosphonates (amino-bisphosphonates)	• At the cellular level, preferential localization to sites of bone resorption, specifically under osteoclasts	Alendronate Risedronate Ibandronate	Fosamax Binosto Actonel Atelvia Boniva	Treatment and prevention of osteoporosis in postmenopausal women, men, and glucocorticoid-induced osteoporosis Paget's disease	• Optimal duration of use not determined • Patients at low risk for fracture, consider drug discontinuation after 3–5 years • Osteonecrosis of the jaw (ONJ)

Parenteral Agents (Intravenous, Intramuscular, and/or Subcutaneous)

Class	Actions	Generic Name	Trade Name(s)[a]	Indications	Disadvantages/ Warnings
Antiresorptive Agents					
Bisphosphonates	• in vitro, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis	Zoledronic acid	Reclast	Treatment and prevention of postmenopausal osteoporosis, for men, and glucocorticoid-induced osteoporosis Paget's disease 5 mg every 1–2 years	• ONJ
Denosumab	• Prolia binds to receptor activator of nuclear factor kappa-B (RANK) ligand • Protein essential for formation, function, and survival of osteoclasts ↓ Osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength	densumab	Prolia	Treatment and prevention of postmenopausal osteoporosis, for men, and glucocorticoid-induced osteoporosis 60 mg subcutaneously (SQ) every 6 months	• Prevention of skeletal-related events in patients with cancer: 120 mg SQ every 4 weeks • ONJ (incidence similar to that of zoledronic acid)
Calcitonin	• Hormonal bone resorption inhibitor; action on bone has not been fully established	Calcitonin (salmon rDNA) Intranasal/ intramuscular/SQ	Fortical Miacalcin	Treatment of postmenopausal osteoporosis in women >5 years post menopause in conjunction with Ca^{2+} and vitamin D	
Teriparatide (Forteo) Recombinant human PTH	↑ New bone formation by stimulation of osteoblastic activity over osteoclastic activity ↑ Skeletal mass ↑ Markers of bone formation and resorption ↑ Bone strength	20 µg daily SQ		Treatment of postmenopausal women with osteoporosis, men with primary or hypogonadal osteoporosis, and glucocorticoid-induced osteoporosis for patients at high risk for fracture	• Not to be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease)

→ leads to; ↑, increases; ↓ , decreases; ?, uncertain.

Table 22-40 Bisphosphonates: indications and usage.

Usage	Indication	Comments	Incidence of MRONJ
>90%	Osteoporosis (>90% usage)	• Postmenopausal • Corticosteroid induced/related • "Male" age-related osteoporosis • Renal osteodystrophy • Male hypogonadism	
~1%	Other/rare conditions	• Paget's disease • Osteogenesis imperfecta • Reflex sympathetic dystrophy (complex regional pain syndrome) • Heterotopic ossification with spinal cord injury • Total hip replacement • Giant cell tumor of bone	<10%
5–10%	Malignancy	Skeletal (bony) metastases (from solid malignancies • Breast cancer • Lung cancer • Prostate cancer Multiple myeloma Hypercalcemia	>90%

MRONJ, medication-related osteonecrosis of the jaws.

Table 22-41 Amino-bisphosphonates and their potency ratings.

Nitrogenous (N-Containing) Bisphosphonates

Generic Name	Trade Name	R2 Group	Potency
Pamidronate	Aredia	Amino	100
Alendronate	Fosamax	Amine	1000
Ibandronate	Bondronate	Long-chain nitrogen	10 000
Risedronate	Actonel	Cyclic nitrogen	10 000
Zoledronate	Zometa	Cyclic nitrogen	>10 000

Potency is calculated on the agents' antiresorptive effect on bone, i.e., the decline in bone resorption.
Source: Adapted from Licata AA. Discovery, clinical development, and therapeutic uses of bisphosphonates. *Ann Pharmacotherapy*. 2005;39(4):668–677.

Calcitonin

Calcitonin preparations are approved by the FDA for Paget's disease, hypercalcemia, and osteoporosis in women more than 5 years post menopause. Calcitonin suppresses osteoclast activity by direct action on the osteoclast calcitonin receptor. Calcitonin produces small increments in bone mass of the lumbar spine. A nasal spray (Fortical®, Upsher-Smith Laboratories, Minneapolis, MN, USA) containing calcitonin (200 IU/day) is available for treatment of osteoporosis in postmenopausal women and as an injectable form (Miacalcin®, Mylan Pharmaceuticals, Canonsburg, PA, USA).[223]

Teriparatide

Teriparatide (Forteo®, Eli Lilly, Indianapolis, IN, USA) is recombinant human parathyroid hormone (rhPTH) peptide 1–34, an anabolic agent that stimulates bone formation. Teriparatide reduces vertebral and nonvertebral fractures in postmenopausal women with established osteoporosis, although data on hip fracture are not yet available. It is given by daily subcutaneous injection in a dose of 20 μg for 18–24 months. rhPTH therapy is indicated in severe cases of vertebral osteoporosis or in women who fail to respond to other therapies.[224]

Antisclerostin Antibody Agents

Romosozumab only gained FDA approval in April 2019. It is given as a monthly subcutaneous injection (see earlier).

Glucocorticoid-Induced Osteoporosis

Iatrogenic osteoporosis is a recognized major complication of the therapeutic use of glucocorticoids. The risk of fractures depends on the dose and duration of glucocorticoid therapy, although data now suggest that there may be no completely safe dose.

Patients needing continuous oral glucocorticoid therapy for 3 months or more (at any dose) should be assessed for coexisting risk factors (age, previous fracture, and hormone status). Postmenopausal women and men aged over 50 years, as well as any individuals who have sustained a fracture, should receive treatment for the prevention of osteoporosis

and its progression, without waiting for BMD assessment. To date, only bisphosphonates have been demonstrated in large clinical trials to reduce the risk of fractures in patients being treated with glucocorticoids. Calcium and vitamin D supplementation also needs to be given.

MEDICATION-RELATED OSTEONECROSIS OF THE JAWS

Medication-related osteonecrosis of the jaws (MRONJ) is a clinical entity in which patients develop localized areas of bone necrosis involving the jawbones, predominantly the mandible, and the maxilla (Figures 22-21 and 22-22).[225] The necrosis, which is the key feature seen with MRONJ, entails cell and tissue injury, resulting in unexpected, premature cell death by an as yet unclear process, although necrosis usually results from trauma, infection, and/or toxins within otherwise unaffected, vital, normal bones of the jaws. Hence, the abbreviated term *osteonecrosis of the jaws* (ONJ) is also used.

There are select medications that have been established to be strongly associated with MRONJ. Of these, the drugs with the greatest and most frequently described associations are those that act to inhibit bone resorption, termed antiresorptive agents. They include the following drugs (or classes of drug):

- Amino-bisphosphonate agents.
- Denosumab, a monoclonal antibody directed against the RANK ligand found on osteoclasts.
- Romosozumab, the first of a new class of antisclerostin antiresorptive agents.[226]
- Antiangiogenic agents, which interfere with the formation of new blood vessels (angiogenesis) that is essential for cancer growth and development. A number of these agents alone, but more commonly when given concurrently with antiresorptive agents, have been associated with the development of MRONJ (Table 22-42).[227–229]

Of note is that other agents that affect bone remodeling and turnover—that is, teriparatide (the humanized recombinant form of human PTH) and strontium ranelate (never marketed in the United States because of the significant adverse risks of heart attacks and blood clots)—are not associated with MRONJ. Strontium ranelate has a dual action stimulating both osteoclastic and osteoblastic activity, and teriparatide is known to have a similar effect, given its anabolic effect on bone turnover. Of interest is that teriparatide has in a small number of case reports shown to be of benefit in established MRONJ.[234–239]

Evolution of the Nomenclature

Until the advent of the antiresorptive agent denosumab in 2010,[240] and reporting of the association between denosumab and ONJ,[241] ONJ was exclusively associated with bisphosphonate agents, and specifically the newly introduced, more potent amino-bisphosphonates. The initial bisphosphonate with a side chain containing nitrogen, termed an amino-bisphosphonate, was pamidronate, which was approved for medical use in 1987.[242] Subsequently, further modification of the nitrogen-containing side groups resulted in newer, highly potent agents with regard to their ability to prevent bone resorption by their interference in that action

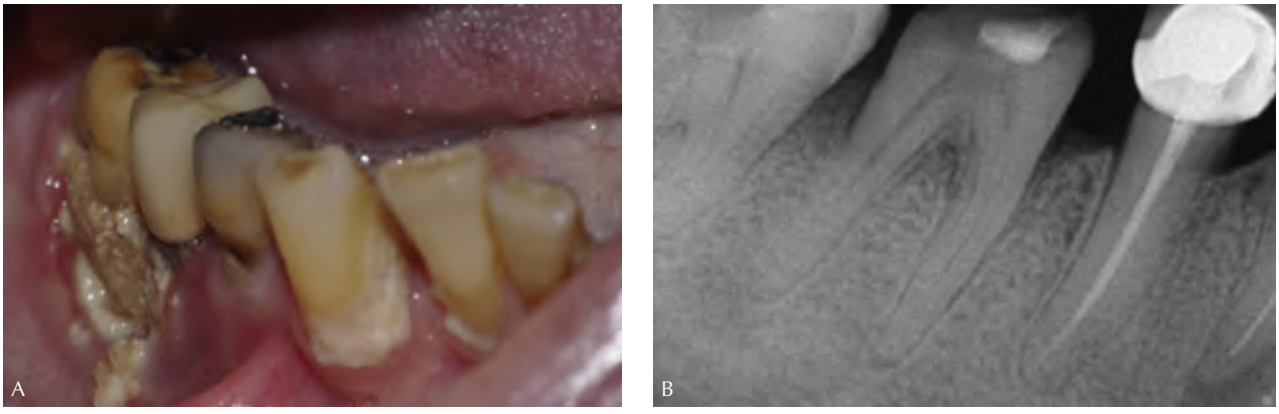


Figure 22-21 Example of exposed medication-related osteonecrosis of the jaw. A patient receiving high-dose denosumab presented with pain of 6 months' duration on the right lower first molar. He was receiving antibiotics. (A) Exposed bone and purulence were observed on the buccal alveolar bone area of the tooth consistent with osteonecrosis of the jaw, exposed type, before dental extraction. (B) Panoramic radiography disclosed alveolar bone loss around the molar tooth. Courtesy of Professor Ourania Nicolatou-Galitis, Dental School, National and Kapodistrian University of Athens. *Source:* Nicolatou-Galitis O, Schiødt M, Mendes RA, et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2019;127(2):117–135.

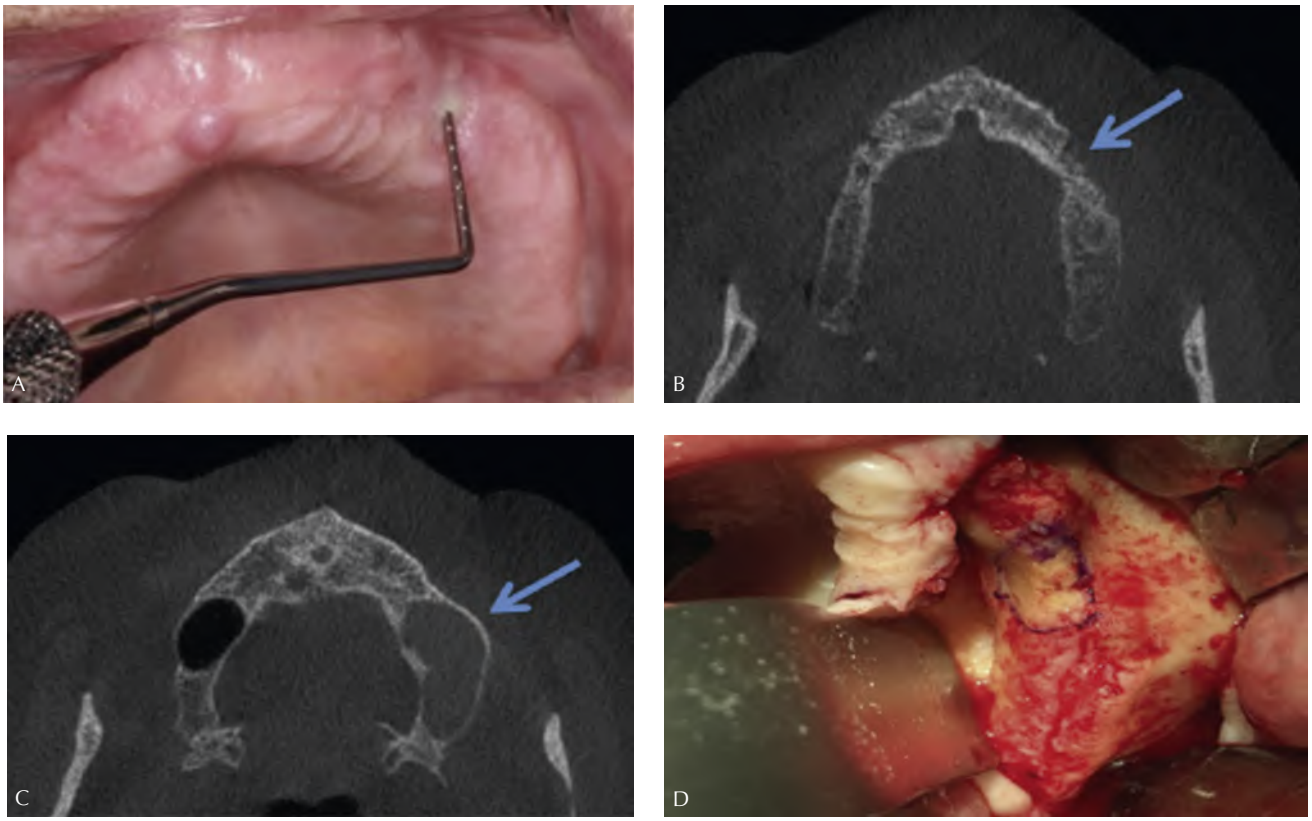


Figure 22-22 Example of nonexposed medication-related osteonecrosis of the jaw. (A) A patient receiving high-dose denosumab presented with pain in an apparently normal edentulous left maxilla. A droplet of pus was seen on palpation and bone was probed through a fistula. (B, C) Cone-beam computed tomography showed sequestrum at regions 24 and 25 (arrow) and infection in the left maxillary sinus. (D) Perioperative view showing osteonecrosis outlined on the bone surface. Uneventful healing was accomplished. Courtesy of Dr. Morten Schiødt, University Hospital of Copenhagen. *Source:* Schiødt M, Wexell CL, Herlofson BB, Ottesen C, Nørholt S-E. Medicinrelateret osteonekrose i kæberne—oversigt og retningslinjer. *Tandlægebladet*. 2015;119:918–930. Published with the permission of the Danish Dental Journal.

and also reducing the number of osteoclasts. Hence there is now widespread use of these potent amino-bisphosphonate agents to treat and prevent osteoporosis, which is caused by relatively excessive bone resorption by osteoclasts that is not matched by bone formation by osteoblasts. Of the amino-bisphosphonates, the most potent is zoledronic acid (zoledronate), marketed as Zometa® and Reclast® (Novartis Pharmaceuticals, East Hanover, NJ, USA), which was introduced in 2001.[243] MRONJ was first reported in 2003.[244] Given that up to 2010 the only drugs shown to be consistently associated with ONJ were bisphosphonates, the term bisphosphonate-related osteonecrosis of the jaws (BRONJ) was adopted, including variations such as bisphosphonate-associated osteonecrosis of the jaws (BAONJ), bisphosphonate-associated osteonecrosis (BON), osteochemonecrosis of the jaws (OCNJ), and "bis-phossy jaw." However, the term medication-related osteonecrosis of the jaws is now preferred and MRONJ has replaced BRONJ, since it has been recognized that ONJ is associated with other agents besides bisphosphonates, including the newer antiresorptive agent denosumab and antiangiogenic agents used in the treatment of various cancers.

Case Definition

The case definition and established diagnostic features of MRONJ are as follows:

- Current or previous treatment with bisphosphonates and/or denosumab, as well as select antiangiogenic agents. However, generally MRONJ occurs when these select antiangiogenic agents have been used concurrently with an antiresorptive agent.
- A localized area of exposed bone, or bone that can be readily probed through fistula, which can be intraoral or extraoral (i.e., through the skin overlying the mandible or maxilla, the nasal cavity of adjacent maxillary sinuses) and has been present or persistent for more than 8 weeks.
- No history of prior radiation therapy to the jaws.
- Exclusion of obvious metastatic disease or deposits of the jaws.

Table 22-42 Antiangiogenic agents associated with medication-related osteonecrosis of the jaws (MRONJ).

Drug	Mechanism of Action	Primary Indication	
Sunitinib (Sutent)	• Tyrosine kinase inhibitor (TKI) • Sunitinib inhibits cellular signaling by targeting multiple receptor tyrosine kinases, including: – Platelet-derived growth factor receptors (PDGFR) – Vascular endothelial growth factor receptors (VEGFRs), which play a role in tumor angiogenesis and cell proliferation[230]	GIST RCC pNET	Gastrointestinal stromal tumor Renal cell carcinoma Pancreatic neuroendocrine tumor
Sorafenib (Nexavar)	• TKI • Sorafenib is a protein kinase inhibitor with activity against many protein kinases, including: – VEGFR – PDGFR – RAF kinases (three serine/threonine-specific protein kinases related to retroviral oncogenes)[231]	HCC RCC	Hepatocellular carcinoma Renal cell carcinoma
Bevacizumab (Avastin)	• Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting: – Vascular endothelial growth factor A (VEGF-A)[232]	mCRC NSCLC Glio mRCC	Metastatic colorectal carcinoma Nonsquamous non-small-cell lung carcinoma Glioblastoma Metastatic renal cell carcinoma
Sirolimus (Rapamune)	• Mammalian target (mTor) of rapamycin pathway • Downregulates the expression of these VEGFs by decreased expression of both the proteins and mRNA: – VEGF-A/VEGFR-2 and VEGF-C/VEGFR-3,which are closely involved in angiogenesis and lymphangiogenesis[233]	Prevention of rejection in renal transplantation	

Source: Adapted from Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72(10):1938–1956.

The case definition has evolved, with the recognition that metastatic disease or deposits of the jaws are important differential diagnoses that need to be considered and excluded, which is best done by histopathologic assessment following biopsy.[245] Caveats apply to this case definition, including increasing recognition of cases in which exposed bone for protracted periods is not necessarily the presenting feature of MRONJ.[246–247]

Staging

The American Association of Oral and Maxillofacial Surgeons staging system of 2014[227] serves to define cases and the severity of the MRONJ identified, but stage-specific treatment approaches have a sound and growing evidence base as to their effectiveness (Table 22-43).[248]

Definitions of High-Dose versus Low-Dose Antiresorptive Therapy

The epidemiology for MRONJ has clearly established that 90% of cases occur in patients with cancer receiving *high-dose* therapy; that is, intensive dosing regimens of intravenous, high-potency bisphosphonates, mainly zoledronic acid (4 mg every 3–4 weeks) or subcutaneous denosumab (120 mg every 4 weeks). Data from prospective studies demonstrated that properly adjudicated MRONJ occurred in 1.3% of cancer patients treated with zoledronic acid and in 1.1% of patients with cancer treated with denosumab.[249] Furthermore, the evidence demonstrates that the increase in the cumulative dose of antiresorptive agent is associated with an increasing incidence of MRONJ. Among patients

Table 22-43 Staging of medication-related osteonecrosis of the jaws (MRONJ).

Stage	Findings
Patients at risk	No apparent necrotic bone in asymptomatic patients who have been treated with intravenous or oral antiresorptive or antiangiogenic therapy
Stage 0 (Nonexposed bone variant)	Patients with no clinical evidence of necrotic bone, but present with nonspecific symptoms or clinical and radiographic findings: **Symptoms** • Odontalgia not explained by an odontogenic cause • Dull, aching bone pain in the body of the mandible, which may radiate to the temporomandibular joint region • Sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall • Altered neurosensory function (patients may complain of altered sensation of the lips) **Clinical findings** • Loosening of teeth not explained by chronic periodontal disease • Periapical/periodontal fistula not associated with pulpal necrosis due to caries **Radiographic findings** • Alveolar bone loss or resorption not attributable to periodontal disease • Changes to bony trabecular pattern: – Dense woven bone – Persistence of unremodeled bone in extraction sockets • Regions of osteosclerosis involving the alveolar bone and/or the surrounding basilar bone • Thickening/obscuring of periodontal ligament: – Thickening of the lamina dura – Decreased size of the periodontal ligament space[150]
Stage 1 (Asymptomatic)	• Exposed and necrotic bone or fistulae that on probing contacts bone, in patients who are asymptomatic and have no evidence of infection. **Radiographic findings**: as seen in Stage 0, may also be present that are localized to the alveolar bone region
Stage 2 (Symptomatic)	• Exposed and necrotic bone *and/or* • Fistulae that on probing contacts bone, with evidence of infection • Patients are symptomatic • **Radiographic findings**: as seen in Stage 0, may also be present that are localized to the alveolar bone region
Stage 3	Exposed and necrotic bone, or fistulae that probe to bone, with evidence of infection and one or more of the following: • Exposed necrotic bone extending beyond the region of alveolar bone – to the inferior border and ramus in the mandible – maxillary sinus and zygoma in the maxilla • Pathologic fracture • Extraoral fistula • Oral antral/oral nasal communication • Osteolysis extending to the inferior border of the mandible or sinus floor

Source: Adapted from Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72(10):1938–1956.

with advanced breast cancer with bony metastases, the incidence of MRONJ at years 1, 2, and 3 was 0.5%, 1.2%, and 1.4%, respectively in those patients who received zoledronic acid, and 0.8%, 1.9% and 2.0%, respectively in those treated with denosumab. The risk of ONJ among patients with cancer exposed to antiresorptive or antiangiogenic medications is about 1%, but ranges between 0.2% and 6.7%.[250] Overall, the benefit provided by antiresorptive therapy outweighs the

risk of development of MRONJ in the settings of both osteoporosis and oncology.

Low-dose antiresorptive medication regimens are those typified by the dosing regimens for osteoporosis in postmenopausal women, which includes oral and intravenous bisphosphonates, with an example of the latter being zoledronic acid (5 mg every 12 months) and denosumab at a dose of 60 mg every 6 months.[251] Such low-dose regimens dominate the use, dose, and frequency of antiresorptive agents for all of their approved indications, *except* in the setting of patients with cancer. It is estimated that over 90% of patients taking antiresorptive agents are receiving low-dose regimens. The risk of ONJ among patients who are managed for osteoporosis using antiresorptive medications is about 0.1% (range 0.004%–0.2%), but this increase, as seen with patients taking oral bisphosphonates to manage osteoporosis with the risk of ONJ after tooth extraction, is estimated to be 1 in 200 (0.5%).[252] However, as has been established, it is not only the intensity of the antiresorptive dosing regimen that affects the rate of MRONJ, it is the overall cumulative dose. For patients receiving oral bisphosphonate therapy to manage osteoporosis, the prevalence of ONJ increases over time from near zero to 0.2% after 4 or more years of bisphosphonate exposure, with ONJ being seen at a median duration of oral bisphosphonate exposure of 4.4 years. Although there is less published data, the same phenomenon was seen in osteoporotic subjects taking denosumab. After 2 years of exposure, the incidence of ONJ was 0.09%, but this doubled to 0.2% after 6 years of exposure to denosumab.[253]

The significance of this epidemiologic evidence regarding the risk and duration of antiresorptive treatment associated with the development of MRONJ is as follows:

- In the majority of patients taking antiresorptive agents, these are low-dose regimens associated with a modest to significantly lower risk of MRONJ occurring.
- Regardless of which antiresorptive agent is involved, patients who are taking these drugs in the setting of cancer have a significantly greater risk of developing MRONJ, >1%, and this risk increases with the greater cumulative dose of the agent taken.
- There are definite "window periods" in which patients on low-dose antiresorptive drug regimens remain at a very low risk for MRONJ, which appears to be up to 4 years of treatment with low-dose antiresorptive agents. In this period, invasive dental procedures such as extractions (and implant placement) can be undertaken with a low risk of MRONJ occurring.

For dentists, this represent a critical period in which patients need to be made as dentally fit as possible, providing patients on such antiresorptive agents with a sustainable and easily maintainable dentition that negates the need for future dental extractions.

Window Periods for Patients on High-Dose Antiresorptive Therapy

The epidemiologic data indicate that up to 4 years of treatment with a low-dose antiresorptive treatment regimen, whether it be an oral or intravenous bisphosphonate agent or denosumab, is associated with very low risk of MRONJ occurring, even with the undertaking of invasive procedures, namely extractions. These data can be extrapolated and applied to patients who are on high-dose antiresorptive therapy in the setting of cancer. The cumulative 4-year low-dose regimen of any specific antiresorptive agent is indicative of the cumulative dose at which the risk of MRONJ substantially increases. This, by way of specific examples, is 20 mg of zoledronic acid (equal to 4 years of treatment at 5 mg per annum) and 480 mg for denosumab (equal to 4 years of treatment at 120 mg per annum; 60 mg given every 6 months). In the setting of cancer, patients will be exposed to 20 mg of zoledronic acid after 15 weeks. The standard dosing regimen for zoledronic acid used in cancer patients is 4 mg every 3 weeks, therefore it will take 15 weeks (~3.5 months) for a dose of 20 mg to be reached. For patients taking denosumab in the setting of cancer, it will take 16 weeks to reach a dose of 480 mg, as denosumab is given at 120 mg every 4 weeks. Note that in a setting of hypercalcemia of malignancy, "loading" doses of 120 mg of denosumab are to be given on days 8 and 15 within the initial 4 weeks, so shortening the tine to reach 480 mg to just 4 weeks; that is, one month. At 4 weeks a patient will have taken 240 mg, with 120 mg of denosumab given on days 0 and 28 and an extra 240 mg (2×120 mg) on days 8 and 15.

This extrapolation of the data suggests that for patients needing zoledronic acid or denosumab for the prevention of skeletal-related events of bony metastases or of the progression of the bony lytic lesions of multiple myeloma, but not when denosumab is used to treat hypercalcemia of malignancy, there is a potential window period of up to 3 months. Within this 3-month window, invasive dental procedures can be undertaken in an effort to make the patient dentally fit and so preventing the need for extractions after the 3-month window expires. However, there is no direct evidence in the form of patient-based studies that have established this premise, which is based on first principles.

Risk Factors

The overriding factor for the assessment of the risk of MRONJ developing is cumulative exposure of the patient to bisphosphonates or denosumab, considering both the dose per treatment and the number of administrations given from the start of the treatment.[254] A secondary consideration should be the relative potency of the agents used. Although to date no clear threshold dose below which MRONJ does

not occur has yet been identified, consensus is emerging in the setting of patients receiving low-dose antiresorptive medication for osteoporosis: some experts argue that the risk of MRONJ is significant after 3 years of therapy,[245] while the American Academy of Oral and Maxillofacial Surgery has stated that for patients who have received 4 years of low-dose antiresorptive treatment, the risk of MRONJ occurring subsequent to invasive dental procedures is low.[227]

The other major risk factors are the presence of infection, since typically MRONJ develops following a local infection and/or trauma to bone or soft tissues, as occurs with invasive dental procedures, namely extractions. Recent data have shown that localized periodontal or dental disease may precede the appearance of MRONJ.[37] Furthermore, alveolar bone necrosis has been documented at the time of dental extraction and the bacterial microbiotome within the necrotic bone is consistent with that seen in periodontal disease.[255,256] Dentists should be aware of the risk of MRONJ when considering invasive procedures (e.g., tooth extraction or implant placement), in cases of pressure sores from ill-fitting dentures, and when there is significant inflammation/infection.[112–114] Other factors have also been associated with an increased risk of MRONJ, including the use of other cancer therapies and/or previous or concurrent corticosteroid use, smoking, poor oral hygiene, and comorbidities, such as diabetes mellitus and renal failure. In particular, the concomitant use of antiresorptives with agents that inhibit angiogenesis—that is, the formation of new blood vessels as part of tumor growth and spread—has been documented to increase the likelihood of MRONJ occurring.[83]

Treatment Goals

The major goals of treatment for patients at risk of developing or who have MRONJ are as follows:

- Education and engagement with patients and their physicians regarding the risks of MRONJ, how these risks can be ameliorated, and keeping them apprised of when MRONJ occurs and how it can be best managed.
- Prioritization and support of the ongoing treatment for oncology patients requiring high-intensity antiresorptive agents and/or antiangiogenic drugs and those on long-term antiresorptive drugs for osteoporosis (that is, beyond 4 years of treatment). It should be noted that oncologic patients and osteoporotic patients obtain significant therapeutic benefit from antiresorptive therapy by controlling bone pain and lowering the incidence of other skeletal complications and osteoporotic-related fractures.
- For patients on antiresorptive agents that have not exceeded the window periods, prioritizing their dental care, removing all immediate and potential likely sources of dental-related infection, and ensuring these patients have a dentition that is sustainable and maintainable, so limiting the need for dental extractions in the future, beyond the designated window periods.

Prevention

Poor dental health—that is, active periodontal disease, and/or infectious and inflammatory complications of caries-induced pulpitis—is an established risk factor for the development of MRONJ in patients on long-term antiresorptive therapy. The converse also applies, in that excellent levels of dental health, supported by preventative dental health measures, have been shown to significantly limit the risks of development of MRONJ, even in patients receiving antiresorptive therapy in the setting of malignancy. This concept needs to be extended, with dental practitioners needing to be mindful of providing a dentition that patients are best able to maintain and that negates the need for future invasive dental procedures, such as extractions or implant placement, given that patients will be in receipt of antiresorptive therapy for long durations (in excess of 5 years) until their BMD score is normalized. For patients who need invasive dental treatment, the risk of such treatment needs to be carefully balanced against the possible risks of such patients developing MRONJ; however, deferring extractions of teeth with a poor to dismal prognosis that are otherwise unrestorable, or unmaintainable, is also associated with risk. In such situations, the presence of ongoing infection and associated inflammation in itself increases the risk of MRONJ occurring, with "spontaneous" cases of MRONJ having been well documented, occurring in 30% of patients without any invasive dental treatment having been undertaken. Patients will continue to receive further antiresorptive treatment for their osteoporosis, as the risks of serious bone fracture and its morbid and possible fatal complications outweigh the risks and complications, such as ONJ.

The risk of MRONJ is now thought to occur in a dose-dependent manner; that is, the greater the dose, the greater the risk of MRONJ occurring. Therefore, it may serve the patient better to undertake the necessary extractions in a planned, preemptive fashion, whereby the risk of MRONJ may be mitigated, than to await a time that extraction becomes inevitable or severe infection develops. Methods to mitigate MRONJ from occurring include the use of a course of pre- and postprocedural antibiotics, with frequent use of antibacterial (chlorhexidine-containing) mouthwashes, a "gentle"—that is, as atraumatic as practical—extraction or oral surgical technique, and primary closure. Such measures may not prevent MRONJ from developing, but may see only MRONJ stage 0 or 1 developing, which is highly amenable to conservative and modest surgical interventions.

Tables 22-44, 22-45, 22-46, and 22-47 estimate and attempt to stratify the risk of MRONJ occurring with invasive dental

Table 22-44 Duration of antiresorptive therapy (in cancer) that is equal to 4 years of treatment for osteoporosis.

Agent	Route of Administration	Osteoporosis Dose Regimen	Total Dose at 4 years	Cancer Dosing Regimen	Duration of Antiresorptive Treatment That Reaches 4-year Total Dose (as for Osteoporosis)	
Zoledronate (Aclasta)	IV	5 mg/year	20 mg	4 mg every 3 weeks	• 20 mg/4 mg = 5 doses • 5 doses given every 3 weeks = 15 weeks **= 3.5 months**	**3 months**
Ibandronate (Bondronat)	IV	3 mg every 3 months	48 mg	6 mg every 4 weeks	• 48 mg/6 mg = 8 doses • 8 doses given every 4 weeks = 32 weeks **= 7 months**	**7 months**
Ibandronate (Bondronat)	Oral	150 mg every month	200 mg	50 mg every day	• 200 mg/50 mg = 144 doses • 144 doses daily = 20 weeks **= 4.6 months**	**4 months**
Pamidronate (Aredia, Pamisol)	IV	60 mg every month	880 mg	90 mg every 3 weeks	• 880 mg/90 mg = 32 doses • 32 doses every 3 weeks = 96 weeks **= 22 months**	**22 months**
Denosumab (Prolia)	SQ	60 mg every 6 months	480 mg	120 mg every 4 weeks	• 480 mg/120 mg = 4 doses • 4 doses every 4 weeks = 16 weeks **= 3.6 months**	**3 months**

IV, intravenous; SQ, subcutaneous.
Source: Prevention of osteonecrosis of the jaw (ONJ) in patients on bisphosphonate therapies. http://www.health.nsw.gov.au/policies/gl/2010/pdf/GL2010_010.pdf

Table 22-45 Bisphosphonates and estimated "window periods" for substantively increased risk of medication-related osteonecrosis of the jaws (MRONJ) with invasive dental procedures.

Name	Generic Name	Route of Administration	Indication	Window Period: Duration of Bisphosphonate Therapy (in Months)*
Zometa	Zoledronic acid	Intravenous	Malignancy-related skeletal events	3
Bondronat	Ibandronate	Intravenous		7
Aredia Pamisol	Pamidronate	Intravenous		22
Bondronate	Ibandronate	Oral		4
Didronel	Etidronate	Oral	Paget's disease; heterotopic ossification with spinal cord injury; total hip replacement	36–48
Zometa	Zoledronic acid	Intravenous	Osteoporosis (noniatrogenic) treatment/ prophylaxis	>36–60?
Aredia Pamisol	Pamidronate			
Actonel	Risedronate	Oral		
Fosomax	Alendronate			

* In which invasive treatment (dental extractions/oral surgery) can be undertaken with a relative lower risk of complications, but not with no risk—risk of MRONJ still is present.
?, uncertain.

procedures. For moderate-risk patients, all the interventions suggested in Table 22-48 should be undertaken and, of course, extensive consultation with the patient's treating physician, and the patient themselves, including providing detailed and informed consent of the risks of MRONJ occurring. For patients stratified (Table 22-46) as being at high risk for developing MRONJ, the risks of the development of MRONJ, versus the benefits of addressing active pain or infection arising from the involved tooth/teeth, need to be outlined. Furthermore, referral of such patients to clinicians and/or specialized centers experienced in the management of MRONJ should be considered.

There also remains considerable doubt regarding the value of "drug holidays" for patients with established MRONJ.[257] However, on discussion with the patient's treating physician, an inquiry regarding the use of non-antiresorptive agents with no known risk for ONJ associated with their use (e.g., teriparatide) may prompt consideration of such alternate agents, especially in those patients with a high risk of developing MRONJ, or who have established MRONJ but still require further invasive dental procedures, such as extractions.

Unfortunately, to date there appear to be no reliable investigations for determining the optimal time to proceed with invasive dental procedures in patients taking antiresorptives. Biochemical markers of bone remodeling, such as CTx and NTx—the cleaved ends of strands of type 1 collagen that are present in the blood and can be assessed on serology, and are indicative of bone turnover—but this test has not been shown to be reliable in determining the risk for MRONJ occurring; therefore, preprocedural serum testing is not presently recommended.[258–262]

Established Medication-Related Osteonecrosis of the Jaws

See Table 22-49. Initially conservative measures only should be undertaken, namely observation. If signs of infection are evident, such as active suppuration or the development of facial swelling, in keeping with an abscess or collection with marked regional lymphadenopathy, then provide the patient with antibiotics: amoxicillin in combination with metronidazole, or a macrolide (e.g., roxithromycin) with metronidazole or clindamycin. Clindamycin has the advantage of coverage of both gram-positive streptococci and anaerobic bacterial species and good bone penetrance. Tetracyclines also have excellent bone penetrance, but bacterial resistance is common, limiting these agents' effectiveness. Frequent use of topical antibacterial mouthwashes, such as chlorhexidine-containing mouthwashes, should also be instituted.

Table 22-46 Risk assessment for medication-related osteonecrosis of the jaws (MRONJ).

Patient-Related Factors	Procedural (Surgical) Factors
Amino-bisphosphonate • Potency • Route of administration • Duration • Clinical indication/ usage **Comorbidities** • Age • Diabetes mellitus (poorly controlled) • Immunosuppression	• One or more surgical sites • Contiguous teeth or multiple separate sites • Extent of surgery • Mandibular posterior (molar) teeth • Proximity of tori
Low-risk patient • Low-dose antiresorptive therapy (e.g., osteoporosis) • For no more than 4 years	**Low-risk procedure** • Routine dental extraction • Facilitated by local anesthetic in the dental chair • Up to 3 contiguous teeth
High-risk patient • Patient on long-term/ high-dose antiresorptive therapy related to malignancy: – Solid cancer metastases (breast, prostate) – Multiple myeloma • Concurrent administration of antiangiogenic agents • Patients aged >70 years • Immunosuppression • Recent (within 2 weeks) cytotoxic chemotherapy (with resultant leukopenia) • High-dose corticosteroid administration • Diabetes mellitus (poorly controlled)	**High-risk procedure** • Extensive oral surgery • Extensive number of dental extractions – 5 teeth or more – >1 dental quadrant • Surgical extraction of mandibular molar teeth with risk of impinging lingual cortical plate and/or the mylohyoid ridge • Surgery with risk of impinging of maxillary or mandibular tori

Table 22-47 Risk calculator for medication-related osteonecrosis of the jaws (MRONJ).

Risk	Patient-Related Risk Factors	+	Surgical Procedure Risk Factors	
Minimal	Low-risk patient	+	Low-risk procedure	• Provide dental treatment required • If undertaking extractions/oral surgery, monitor regularly for development of MRONJ
Significant	Low-risk patient	+	High-risk procedure	• **Seek expert guidance** of an oral and maxillofacial surgeon (OMFS) or an oral oncology center with experience in the management of patients with MRONJ
	High-risk patient	+	Low-risk procedure	
Highly significant	High-risk patient	+	High-risk procedure	• **Refer the patient** to an OMFS or an oral oncology center with experience in the management of patients with MRONJ

DISORDERS OF INTERMEDIATE METABOLISM

Inheritable Disorders of Connective Tissue: Skeletal Dysplasia

These include a large group of heterogeneous disorders of collagen adversely affects the proper development of bone and the connective tissues. All have considerable stomatognathic manifestations and complications.

Marfan's Syndrome

Marfan's syndrome (MFS) is one of the most common autosomal dominant inherited disorders of connective tissue, affecting approximately 1 in 5000 of the population worldwide, with some 25% of individuals having developed MFS as a consequence of a new mutation.[263] It causes cardiovascular problems, especially of the heart, with sufferers developing aortic aneurysms and dissection, which can be fatal, mitral valve prolapse, and a typical body habitus consisting of a tall thin body, with long arms, legs, and fingers; scoliosis and problems with their eyes, such as dislocated lenses and retinal detachment.

Investigations

Investigations are centered on the cardiovascular system and the heart:

- Imaging: chest X-ray may be normal, but often there are signs of aortic aneurysm, widening of mediastinum, and pneumothorax is a common complication, as is scoliosis. Computed tomography (CT) is useful to detect aortic dilatation and for monitoring its progression.
- Echocardiography demonstrates mitral valve prolapse and mitral regurgitation in the majority of patients.
- Electrocardiography (ECG): 40% of patients usually have arrhythmia, with premature ventricular tachycardia and atrial arrhythmias.

Table 22-48 Interventions to mitigate the risk of medication-related osteonecrosis of the jaws (MRONJ).

Antibacterial mouthwashes	Pre- (up to 7 days) and postprocedural (up to 7 days), frequent (daily) and after meals
Antibiotics	Pre- (up to 7 days) and postprocedural (up to 7 days)
Antibiotic regimens	
Amoxicillin 500 mg 3 times/day) + metronidazole 400 mg 3 times/day	
Roxithromycin 150 mg twice/day + metronidazole 400 mg 3 times/day	
Clindamycin 300 mg daily (5 days only)	

Management

- Beta blocker therapy slows the rate of dilatation of the aortic root.
- Sedentary activities are encouraged because of the potential adverse effects of exertion on the heart, pain and potential deformities of the joints, and risk of retinal detachment and lens displacement.
- Annual or more frequent echocardiograms to monitor aortic root dilatation. If the aortic root diameter exceeds 5 cm, this is an indication for aortic root replacement surgery.

Stomatognathic Manifestations and Complications

- Hypermobility with dislocation of the temporomandibular joint.

Table 22-49 Stage-specific treatment for medication-related osteonecrosis of the jaws (MRONJ).

Staging of MRONJ		Recommended Treatment/Treatment Provider	
Stage 0	• No clinical evidence of necrotic bone *but* • Nonspecific clinical findings, radiographic changes, and symptoms	• Antibacterial mouth rinse • Quarterly follow-up/review • Patient education and review of indications for continued antiresorptive therapy • Symptomatic treatment with oral antibiotics and antibacterial mouth rinse • Pain control • Debridement to relieve soft tissue irritation and infection control	• By dentist
Stage 1	• Exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection		
Stage 2	• Exposed and necrotic bone or fistulas that probe to bone associated with • Infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage	• Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement or resection for longer-term palliation of infection and pain	• Seek expert guidance of an oral and maxillofacial surgeon (OMFS) or an oral oncology center with experience in the management of patients with MRONJ
Stage 3	• Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one of the following: • Exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) • Resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor		• Refer the patient to an OMFS or an oral oncology center with experience in the management of patients with MRONJ
Regardless of MRONJ stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. Extraction of symptomatic teeth within exposed necrotic bone should also be considered because it is unlikely that extraction will exacerbate the established necrotic process			

Source: Adapted from Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014;72(10):1938–1956.

- High and narrow palatal vault, severe malocclusions with maxillary retrognathy, and micrognathia and marked tooth crowding.
- Sleep apnea.

Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome (EDS) is a highly heterogeneous group of disorders of collagen, with 10 different subtypes recognized associated with varying degrees of skin fragility, skin hyperextensibility, and joint hypermobility.[264]

- *Types I, II, and III*: autosomal dominant inheritance. The biochemical basis to these forms of EDS are yet to be determined.
- *Type IV* (vascular type): autosomal dominant. It involves the arteries, the bowel, and the uterus, as well as the skin. Mutations in the *COL3A1* gene produce abnormalities in the structure, synthesis, and secretion of Type III collagen.
- *Type VI*: inheritance is autosomal recessive.
- *Type VII*: an autosomal dominant disorder in which there is a defect in the conversion of procollagen to collagen; *COL1A1* and *COL1A2* mutations delete the N-proteinase cleavage sites.

There are also other rare forms of EDS.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a heterogeneous group of mainly autosomally dominant inherited disorders.[265] There are four main types of OI (I–IV), with other clinical subtypes also described (V, VI, and VII). The major clinical feature is bone fragility, but other collagen-containing tissues are also involved, such as tendons, the skin, and the eyes, and of course the teeth, as dentinogenesis imperfecta.

- *Type I*: mild bony deformities, blue sclerae, defective dentine, early-onset deafness, hypermobility of joints, and heart valve disorders.
- *Type II*: perinatal death.
- *Type III*: severe bone deformity, blue sclerae.
- *Type IV*: fewer fractures, normal sclerae, normal lifespan.

Treatment involves bisphosphonates (particularly intravenous pamidronate), given from an early age, that is stopped at about 18–21 years with growth arrest, and this has considerably improved bone cortical thickness and skeletal development. Overall prognosis is still variable and dependent on the severity of the disease. To date no cases of ONJ with the use of bisphosphonates in this clinical setting have been reported.

Achondroplasia ("Dwarfism")

Achondroplasia is an autosomal dominant disease, but spontaneous mutations can also occur.[266] The condition is caused by a defect in the fibroblast growth factor receptor-3 gene. The trunk is of normal length, but the limbs are very short and broad due to abnormal endochondral ossification. The vault of the skull is enlarged, the face is small, and the nose bridge is flat. Intelligence is unaffected. Diagnosis is usually made by fetal ultrasound by progressive discordance between the femur length and the head circumference and diameter. Dental malocclusion is common.

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This site covers the broad area of clinical endocrinology, emphasizing clinical endocrine practice, including the most current information on the manifestations of endocrine disease, diagnosis, and treatment.

EndocrineWeb. https://www.endocrineweb.com/

EndocrineWeb, from Remedy Health Media, addresses endocrine disorders, including thyroid disorders, diabetes, Addison's disease, obesity, low testosterone, growth disorders, and more.

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23

Neurologic Diseases

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Neurologic diseases currently impact over 100,000 million Americans, with a similar prevalence world-wide, resulting in years lost to disability and economic impact greater than all other categories of disease.[1] Thus, oral healthcare providers will encounter patients who have a neurologic disease diagnosis. The signs and symptoms, as well as the complications, of these disorders and their treatment can have significant impact on oral health, as well as dental management decisions. This chapter focuses on common neurologic diseases, especially those with greater impact on the orofacial region and/or dental treatment.

CEREBROVASCULAR DISEASE

Epidemiology and Etiology

Cerebrovascular disease refers to disorders of the cerebral blood vessels that cause impaired cerebral circulation. Stroke is an impairment in blood flow to the brain due either to lack of blood flow (ischemia) or hemorrhage, resulting in cell injury and death, causing loss of neurologic function, including loss of motor, sensory, visual, and cognitive function, depending on the location of the injury. Ischemic stroke

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accounts for 85% of all strokes, while cerebral hemorrhage accounts for the remaining 15% and can be further divided into primary intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), subdural hematoma, and epidural hematoma. Transient ischemic attack (TIA) is defined as an acute, short-duration, focal neurologic deficit, typically lasting less than 1 hour, without evidence of infarction on brain imaging.[2]

Stroke is the second most frequent cause of mortality world-wide[3] and the fifth most frequent in the United States,[4] with a prevalence of 2.6% in those over 20 years of age, despite a decrease in the incidence of stroke and stroke mortality over the past 30 years.[5,6] Stroke disproportionately affects the elderly, ethnic minorities, and those of lower educational achievement.[7] In 2013, the total estimated cost of stroke was estimated to be $75.2 billion in the United States alone and these costs will continue to increase due the aging population.[8] Risk for stroke increases with age, with a crude age-adjusted rate per 1000 persons of 0.5 for ages 18–44 years, 2.5 for ages 45–64 years, 6.9 for ages 65–74 years, and 12.4 for ages 75 years and older.[9] Approximately 20% of all strokes are heralded by a TIA; the short-term risk of stroke after TIA is 10% at 90 days, with the highest risk being in the first 24 hours;[10–12] 80% of all strokes following TIA are preventable. Within 1 year of a TIA, 12% of patients die.[13,14]

Impaired cerebral blood flow leading to ischemia and energy failure is the common pathogenic mechanism for stroke. A 50% decrease in blood flow to the brain for as few as 3–4 minutes can result in irreversible brain injury. Following infarction, edema and excessive neurotoxic excitation contribute to further regional tissue injury and death. Ischemic strokes occur through three mechanisms: (1) primary thrombosis of artery or vein; (2) embolism of debris to the central nervous system (CNS) from a proximal site; or (3) systemic hypoperfusion.[15] Thrombotic stroke occurs due to primary occlusion of a blood vessel supplying the CNS. They can be further divided into large vessel or small vessel strokes. Large vessel stroke includes the carotid and vertebral arteries and their major branches. The major cause of primary occlusion of these vessels is atherosclerosis, but dissection, trauma, and vasculitis are other etiologies.[15] Strokes are characterized by extensive downstream ischemia, usually due to a thromboembolic event along the distribution of these vessels. Small vessel or lacunar strokes result from obstruction of the small (<5 mm diameter) penetrating arterioles supplying the basal ganglia, anterior limb of the internal capsule, and (less commonly) deep cerebral white matter. Age and uncontrolled hypertension are the greatest predisposing factors.[16,17] Symptoms usually include unilateral motor or sensory deficit without visual field changes or disturbances of consciousness or language. Embolic strokes result from debris that originates from a source outside the CNS, typically the heart or aorta. Sources include atrial fibrillation, valvular heart disease, ventricular thrombus, heart failure with low cardiac function, patent foramen ovale, infectious endocarditis, hypercoagulability, and aortic atherosclerosis.[18] Strokes may occur due to periods of sustained systemic hypoperfusion resulting in decreased cerebral perfusion in conditions such as cardiac arrythmias or arrest.

Approximately 15% of strokes result from hemorrhagic events leading to infarction, most often related to hypertension, trauma, substance abuse, or aneurysmal rupture.[19] Primary cerebral ICH typically occurs from rupture of small arteries in the subcortical brain tissue, resulting in a hematoma that expands slowly until it is stopped by intracranial pressure. The most common cause is chronic or acute hypertension, but trauma, sympathomimetic drug abuse, amyloid angiopathy (cortical ICH), or vascular malformations are other causes.[20] Headache, nausea, and decreased consciousness typically accompany neurologic deficits coinciding with the location of the ICH. The major cause of SAH is rupture of arterial intracranial aneurysms, but other etiologies include trauma, vascular malformations, and amyloid angiopathy. The aneurysmal rupture releases blood into the cerebral spinal fluid surrounding the brain under arterial pressure, which results in a sudden increase in intracerebral pressure with abrupt changes in consciousness, severe headache, and focal neurologic deficits. The aneurysmal SAH may occasionally be preceded by a subtle bleeding episode with headache only, called a sentinel hemorrhage.[21] Acute interventional treatment with catheter-based or open surgical clipping of aneurysm is often required to prevent rebleeding of the aneurysm, which is frequently fatal.

Clinical Manifestations

The hallmark of stroke is a sudden loss of brain function. The clinical manifestations of stroke vary depending on the size and location of the affected brain region. The most common signs and symptoms include sensory and motor deficits, changes (paresis) in extraocular muscles and eye movements, visual defects, sudden headache, altered mental status, dizziness, nausea, seizures, impaired speech or hearing, and neurocognitive deficits such as impaired memory, reasoning, and concentration.[19,22,23]

Diagnosis

Stroke should be considered whenever a patient experiences the clinical manifestations described above, with the additional goals of ensuring medical stability and identifying the cause of the deficits. Other nonstroke causes for these signs and symptoms, particularly when focal, may include seizures, hypoglycemia, intracranial tumors, trauma, infection,

encephalitis, multiple sclerosis (MS), and prolonged migrainous aura.[22] In addition to a thorough neurologic and cardiovascular examination, anatomic and functional brain imaging is central to the diagnosis of stroke. Time is of the essence for instituting treatment to manage acute stroke due the potential to employ reperfusion strategies, which are now the standard of care in ischemic stroke. Intracranial hemorrhage must be quickly excluded before life-saving thrombolytic therapy can begin. While brain magnetic resonance imaging (MRI) provides greater anatomic detail and sensitivity for detection of early infarction, noncontrast computed tomography (CT) scan is the first line of imaging because of its speed, low cost, and availability (see Figures 23-1 and 23-2).[24–26] Laboratory evaluation of the stroke patient includes compete blood count, comprehensive metabolic panel, urinalysis, coagulation profile, and, when indicated, blood culture, echocardiography, and lumbar puncture.[22]

Treatment

The outcome of stroke and TIAs is significantly affected by the timeliness of treatment. Early intervention is critical to prevention, treatment, and recovery. The critical issue in treatment of ischemic TIA is identification of the cause, as large number of strokes following TIAs or minor strokes are preventable. This evaluation includes laboratory work to exclude anemia, erythro/thrombocytosis, coagulopathies, and hypoglycemia that can mimic stroke; as well as cardiac evaluation with electrocardiogram (ECG), long arrhythmia monitoring, and echocardiogram to exclude atrial fibrillation and other cardiac sources of embolism. Vascular imaging of neck and head with ultrasound, CT, or magnetic resonance angiography (MRA) will identify large vessel sources of stroke such as carotid stenosis. Structural brain imaging with CT or MRI is also necessary to rule out mimics such as brain tumors. TIAs are treated by reduction in hypertension (lifestyle changes such as diet, exercise, smoking cessation, and stress reduction; medical therapy for hypertension; and anticoagulant or antiplatelet medications), or large vessel revascularization.[27] The reader is referred to Chapters 14 and 18 in this textbook that describe more thoroughly anticoagulant and antihypertensive therapies.

The core principle of acute stroke care is recanalization of occluded vessel (reperfusion of ischemic tissue that can be saved, known as the penumbra), optimization of collateral flow, and avoidance of secondary brain injury. Management of acute stroke includes medical therapy to reduce bleeding or thromboembolic occlusion, medical therapy to reduce brain edema and neurotoxicity/nerve injury, and surgical interventions (revascularization, hemorrhage control).[22,23,27]

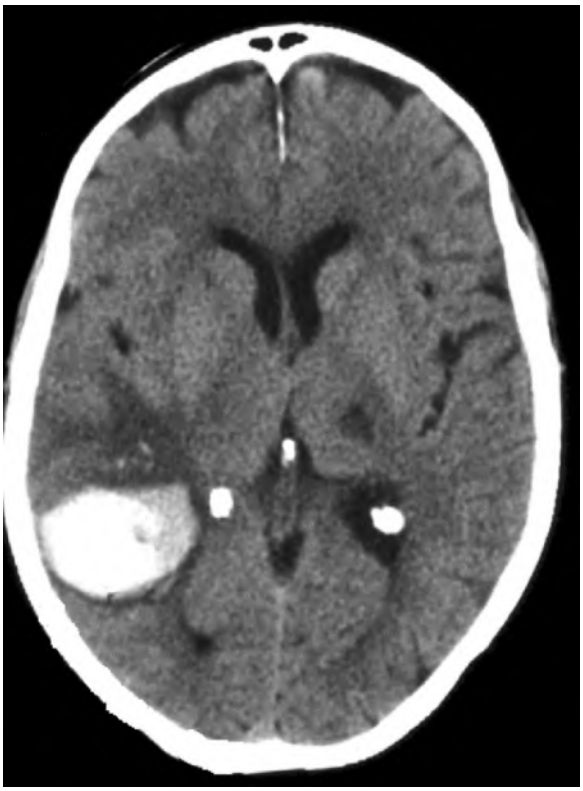

Figure 23-1 Noncontrast head computed tomography demonstrating a left parietal lobe intracerebral hemorrhage.

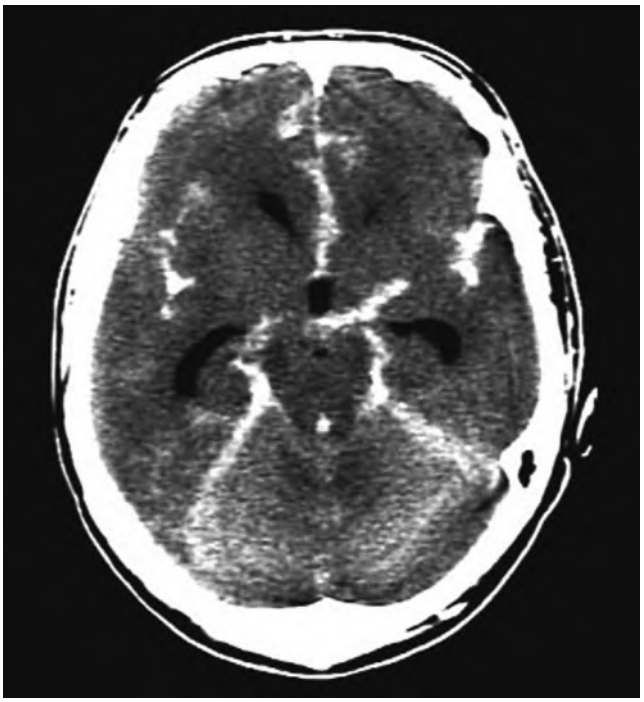

Figure 23-2 Noncontrast head computed tomography demonstrating a diffuse subarachnoid hemorrhage resulting from acute rupture of an anterior cerebral aneurysm.

Once intracranial hemorrhage has been excluded as the source of acute cerebral ischemia, thrombolysis with intravenous tissue plasminogen activator (t-PA) can improve reperfusion, minimize infarction, and reduce disability.[28] The American Heart Association and American Stroke Association advisory statement recommends administration of t-PA from 3 to 4.5 hours after stroke onset.[29,30] Advance perfusion imaging techniques now enable identification of patients who may benefit from treatment of ischemic stroke up to 24 hours after, utilizing catheter-based mechanical thrombectomies for large cerebral occlusions where brain tissue can be still be rescued.[31] No neuroprotectant agent has been found for acute stroke, although extensive investigation continues to develop and test new neuroprotective drugs to minimize neurotoxicity, reduce edema, and correct ischemia, mostly among excitatory amino acid antagonists, free radical scavengers, and cytokine inhibitors.[23,27] Once acute stroke management is complete, etiologic evaluation of ischemic stroke follows a similar pathway to that of TIA and identification of cause is critical to preventing recurrent stroke.

Primary hemorrhagic stroke is typically managed conservatively, although SAH, subdural, and epidural hemorrhages may require surgical intervention aimed at treating the specific mechanism or lesion.

Oral Health Considerations

Following stroke, patients may experience several oral problems (see Table 23-1). These problems can lead to impairment of food intake, poor nutrition, and weight loss due to diminished taste satisfaction, chewing capacity, and swallowing; choking; and gagging.[32–34] Diminished motor function of masticatory and facial muscles may also reduce food clearance from the mouth and teeth and, alone or combined with the presence of diminished dexterity of the arms or hands, may adversely affect oral hygiene and increase the risk for caries and periodontal disease.[34,35] Creative and effective use of adjuvant oral hygiene techniques and devices (oral antimicrobial rinse, oral irrigation, floss holders, etc.) represents an important approach to oral health promotion and disease prevention, supported by frequent recall examination and prophylaxis. Replacement of missing teeth and adequacy of removable and fixed prostheses are essential to effective chewing and diet.

Table 23-1 Orofacial findings associated with stroke.

Extraoral	Intraoral
• Sensory/motor deficits • Weakness in extraocular muscles/ocular movements • Visual defects • Sudden headache • Impaired speech • Muscle paralysis – Facial muscles – Masticatory muscles • Sensory impairment/loss • Calcified carotid artery atheroma on panoramic imaging may be associated with stroke risk	• Sensory impairment/loss – Taste – Touch • Gag reflex impairment • Dysphagia • Poor oral hygiene, due to diminished manual dexterity and/or above factor(s) – Increased risk of periodontal disease – Increased risk of dental caries

Dental management of the patient with a history of TIA or stroke presents several challenges.[32–34,36] Physical limitations secondary to stroke, such as hemiplegia or paralysis, must be assessed to determine practical aspects of delivering oral healthcare. Ambulatory patients may require assistance getting into the dental operatory and transferring to the dental chair.[37] These patients may also require chair modifications, such as commercially available pillow and wedge support devices, to maintain an upright position and comfort during dental treatment.[37] If the patient is in a wheelchair, it must be determined whether transfer to the dental chair is feasible.[37,38] The dental team should be familiar with various transfer techniques to ensure the safety of all those involved in the process.[38] Dental treatment may need to be administered to patients in wheelchairs if they are not able to transfer, which can pose various challenges to oral healthcare providers.[38]

Stroke prevention through routine monitoring of blood pressure is an important step in hypertension risk, detection, and reduction through referral and effective management. Identification of calcified carotid artery atheroma (CCAA) in the neck on panoramic imaging may represent findings associated with stroke risk. CCAA-related calcifications occur in the common carotid artery at the bifurcation of the internal carotid artery and the external carotid artery, located lateral and inferior to the hyoid bone or in either branch (see Figure 23-3).[39] These radiographic findings provide reasonable accuracy in the detection of vessel stenosis, but do not infer the presence of hemodynamically significant disease related to risk of stroke.[39] Patients with identified CCAA on panoramic imaging should be informed of the findings and referred to a medical provider for further evaluation. Prior history of TIA or stroke increases the risk of a future or second stroke, with the highest risk during the first 90 days.[13,14,40,41] A comparative retrospective study[42] examining complications of invasive dental treatment following acute stroke found no evidence to support the historical intuitive guideline to defer elective dental treatment for 6 months following a stroke or for a patient with active TIAs. With optimal medical monitoring and poststroke care, patients can safely undergo invasive dental treatment, with appropriate consideration for stress reduction, medication interactions,

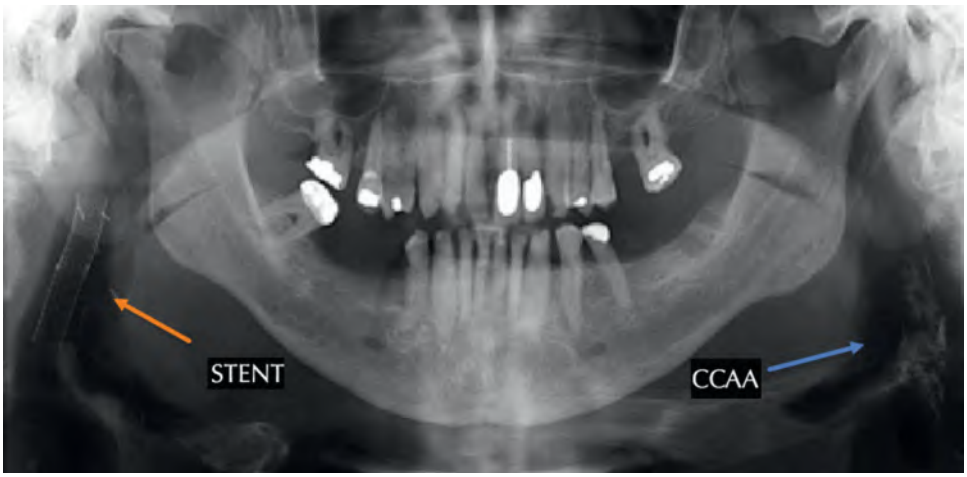

Figure 23-3 Panoramic radiograph. Note the heterogeneous radiopacity with radiolucent voids in a vertical, linear distribution in the area of the carotid arteries on the left side (blue arrow), depicting a calcified carotid artery atheroma (CCAA). A stent is in the right extracranial carotid artery (orange arrow). *Source:* Adeyinka F. Dayo, BDS, MS.

adverse effects, neurologic deficit management, and control of underlying cardio/cerebrovascular risk factors.[42]

Use of antiplatelet and anticoagulant medications is common in patients with a history of stroke and TIAs. This includes oral aspirin, oral antiplatelet drugs, such as ticlopidine and clopidogrel, subcutaneous low molecular weight heparin, and warfarin. These medications, taken in therapeutic dosages, and for warfarin with an international normalized ratio (INR) ≤3.5, rarely require dose modification before routine dental and minor oral surgical treatment.[43–47] Novel anticoagulants, such as factor Xa inhibitors—that is, apixaban (Eliquis), rivaroxaban (Xarelto), edoxaban (Savaysa)—and direct thrombin inhibitors (DTIs)—that is, dabigatran (Pradaxa)—are now commonly used in stroke prevention. Current evidence suggests that these medications should not be discontinued for basic dental treatment and minor invasive dental procedures due to risk of a thromboembolic event.[48] Bleeding complications arising in patients using these medications are typically managed with local measures, including pressure, topical hemostatic agents, and primary closure.[48,49] However, an individualized approach should be considered in all cases of patients taking these medications who undergo invasive dental procedures, accounting for type of procedure, risk of bleeding, and risk of embolism.[50] For additional information regarding management of patients taking antiplatelet and anticoagulant medications, the reader is referred to Chapter 14 in this textbook. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for bleeding, and their long-term use may reduce the protective effect of aspirin. Potential drug interactions of note include, but are not limited to, use of metronidazole, erythromycin, and tetracycline, which may alter the bioavailability of warfarin.

Stress reduction and confidence building for the patient during dental visits are important behavioral goals to make the patient comfortable and minimize anxiety-related elevation in blood pressure. Epinephrine-containing impression cord should not be used.[36,42] Blood pressure should be monitored at every visit and during a visit if long and stressful.

MULTIPLE SCLEROSIS

Epidemiology and Etiology

MS is a disorder of variable clinical features resulting in deficits in cognitive, sensory, motor, and bladder function. It is characterized pathologically by inflammation, axonal injury, and demyelination of the CNS.[51] The typical presentation of MS is of recurrent, focal neurologic deficits that typically improve over several weeks or months, but over time these recurrent episodes evolve into progressive loss of neurologic function. In Western societies, MS is second only to trauma as a cause of neurologic disability in early to middle adulthood.[51] The age at onset is typically between 20 and 31 years; rarely does MS appear clinically before the age of 10 or after age 60.[51,52] MS is more common among women than men (2.3:1 ratio); however, in patients with later onset of MS, the sex ratio tends to be more even.[53] The concept that the prevalence of MS increases with increasing distance from the equator has been disproved.[54] When racial differences are correlated with prevalence rates for MS worldwide, white populations are at greatest risk and both black and Asian populations have a low risk of disease.[52]

The cause of MS is unclear, and the most widely accepted theory is that MS is an inflammatory autoimmune disorder

caused by autoreactive lymphocytes resulting in demyelination of axons in the CNS.[55] Myelin is critical for the propagation of nerve impulses and when it is destroyed in MS, slowing and/or complete block of impulse propagation is manifested by abnormal muscular and neurologic signs and symptoms. While loss of myelin is a hallmark of disease, it appears that neuronal and axonal loss is also important in disease progression.[56,57] This results in brain lesions called plaques. MS lesions or "plaques" vary in size and are characterized by perivenular cuffing with inflammatory mononuclear cells, predominantly macrophages and T cells, which is generally limited to the white matter and periventricular areas of the CNS.[58] Studies have established that demyelinated lesions are also commonly found in the cortical gray matter and meningeal inflammation is prominent in early MS.[59] Plaques may be found in both the brain and the spinal cord, and within the plaques there is variable destruction of myelin and neuronal axons, with preservation of the ground structure.[52] Uniform areas of incomplete myelination are called shadow plaques and may be evident in chronic lesions of MS.[51] Although an inflammatory and autoimmune mechanism is involved in the disease, it is unclear whether this is a primary process or a reaction to an infectious agent or underlying primary neurologic degeneration.[60]

Substantial evidence suggests that autoimmune mechanisms are involved in the pathogenesis of MS.[61] Myelin basic protein (MBP) is an important T-cell antigen that is critical in the development of experimental allergic encephalomyelitis (EAE) in animals. Certain forms of EAE are pathologically similar to MS and activated MBP-reactive T cells are often found in the blood or cerebrospinal fluid (CSF) of MS patients, supporting the autoimmune theory of MS pathogenesis.[61] Increased levels of immunoglobulin G (IgG) and cytokines such as tumor necrosis factor are commonly detected in the CSF of patients with MS.[62] A genetic susceptibility to MS clearly exists, and it is thought that an initial trigger leads to autoimmune mechanisms causing demyelination. The major histocompatibility complex (MHC) on chromosome 6p21 (*HLA-DRB1* gene) has been identified as one genetic determinant for MS.[63] The MHC encodes the genes for the human leukocyte antigen (HLA) system, and susceptibility to MS lies with the class II alleles, particularly the class II haplotypes DR15, DQ6, and Dw2.[52]

Epidemiologic evidence supports the role of an environmental exposure in MS, and two common infectious agents to be implicated in the pathogenesis of this disease are Epstein–Barr virus and human herpesvirus 6.[64] Other viruses that have been implicated in the pathogenesis of MS include measles, mumps, rubella, *Chlamydia pneumoniae*, parainfluenza, vaccinia, and human T-lymphotropic virus 1.[52,64] There does appear to be a relationship between a lack of sun exposure and low serum vitamin D levels with the risk of MS.[65] This finding initially led to the belief that MS was more prevalent in northern latitudes, but more recent data have not supported this finding. There has been no association with vaccination and MS.[66]

Clinical Manifestations

The onset of MS may be insidious or abrupt, and symptoms range from trivial to severe. The clinical course of disease generally extends for decades, but a rare few cases are fatal within a few months of onset. The clinical manifestations of MS depend on the areas of the CNS involved, and frequently affected areas include the optic chiasm, brainstem, cerebellum, and spinal cord.[52,58] The sudden onset of optic neuritis (diminished visual acuity, dimness, or decreased color perception), without any other CNS signs or symptoms, is often considered the first symptom of MS.[67] Other common visual signs in patients with MS include diplopia, blurring, nystagmus, gaze disturbances, and visual field defects.[58]

Limb weakness is characteristic of MS and can manifest as loss of strength or dexterity, fatigue, or gait disturbances. Spasticity associated with painful muscle spasms is often observed in the legs of patients with MS and may interfere with a patient's ability to ambulate. Ataxia may affect the head and neck of MS patients and may result in cerebellar dysarthria (scanning speech). Bladder dysfunction and bowel dysfunction frequently coexist and are present in >90% of MS patients. The most common complaints are urinary urgency and constipation. Sensory symptoms are the most common feature of MS, present in almost 100% of patients, and include numbness, paresthesia, and hyperesthesia in the limbs and thorax.[68] Impairments of vibratory and position sense can also exist. Paroxysmal attacks of pain and muscle spasm can occur, often triggered by specific sensory stimuli. The classic Lhermitte sign is described as sensory shock that runs up and down the spine, which is typically brought on by neck flexion. Fatigue, sleep disorders, depression, cognitive dysfunction, sexual dysfunction, vertigo, and chronic pain are frequently observed in patients with MS.[52,69] Patients with MS often experience exacerbation of neurologic symptoms in response to an elevation of the body's core temperature. This is referred to as Uhthoff's symptom and is generally seen in response to increased physical activity.[52]

Diagnosis

There is no definitive diagnostic test for detection of MS and the disease remains a clinical diagnosis, although MRI demonstrates characteristic abnormalities of MS in >95% of patients.[52] MS plaques are visible as hyperintense focal

areas on T_2-weighted images that are characteristic of chronic lesions. T_1-weighted images reveal hypointense areas that are usually indicative of active MS lesions.[52] Evoked potentials measure CNS electrical potentials, and abnormalities are detected in up to 90% of patients with MS. CSF is often analyzed in patients suspected of having MS and CSF-specific oligoclonal bands are found in 95% of patients, which indicates evidence of chronic autoimmune dysfunction.[70] Recent formulations of the diagnostic criteria for MS begin with an initial clinical presentation typical for an MS attack known as the McDonald criteria.[71] These are relatively complex criteria, but essentially rely on the presence of at least one distinct monophasic clinical episode lasting greater than 24 hours, which is then supported by confirmation of at least two distinct objective correlating findings, either on MRI imaging, evoked potentials, optical imaging, or the presence of CSF-specific oligoclonal bands.[71] These criteria require evidence of more than one distinct lesion occurring at different times (time and space), as the differential diagnosis of a single monophasic attack is broad and includes CNS vascular events, neoplasm, and infections.[71]

Treatment

Therapy for MS can be divided into three categories: (1) treatment of acute attacks; (2) disease-modifying therapies; and (3) symptomatic therapy.[51,52] Corticosteroids are used to manage both initial attacks and acute exacerbations of MS. High-dose corticosteroids have been shown to hasten recovery.[72] Intravenous methylprednisolone is typically administered at a dose of between 500 and 1000 mg/d for 3–5 days to reduce the severity and length of an attack.[58] Over the last two decades, a large number of disease-modifying agents have been approved for the treatment of MS that have shown various benefits to patients by decreasing relapse rate, clinical disease progression, and imaging-based progression.[73–75] The choice of drugs is made based on the progression of disease, side effects, risk of complications, type of administration, patient preference, and response rate.[73–75] Disease-modifying agents include subcutaneously injectable interferon (IFN)-β1a, IFN-β1b (cytokines that modulate immune responsiveness), and glatiramer acetate (mimics MBP).[76] Fingolimod (inhibits T-cell migration), teriflunomide (inhibitor of pyrimidine synthesis), dimethyl fumarate (activates nuclear factor erythroid 2-related factor), cladribine (purine antimetabolite agent), and siponiod (sphingosine 1-phosphate receptor modulator) are oral agents approved for the treatment of MS. Mitoxantrone (Novantrone) is a chemotherapeutic agent administered intravenously that is effective in reducing neurologic disability and frequency of clinical relapses in patients with MS.[77] Natalizumab (binds α-4 integrin), ocrelizumab (anti-CD 20), and alemtuzumab (binds CD52 surface proteins) are monoclonal antibodies that are given intravenously. Common agents employed for the management of specific MS symptoms include anticonvulsants, benzodiazepines, tricyclic antidepressants, smooth muscle relaxants, anticholinergic agents, and various pain medications.[51,78]

The prognosis for MS is variable. It is difficult to predict the course of MS in an individual patient; however, earlier age of onset, female sex, fewer number of baseline brain MRI lesions at time of clinical diagnosis, and less disability 5 years after onset are generally considered favorable prognostic signs.[52] Most patients with MS experience progressive neurologic disability and gait disturbances and/or difficulty with ambulation, as these are common clinical sequelae for patients with this disease.[79] Mortality as a direct consequence of MS is uncommon, and death usually results from a complication of the disease, such as pneumonia.[80]

Oral Health Considerations

Individuals may present to the oral healthcare provider with signs and symptoms of MS. Trigeminal neuralgia (TGN), which is characterized by electric shock–like pain, may be an initial manifestation of MS in up to 5% of cases.[51,81–84] MS-related TGN is similar to idiopathic TGN, and the reader is referred to Chapter 11 in this textbook that describes idiopathic TGN more thoroughly. Features of MS-related TGN include **the** possible absence of trigger zones and continuous pain with lower intensity.[82] Glossopharyngeal neuralgia (GN) affects the sensory distribution of the glossopharyngeal or vagus nerve and clinically presents as a severe, stabbing pain in the region of the ear, base of the tongue, angle of the mandible, and/or tonsillar fossa. Prevalence of GN has been reported in 0.5% of patients with MS.[85] Several medications can be used to manage TGN and GN and the reader is referred to Chapter 11 that describes these medications and alternative therapies.

Patients with MS may also demonstrate neuropathy of the maxillary (V2) and mandibular branches (V3) of the trigeminal nerve, which may include burning, tingling, and/or reduced sensation.[85] Neuropathy of the mental nerve can cause numbness of the lower lip and chin.[83,84] Myokymia may be seen in patients with MS and consists of rapid, flickering contractions of the facial musculature secondary to MS lesions affecting the facial nerve.[86] Facial weakness and paralysis may also be evident in MS patients. Dysarthria that results in a scanning speech pattern is often seen in patients with MS. Other orofacial pain conditions that may be present at higher frequency in patients with MS compared to

the general population include temporomandibular disorder and headache.[87,88] If MS is suspected, oral healthcare professionals should carefully evaluate cranial nerve function. If cranial nerve abnormalities are detected upon examination, the individual should be referred to a neurologist for further evaluation. In addition, MS patients may experience increased frequency and severity of oral disease, such as xerostomia and gingival bleeding, compared to healthy individuals.[89]

It is recommended to avoid elective dental treatment in MS patients during acute exacerbations of the disease, due to limited mobility and possible airway compromise.[90,91] Emergency dental treatment may be considered in patients experiencing an acute flare of MS in consultation with the patient's physician to ensure medical stability.[37] MS patients with significant dysfunction and/or who are medically unstable may require dental treatment in an operating room under general anesthesia due to the inability to undergo treatment in an outpatient setting. In addition, electric toothbrushes and oral hygiene products with larger handles may be necessary for completing oral hygiene in patients with significant motor impairment. It is critical for oral healthcare providers to maintain accurate medication inventories for patients with MS and to be aware of possible interactions of these medications with those commonly used and prescribed in dentistry, as well as oral and systemic side effects of these agents. MS patients managed with immunosuppressants may place those individuals at increased risk for opportunistic and community-acquired infections, emphasizing the need for optimal oral hygiene (see Table 23-2).[90]

Table 23-2 Orofacial findings associated with multiple sclerosis.

Extraoral	Intraoral
• Ocular symptoms – Diminished visual acuity – Diplopia – Nystagmus • Neuropathic pain – Trigeminal neuralgia – Glossopharyngeal neuralgia – Peripheral neuropathy • Myokymia • Facial weakness/paralysis • Ataxia • Dysarthria • Headache • Temporomandibular disorder • Vertigo	• Xerostomia – Increased risk of periodontal disease – Increased risk of dental caries – Increased risk of oral candidiasis • Increased risk of opportunistic infections (bacterial/viral/fungal) due to immunosuppressants

ALZHEIMER'S DISEASE

Epidemiology and Etiology

Dementia is defined as an acquired deterioration in cognitive abilities that impairs the successful performance of activities of daily living.[92] Memory is the most common cognitive ability lost with dementia; other mental faculties affected include problem-solving skills, judgment, visuospatial ability, and language. The global prevalence of dementia is estimated at 24 million and has been predicted to quadruple by the year 2050.[93,94] Alzheimer's disease (AD) is a disease of older age and is rare except for those with inherited forms prior to age 65. The disease doubles in prevalence every 5 years past the age of 65. The clinical features of AD were first described in 1906 by Alois Alzheimer;[95] more than a century later, the molecular basis of AD has been greatly elucidated, and enhanced diagnostic modalities have enabled clinicians to visualize neurologic changes secondary to AD.

The neuropathology of AD is characterized by neuritic plaques (extracellular beta-amyloid deposition) and neurofibrillary tangles (intracellular hypophosphorylated tau protein), coupled with a degeneration of neurons and synapses. In addition, cerebral amyloid angiopathy, inclusion of alpha synuclein (Lewy bodies and vascular brain injury), and loss of hippocampal pyramidal cells are commonly seen.[96–98] The most severe pathology associated with AD is atrophy, usually found in the medial temporal lobe structures and cortical areas of the brain.[99] While the exact pathogenesis of AD is unclear, an imbalance between the production and clearance of Aβ in the brain, termed the amyloid cascade hypothesis, is thought to be the disease-initiating event that ultimately leads to neuronal degeneration and dementia.[99] Studies have suggested a more complex pathophysiology regarding Aβ processing than previously thought.[93,100] Amyloid deposited around meningeal and cerebral vessels, termed amyloid angiopathy, may lead to cerebral lobar hemorrhages. The pathogenesis also involves tau, a microtubule-associated protein. Neurofibrillary tangles are twisted neurofilaments in neuronal cytoplasm that represent abnormally phosphorylated tau protein and appear as paired helical filaments by electron microscopy.[92] Tau protein is thought to aid in assembly and stabilization of the microtubules that convey cell organelles and glycoproteins through the neuron. In AD, tau becomes hyperphosphorylated and leads to sequestration of normal tau and other microtubule-associated proteins, thus impairing axonal transport and normal neuronal function. In addition, tau becomes prone to aggregation into insoluble fibrils that develop into tangles, further compromising neuronal function.[99]

The genetic basis of AD has been studied extensively, and specific genetic mutations have been implicated in both the familial and sporadic forms of the disease. Familial AD is an autosomal dominant disorder with onset typically prior to age 65 years. Mutations in the *APP* gene on chromosome 21 were the first to be identified as the cause of familial AD; subsequent investigations have demonstrated mutations in the presenilin 1 and 2 genes (*PSEN1* and *PSEN2*, respectively) that account for the majority of familial AD cases.[101,102] The most commonly reported gene associated with sporadic AD is apo-lipoprotein E (*APOE*) on chromosome 19, which is involved in cholesterol transport.[92,99,101] The e4 allele accounts for most of the genetic risk in sporadic AD.[99] Mutations of the sortilin-related receptor (*SORL1*) have been associated with both late-onset AD and sporadic AD.[93,103]

Clinical Manifestations

AD is a slowly progressive disorder represented by a continuum of clinical characteristics. It is a disease of the elderly; it is unusual to present prior to age of 60 unless a familial form is present. Updated clinical criteria recognize three stages of AD: (1) preclinical AD; (2) mild cognitive impairment due to AD; and (3) dementia due to AD.[104] Preclinical AD occurs before changes in cognition and everyday activities are observed and is primarily used for research purposes.[105] Cognitive impairment due to AD is characterized by mild changes in memory and other cognitive abilities that are noticeable to patients and families, but are not sufficient to interfere with day-to-day activities. Dementia due to AD is characterized by changes in two or more aspects of cognition and behavior that interfere with the ability to function in everyday life.[104] The initial signs of AD involve retrograde amnesia from progressive declines in episodic memory.[106] This may initially go unrecognized or be viewed as forgetfulness; however, as the disease progresses, memory loss begins to affect the performance of daily activities, including following instructions, driving, and normal decision-making. As AD progresses, the individual is often unable to work, gets confused and lost easily, and may require daily supervision. Language impairment, loss of abstract reasoning skills, and visuospatial deficits begin to interfere with simple, routine tasks. Advanced AD is characterized by loss of cognitive abilities, agitation, delusions, and psychotic behavior.[92] Patients may develop muscle rigidity associated with gait disturbances and tend to wander aimlessly. In end-stage AD, patients frequently become rigid, mute, incontinent, and bedridden.[99] Help is needed for basic functions, such as eating and dressing, and patients may experience generalized seizure activity. Death typically results from malnutrition, heart disease, pulmonary emboli, or secondary infections.[92]

Diagnosis

The formal diagnosis of AD requires histologic confirmation, which typical occurs post mortem, although clinical criteria exist. The clinical diagnosis should be entertained in any adult with onset of insidious and progressive memory decline and impairment of at least one other cognitive function in the absence of another confounding medical or neurologic disorder. Probable AD is defined by the decline or loss of the ability to function at work or at one's usual activities, onset of delirium or major psychiatric disorder, and cognitive impairment on objective bedside memory tests (includes the following domains: reasoning, judgment, ability to acquire and remember new information, language function, behavior, visuo-spatial abilities).[107] These bedside scales include the Mini-Mental Status Exam, Montreal Cognitive Assessment, and the standardized neurologic exam of the American Academy of Neurology. Possible AD refers to those who meet the criteria for dementia, but have another illness that may contribute to the neurologic status, such as hypothyroidism or cerebrovascular disease.[107]

Diagnostic analysis of CSF may show a slight increase in tau protein and a lower concentration of Aβ peptide compared with healthy individuals or those with other dementias. Electroencephalographic (EEG) studies typically demonstrate generalized slowing without focal features. Neuroimaging is important in evaluating suspected AD to exclude alternative causes of dementia, such as cerebrovascular disease, subdural hematoma, or brain tumor. MRI and CT typically reveal dilatation of the lateral ventricles and widening of the cortical sulci, particularly in the temporal regions.[101] Volumetric MRI uniformly demonstrates shrinkage in vulnerable brain regions, especially the entorhinal cortex and hippocampus.[101] Positron emission tomography (PET) can identify areas of hypometabolism in the temporal, parietal, and posterior cingulated cortices and has a high ability to differentiate AD from other dementias.[99] Slowly progressive decline in memory and orientation, normal results on laboratory tests, and neuroimaging showing only diffuse or posteriorly predominant cortical and hippocampal atrophy are highly suggestive of AD.[92]

Treatment

There is no cure for AD, and therapy is aimed at slowing the progression of the disease. Cholinesterase inhibitors are approved by the US Food and Drug Administration (FDA) to treat mild to moderate cases of AD and are considered the standard of care.[108,109] They provide a proven, modest symptomatic benefit for patients with AD. The three types of cholinesterase inhibitors currently available are donepezil, rivastigmine, and galantamine; these medications decrease

the hydrolysis of acetylcholine released from the presynaptic neuron into the synaptic cleft by inhibiting acetylcholinesterase, resulting in stimulation of the cholinergic receptor.[101] Common side effects of these medications include nausea, vomiting, diarrhea, weight loss, bradycardia, and syncope.[108] Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist believed to protect neurons from glutamate-mediated excitotoxicity, is used for treatment of moderate to severe AD.[108] Studies have demonstrated greater cognitive and functional improvement when memantine is used in conjunction with cholinesterase inhibitors compared to monotherapy.[110] Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are commonly used to treat depression, which is often seen in the mild to moderate stages of AD.[99,111] Antipsychotic agents are used for those patients who display aggressive behavior and psychosis, especially in the later stages of the disease. Other agents that have been reported to be of clinical value in the treatment of AD include antioxidants, such as selegiline and α-tocopherol (vitamin E).[99,108,110] Currently, disease-modifying agents aimed at reducing Aβ production, preventing Aβ aggregation, promoting Aβ clearance, and targeting tau phosphorylation and assembly are being investigated for future clinical use in the treatment of AD.[110,112,113] Caregivers of patients with AD must be involved in the overall treatment, since they are responsible for maintaining the patient's general health and ensuring a meaningful quality of life; it is often necessary to provide educational, emotional, and psychological support to these individuals, as the task for caring for patients with AD can be extremely challenging.

Oral Health Considerations

Oral and dental health is a major issue in patients with AD, because significant deterioration in oral health status is commonly observed with advancing disease.[114,115] Patients with AD appear to be at higher risk for developing coronal and root caries, periodontal infections, temporomandibular joint abnormalities, and orofacial pain compared to healthy subjects.[116,117] Oral healthcare providers should be able to recognize symptoms of AD and refer patients for further medical evaluation, if necessary. Patients with AD can become frustrated, irritable, and possibly combative when confronted with unfamiliar circumstances or with questions, instructions, or information that they do not understand.[114] The presence of a caregiver may be beneficial, as they can verify patient information, interpret patient behavior, and alleviate anxiety.[116] The oral healthcare provider must approach AD patients with empathy and explain all procedures and instructions clearly, since communication is essential in the management of dental patients with AD.[118,119]

Patients with AD should be placed on an aggressive preventive dentistry program, including a 3-month recall, oral hygiene education, and prosthesis adjustment, as poor oral health status can have a negative impact on the systemic health and wellbeing of patients with AD.[120,121] Specially adapted products, such as modified toothbrushes and foam mouth props, may be useful for oral hygiene and provision of dental care in patients with AD.[116] It is recommended to complete restoration of oral healthcare function in the earliest stages of AD, because the patient's ability to cooperate diminishes as cognitive function declines.[114] Time-consuming and complex dental treatment should be avoided in persons with severe AD.[122]

Medications used to treat AD can cause a variety of orofacial reactions and potentially interact with drugs commonly used in dentistry. Cholinesterase inhibitors may cause sialorrhea, whereas antidepressants and antipsychotics are often associated with xerostomia. In addition, dysgeusia and stomatitis have been reported with use of antipsychotic agents.[114] Antipsychotic medications also increase the risk of involuntary jaw movements, which can lead to oral hard and/or soft tissue injuries (see Table 23-3).[37] Antimicrobials, such as clarithromycin, erythromycin, and ketoconazole, may significantly impair the metabolism of galantamine, resulting in central or peripheral cholinergic effects.[114] Anticholinesterases may increase the possibility of gastrointestinal irritation and bleeding when used concomitantly with NSAIDs.[114] Local anesthetics with adrenergic vasoconstrictors should be used with caution in AD patients taking tricyclic antidepressants, due to the potential risk of cardiovascular effects, such as hypertensive events or dysrhythmias.[110]

Table 23-3 Orofacial findings associated with alzheimer's disease.

Extraoral	Intraoral

• Orofacial pain
• Temporomandibular disorder
• Muscle rigidity
• Medication-induced reactions
  • Involuntary jaw movements—antipsychotics
	• Deterioration of oral health in advancing disease
	  – Increased risk of periodontal disease
	  – Increased risk of dental caries
	• Medication-induced reactions/side effects
	  – Sialorrhea—cholinesterase inhibitors
	  – Xerostomia—antidepressants, antipsychotics
	  ○ Increased risk of oral candidiasis
	  • Dysgeusia—antipsychotics
	  • Stomatitis—antipsychotics
	  • Hard/soft tissue injuries—antipsychotics

SEIZURE DISORDERS

Epidemiology and Etiology

An epileptic seizure is a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain."[123] The term *epilepsy* is a neurologic disease characterized by either an individual who has a known epileptic syndrome, or evidence that the patient's brain demonstrates a pathologic tendency to have recurrent seizures following the occurrence of at least one unprovoked seizure.[124] Epilepsy is considered resolved if a patient has been seizure free for more than 10 years while not using antiepileptic drugs (AED) for the last 5 years of this period.[125] The incidence of epilepsy in developed countries is approximately 50 per 100,000 people per year (approximately 1% of the US population), affecting over 75 million people.[126] Of these patients, 75% are untreated.[126]

The International League Against Epilepsy (ILAE) originally developed a classification system of epilepsies and epileptic syndromes based on the clinical features of seizure activity and associated EEG changes.[127] Subsequent revisions of the classification scheme have taken into consideration several other factors in classifying epileptic syndromes, such as focal or generalized onset, genetics, age at onset, and pathophysiologic mechanisms of disease.[128] Focal, generalized, and unknown seizures are currently the three major categories of seizure activity used in clinical practice.[128]

Onset of seizure activity may occur at any point throughout an individual's life, and etiology usually varies according to patient age. The most common seizures arising in late infancy and early childhood are febrile seizures without evidence of associated CNS infection; these generally occur between 3 months and 5 years of age and have a peak incidence between 18 and 24 months.[129,130] Isolated, nonrecurrent, generalized seizures among adults are caused by multiple etiologies, including metabolic disturbances, toxins, drug effects, hypotension, hypoglycemia, hyponatremia, uremia, hepatic encephalopathy, drug overdoses, and drug withdrawal.[131,132] Cerebrovascular disease may account for approximately 50% of new cases of epilepsy in patients older than 65.[133] Other etiologies for epilepsy include degenerative CNS disease, developmental disabilities, and familial/genetic factors.[131,133] Epilepsy occurs more frequently in individuals who have neurologic-based disabilities, such as cerebral palsy and autism.[134,135]

Six etiologic categories now exist for seizures: (1) structural, (2) genetic, (3) infectious, (4) metabolic, (5) immune, and (6) unknown; prior terms, such as symptomatic and cryptogenic, are no longer used.[124] Structural implies a structural lesion on neuroimaging in combination with EEG data, suggesting that the lesion is the cause of the seizure. Causes include stroke, trauma, or tumor. Genetic implies the existence of known or presumed genetic mutation(s) where seizures are a known complication of the genetic disorder that is the result of the mutation(s). This etiology includes some of the well-known genetic epilepsy syndromes, such as juvenile myoclonic epilepsy, or may include an unknown mutation but obvious familial inheritance pattern.[124] Infectious etiologies include neurocysticercosis, human immunodeficiency virus (HIV), cytomegalovirus (CMV), cerebral toxoplasmosis, and prior meningitis or encephalitis.[124] Metabolic etiologies are due to a metabolic disorder, with the core tenet being that a change in diet or supplementation may affect the disease course.[124] An immune cause of seizures is defined either by a causal autoimmune disorder such as paraneoplastic syndrome or by an immune therapy used to treat the immunologic disease.[124]

Clinical Manifestations

Classification begins with whether the seizure is focal (occurs in one hemisphere) or generalized (arises at some point in the brain and rapidly engages the entire brain network).[124] If the seizure onset is unclear, the seizure is defined as unknown.[124] The terms "partial" and "partial tonic–clonic" are no longer used.

Focal Seizures

Focal seizures, by definition, originate from the neural network in one hemisphere, and are further divided by whether the patient has a change in awareness. Awareness is defined by whether the patient knows what is going on around them during the seizure. The focal seizure is then further classified by the first, most prominent motor or nonmotor feature, which aids in the localization of the seizure onset in the neural network. Motor features include automatisms, atonic, clonic, spasms, myoclonus, tonic movements, and nonmotor features, including autonomic, behavioral arrest, emotional, cognitive, and sensory symptoms.[124] Motor automatisms are unconscious movements of the body and include licking of lips, rubbing of hands, picking at objects, walking, or undressing. Atonic motor events are a loss of motor tone and strength in a limb or other body part. Clonus indicates rhythmic movement of a body part, whereas myoclonus is irregular jerking of a limb or face on one side of the body. Spasm is a sudden flexion or bending of the trunk or extension of a limb for a few seconds. The final finding used in the classification of a focal seizure is whether the seizure evolves into a bilateral tonic–clonic seizure.

Generalized Seizures

Generalized seizures, by definition, arise at some point in the brain and rapidly involve the entire brain network. A change in consciousness is involved in all seizures, so they are first defined by the presence of motor or nonmotor

symptoms. Motor findings are subdivided similarly to those found in the focal seizures subtype, with the addition of a tonic–clonic subtype.[124] The typical tonic–clonic generalized seizure lasts less than 3 minutes. It characteristically begins with loss of consciousness, followed by the entire musculature contracting forcibly (tonic phase).[136] Contraction of the muscles of the larynx and forced expiration can produce a loud moan, often termed an "epileptic cry." Patients often become cyanotic during the tonic phase secondary to forceful closing of the mouth accompanied by forced continued expiration. The clonic phase follows the tonic phase, with the entire body rhythmically jerking for a period that usually lasts no longer than 1 minute. In the postictal phase, the patient may be unresponsive for minutes to hours, awakening gradually, often with no memory of the event.[136] Physical injury from falling or muscular convulsions and evidence of bladder emptying, tongue biting, or aspiration pneumonia are frequently experienced during the postictal phase.[129] Patients gradually regain consciousness and typically complain of fatigue and headache after a tonic–clonic seizure. Generalized tonic–clonic seizures may not abate spontaneously or may recur without the patient regaining consciousness. This condition is referred to as generalized convulsive status epilepticus and is considered a medical emergency due to the number of serious sequelae of this condition, including bodily injury, cardiorespiratory dysfunction, metabolic derangements, and irreversible neurologic damage.[137]

Generalized nonmotor seizures or absence seizures include typical, atypical, myoclonic, or eyelid myoclonic.[124] Absence seizures are characterized by seconds of unconsciousness with no loss of body tone, sometimes with eye fluttering, head nodding, or automatisms.[136] Patients suffering from absence seizures appear to be "daydreaming," although they often have the ability to continue performing a previously started motor or intellectual activity after cessation of the seizure activity. There is generally no postictal confusion in patients experiencing absence seizures. Absence seizures generally begin in childhood and up to 90% of patients with these seizures have a spontaneous remission before adulthood.[138]

Unknown Seizures

The unknown seizure type exists for seizures where the onset, either focal or generalized, is not known. They are further classified by the presence of motor or nonmotor features. If this information is not known, they remain unknown and are considered unclassified.[124]

Diagnosis

The primary goals of evaluating a patient with new onset of seizure activity are to (1) establish whether the reported episode was a true seizure; (2) determine the cause of the seizure by identifying possible risk factors and precipitating events; and (3) determine the need for AED therapy in addition to treatment of any underlying illness.[129] An in-depth history and physical examination are critical, as the diagnosis of a seizure may be based on clinical findings only. A complete neurologic examination is required for all patients with suspected seizure activity, including testing of cranial nerve function, assessment of mental status, and testing of motor function. Blood studies, such as a complete blood count, electrolytes, glucose, magnesium, calcium, paraneoplastic titers, and genetic testing, are performed routinely to identify metabolic, genetic, and immune-mediated causes of seizure activity.[139] Other useful screening tests include toxin screens to identify seizure activity due to drugs, and lumbar puncture to rule out any infectious immune (paraneoplastic) etiologies.

All patients with a possible seizure disorder are referred for brain imaging to determine underlying CNS structural abnormality and/or pathology. MRI is the diagnostic modality of choice for the detection of hippocampal sclerosis, malformations of cortical development, vascular malformations, tumors, and acquired cortical damage, all of which are common etiologies for structural seizure disorders.[140,141] Functional imaging, including nuclear medicine studies and functional MRI (fMRI), may help to localize focal structural abnormalities and aid in surgical planning.[141] CT is valuable for investigating intracranial calcification, skull fractures, and suspected CNS infection, which may not be as readily apparent on an MRI.[140]

An EEG is an important diagnostic tool for patients with suspected seizures and is helpful for classifying seizures, identifying the etiology of the seizure, and potentially aiding in the choice of AED treatment.[132,138] The EEG measures the electrical activity of the brain, interictal epileptiform discharges, and the presence of abnormal, repetitive, rhythmic electrical activity, having an abrupt onset and termination during the clinical event, defined as electrographic seizures, which confirm the diagnosis (see Figure 23-4).[129]

Treatment

Pharmacologic therapy is considered the mainstay of epilepsy treatment and the goal is to choose an AED that is most appropriate for the specific type of seizure activity, and to administer it in the proper dose to achieve control of seizure activity with minimal side effects.[130,142]

Multiple AEDs are currently available for the treatment of epilepsy and selection of a particular agent is often influenced by several factors, including medical comorbidities, side effects, drug availability, and cost.[138,142] Topiramate, phenobarbital, carbamazepine, and phenytoin are indicated for the treatment of focal seizures and generalized motor seizures.[131] Topiramate may cause bone marrow suppression

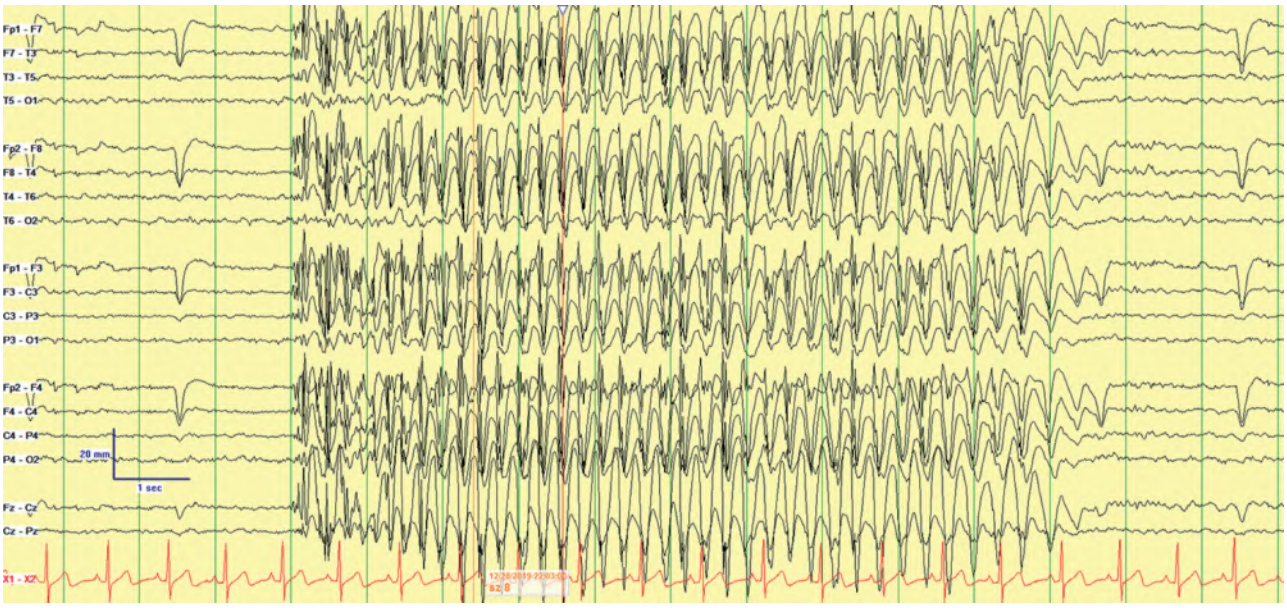

Figure 23-4 Electroencephalogram (EEG). EEG recording in the standard 10-20 system (double banana montage) of generalized 3 Hz spike-and-wave generalized myoclonic 10 second seizure. The patient had brief loss of consciousness and myoclonus of the extremities during the electrographic event.

and hepatotoxicity, which requires laboratory monitoring. Topiramate has significant cognitive effects at higher doses, but is used frequently in treatment of headache in addition to its use in treatment of seizures. Phenobarbital is a widely used drug world-wide because of its cost and long duration of action. Its main adverse side effect is sedation and effect on cognition. Phenytoin has a long half-life and is dosed less frequently than carbamazepine and lamotrigine, leading to increased patient compliance. Phenytoin is associated with gingival overgrowth, hirsutism, and coarsening of facial features. Carbamazepine can cause hepatotoxicity, leukopenia, and aplastic anemia. Next-generation carbamazepine-like drugs (eslicarbazepine and oxcarbazepine) have similar indications and side effects to carbamazepine, but have improved hepatic metabolism and drug interactions.[143]

Lamotrigine and valproic acid (VA) are indicated for treatment of focal and generalized seizures, including generalized absence seizures. Lamotrigine's major associated side effect is rash, with the potential of Stevens–Johnson syndrome. VA should be avoided in patients with preexisting bone marrow or liver disease. Levetiracetam, although not approved by the FDA for monotherapy for focal and generalized seizures, is nonetheless used clinically as a first-line drug for the treatment of these disorders in the United States due to its efficacy and safety profile.[144]

Ethosuximide has been shown to be particularly effective for the treatment of absence seizures. Perampanel, a novel AED influencing glutamatergic postsynaptic transmission, has been introduced as an adjunctive treatment for refractory focal seizures.[145] Clobazam and clonazepam are benzodiazepines that have long durations of action allowing once-a-day dosing, are indicated in the treatment of generalized seizures, and are used as adjunctive therapy. Sedation is the most significant side effect associated with their use.[144] Pregabalin and gabapentin are narrow-spectrum agents for the treatment of focal seizures, but the drug is used for the treatment of multiple other neurologic and pain disorders. It is typically well tolerated, with its major side effects being fatigue and sedation. Tiagabine is a relatively well-tolerated AED for adjunctive therapy for focal seizures. Zonisamide is a long-acting AED approved for the treatment of generalized seizures and as an adjunct for focal seizures. Zonisamide's major side effects are weight loss and sedation. Lacosamide has limited indication against focal seizure, with the major side effect being a dose-dependent PR interval prolongation.[144]

Discontinuation of pharmacologic therapy is considered when seizure control has been achieved. The following patient characteristics yield the greatest chance of remaining seizure free after discontinuation of drug therapy: (1) complete medical control of seizures for 1–5 years; (2) single seizure type; (3) normal neurologic examination, including intelligence; and (4) a normal EEG.[129] Many patients are often withdrawn successfully from medication after an interval of 2–4 years without seizures who meet the above criteria and who clearly understand the risks and benefits.[142]

In patients with refractory epilepsy, it often becomes necessary to use a combination of AEDs to attempt seizure control. Patients may use three or more drugs to successfully

treat refractory epilepsy; however, up to 30% of patients are resistant to all medical therapies.[145] Surgical procedures may be indicated for these patients, including limited removal of the hippocampus and amygdala, temporal lobectomy, or hemispherectomy.[129] Those patients who are not candidates for resective brain surgery may benefit from vagus nerve stimulation (VNS), which involves placement of an electrode on the left vagus nerve that receives intermittent electrical pulses from an implanted generator. Stimulation of vagal nuclei has been shown to lead to widespread activation of cortical and subcortical pathways and an associated increased seizure threshold.[146] Deep brain stimulation (DBS) and responsive neurostimulation systems (RNS) are also used for treatment of refractory epilepsy.[147] Gene therapy is currently being investigated as an alternative treatment modality for epilepsy refractory to standard therapies.[148,149]

Oral Health Considerations

Patients with seizure disorders are routinely evaluated and managed in the dental setting. This patient population has a higher rate of physical injuries, including dental and facial trauma, compared to healthy subjects.[150–152] In addition, patients with epilepsy demonstrate poor oral health and dental status compared to age-matched healthy subjects in long-term studies (see Figures 23-5 and 23-6).[153,154] A complete evaluation of a patient's seizure disorder is necessary prior to initiation of any dental treatment to determine the stability of the condition and an appropriate venue for treatment. Important features for the clinician to assess include the type of seizures, etiology of seizures, frequency of seizures, known triggers of seizure activity, presence of aura prior to seizure activity, and history of injuries related to seizure activity. If a patient demonstrates signs of poorly or uncontrolled seizure disorder, consultation with the patient's physician and/or neurologist is recommended.[155] Patients with poorly or uncontrolled seizure disorder may not be suited for outpatient dental care and should be referred to a hospital setting for routine dental care.[156] Patients with implanted VNSs do not require antibiotic prophylaxis prior to invasive dental procedures.[157] It is recommended not to use dental devices utilizing diathermy for these patients as it may interfere with VNS function.[158]

While providing dental care, it is prudent to avoid any known triggers of the patient's seizure activity. Patients with poorly controlled seizures often present with signs of intraoral trauma, such as fractured teeth and/or soft tissue lacerations.[157] Patients with poorly controlled disease or stress-induced seizures may require sedative medications prior to treatment; this should be determined in consulta-

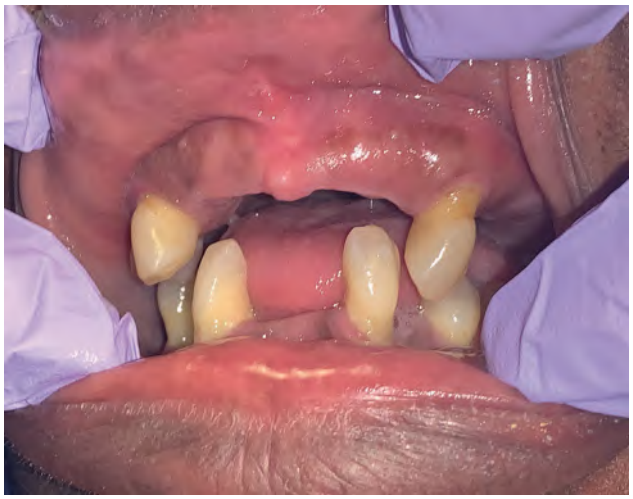

Figure 23-5 Poor dentition in a patient with tonic–clonic generalized seizures.

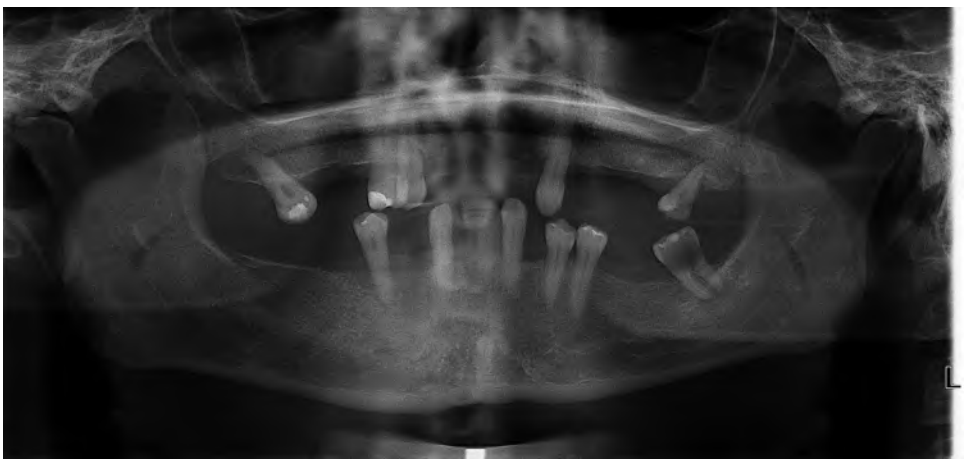

Figure 23-6 Panoramic radiograph demonstrating poor dentition in a patient with tonic–clonic generalized seizures. Note fractured molar in left posterior maxilla and grossly decayed molar in left posterior mandible.

tion with the patient's physician.[157] To minimize risk of injury and aspiration during dental treatment, use of dental floss–secured mouth props (which are easily retrievable) and a rubber dam is recommended.[37,49] Placement of metal fixed prostheses is recommended rather than removable prostheses to decrease the risk of displacement and aspiration during seizure activity.[159]

AEDs can induce significant blood dyscrasias that can affect the provision of dental care. Several AEDs, including phenytoin, carbamazepine, and VA, can cause bone marrow suppression, leukopenia, thrombocytopenia, and secondary platelet dysfunction, possibly resulting in an increased incidence of microbial infection, delayed healing, and both gingival and postoperative bleeding.[142] Patients taking these medications may require laboratory evaluation prior to dental treatment, including a complete blood count with differential, to assess white blood cell and platelet counts, and coagulation studies to assess clotting ability. Patients on long-term carbamazepine should have serum blood levels evaluated prior to initiating dental treatment, as insufficient doses may result in inadequate seizure control and excessive doses have been associated with hepatotoxicity.[142] Aspirin and NSAIDs should be avoided for postoperative pain control in patients taking VA as they can enhance the possibility of increased bleeding.[160] There are no contraindications to local anesthetics, when used in appropriate amounts, in patients with seizure disorders.[90]

Gingival overgrowth is a significant oral complication among seizure disorder patients taking AEDs, most notably phenytoin.[161] The prevalence rate of gingival overgrowth varies and has been reported in up to 50% of individuals taking phenytoin.[161] The anterior labial surfaces of the maxillary and mandibular gingivae are most commonly affected and may be seen within 2–18 months after starting the medication (see Figure 23-7). Historically, this condition has been attributed to an increased number of fibroblasts in gingival connective tissue.[161] Studies have shown that phenytoin alters molecular signaling pathways that control collagen degradation by gingival fibroblasts, and that accumulation of collagen leads to clinically evident gingival overgrowth.[162] Inflammation can exacerbate this condition; therefore, frequent professional cleanings and use of an electric toothbrush are recommended to maintain optimal oral hygiene. Some clinicians advocate the use of chlorhexidine and/or folic acid rinses to minimize gingival inflammation among seizure disorder patients with gingival overgrowth.[163] Surgical reduction of gingival tissue may be necessary if significant overgrowth exists. In addition to gingival overgrowth, other oral side effects of phenytoin include development of intraoral lesions that clinically resemble lupus lesions and lip enlargement.[157,164]

Reduced salivary flow may result from the use of AEDs, and oral healthcare providers may observe increased frequency and/or severity of dental caries and oral candidiasis in patients using these agents. Topical fluoride should be considered for patients with seizure disorders who are at increased risk of developing dental caries, and antifungal agents should be prescribed if oral candidiasis develops. Additional oral findings in patients taking AEDs may include stomatitis, glossitis, and ulcerations (see Figures 23-8 and 23-9 and Table 23-4).[37,49]

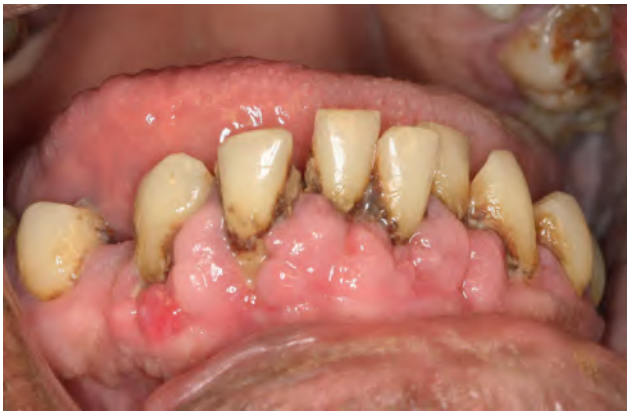

Figure 23-7 Gingival overgrowth of the mandibular anterior segment in a patient taking phenytoin for seizure management.

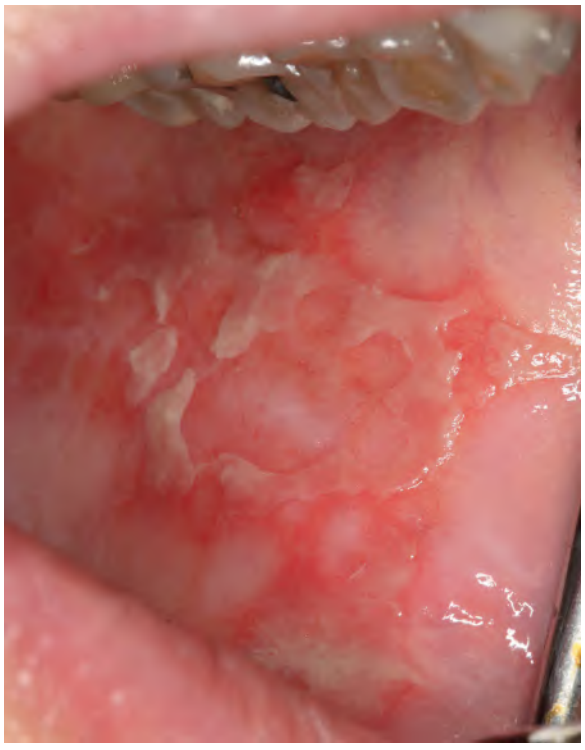

Figure 23-8 Stomatitis on the left buccal mucosa representative of oral sequelae from use of antiepileptic drugs.

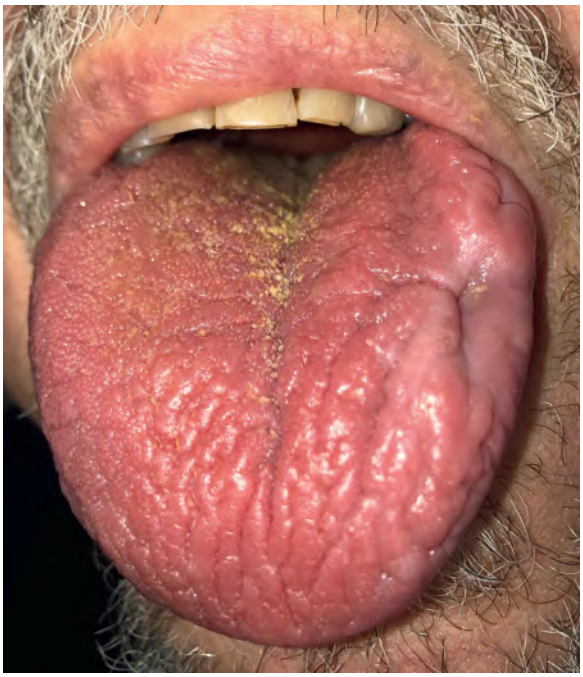

Figure 23-9 Oral sequelae of xerostomia and glossitis from use of antiepileptic drugs.

Table 23-4 Orofacial findings associated with seizure disorders.

Extraoral	Intraoral
• Motor features of seizures affecting head and neck region – Automatisms (unconscious movements) – Atonic (loss of tone) – Clonus (rhythmic movement) – Spasm (sudden flexion) – Headache • Facial trauma	• Trauma – Dental – Soft tissue • Medication-induced reactions/ side effects – Gingival overgrowth—phenytoin – Lip enlargement—phenytoin – Xerostomia—multiple AEDs* ○ Increased risk of periodontal disease ○ Increased risk of dental caries ○ Increased risk of oral candidiasis – Gingival bleeding due to thrombocytopenia and / or platelet dysfunction—multiple AEDs – Increased risk of microbial infection due to leukopenia—multiple AEDs – Stomatitis—multiple AEDs – Glossitis—multiple AEDs – Oral ulcers—multiple AEDs

AEDs, antiepileptic drugs.

PARKINSON'S DISEASE

Epidemiology and Etiology

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder characterized historically by its cardinal motor symptoms of resting tremor, rigidity, gait disturbance, and bradykinesia. A more contemporary view recognizes PD as a complex neurologic disorder with familiar motor symptoms as well as a broader spectrum of clinical features, including cognitive deficits, neuropsychiatric changes, and dysautonomia.[165–169] The disease is now divided into preclinical, prodromal, and clinical phases that impact management and diagnosis. The American Academy of Neurology has developed diagnostic, assessment, and treatment guidelines to distinguish idiopathic PD from "parkinsonian syndromes" such as corticobasal degeneration, progressive nuclear palsy, dementia with Lewy bodies, and Parkinson's disease dementia, which share similar symptoms but have different risk factors, pathologic processes, and clinical courses.[170,171]

PD is second only to AD among neurodegenerative diseases, as PD has a prevalence of approximately 1% and an annual incidence of approximately 446 cases per 100,000 population, with 50% fewer cases among African Americans and Asian Americans than among Caucasians.[172,173] Prevalence increases with advancing age, to a mean of 1.6% among individuals aged 65 years and older.[172,173] A population-based study of US Medicare beneficiaries reported significant differences in regional prevalence, with rates as high as 13.8%.[173] Areas with the highest rates included the northeastern coast and the Midwest/Great Lakes regions, where the highest prevalence was attributed to elevated agricultural and industrial exposure.[173] Mortality among elderly PD patients is 2–5 times that of age-matched controls.[173] The public health and economic burden for PD is significant and growing as the population ages, with annual costs in the United States exceeding $14 billion and prevalence projected to more than double by 2040.[174–176]

The pathology of PD is defined by the loss of dopaminergic cells in the pars compacta of the substantia nigra and presence of Lewy bodies in the brainstem.[177] The loss of dopaminergic cells leads to depletion of the neurotransmitter dopamine in the basal ganglia (caudate nucleus and putamen). Motor symptoms begin when cell loss reaches 60%–80%.[178] Lewy bodies, inclusion structures comprised of packed proteins (α-synuclein and ubiquitin) resulting from failed protein degradation, accumulate and displace essential neuronal organelles and are pathognomonic features of PD.[179,180] PD is a very heterogeneous disease in its clinical variations of motor and nonmotor symptoms, age of onset, progression, and response to therapy. The majority of PD is

likely caused by multiple factors resulting from an elaborate interplay of several genes, modifying effects by susceptibility alleles, environmental exposures, and gene–environment interactions, and their direct impact on the developing and aging brain.[181] Isolated genetic etiologies are likely only responsible for 5% of sporadic cases, with a handful of clearly identified mutations that conclusively cause monogenic PD.[181] Environmental factors and toxins appear to play an important role in the risk for PD: the protoxin n-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), used to develop animal models for testing new therapies in the human disease, has been shown to cause parkinsonism in both humans and nonhumans,[182–184] and pesticides, heavy metals, well water, woodworking, and head injury have also been linked.[177] Significant protective effects have been demonstrated for tobacco use and caffeine consumption.[183,185]

Clinical Manifestations

PD usually affects people over the age of 50, although it can occur at any age, and earlier cases occur more commonly in the familial forms of PD. PD is a progressive neurodegenerative disease and can be divided into three stages: (1) preclinical phase, where neurodegeneration has begun but the patient is asymptomatic; (2) prodromal phase, where symptoms are present but are insufficient to make the diagnosis; and (3) clinical phase, where parkinsonian symptoms are recognizable and meet the criteria for PD.[177] Premotor signs can be subtle, but typically occur to some degree in all cases of PD, including constipation, anosmia, REM sleep disorder, and depression.[177] The four cardinal motor signs of PD are resting tremor (in hands, arms, legs, jaw, and face), rigidity or stiffness (limbs and trunk), bradykinesia (slowness of movement), and postural instability or impaired balance and coordination.[177] These primary motor symptoms are often asymmetric, affecting one half of the body more than the other. Secondary motor symptoms include masked face, hypophonia, decreased blink, and arm swing. Between 30% and 50% of individuals with PD develop dementia and the majority also exhibit behavioral/psychiatric symptoms, including depression, anxiety, apathy, and irritability.[167,172] Autonomic dysfunction is common and can develop early, including orthostatic hypotension, constipation, urinary frequency and urgency, and abnormal sweating.[169] Sleep disorders are common and include insomnia, somnolence, restless leg syndrome, and REM sleep disorder.[186] As symptoms become more pronounced, patients become increasingly impaired. Though the rate of decline varies widely, PD is inevitably progressive and destructive. Age of onset is the strongest independent predictor of motor decline, with motor impairment occurring to the highest degree in late-onset PD.[170]

Diagnosis

There are currently no laboratory tests specific for idiopathic (classic) PD.[165] Clinical genetic markers are available for risk assessment where hereditary patterns of PD exist. Therefore, the diagnosis is based on the health history, neurologic examination, and response to levodopa therapy.[170] The presence of asymmetric primary motor signs and a good response to dopaminergic agents are a strong indication of the diagnosis. When symptoms are subtle and the presentation is incomplete, the diagnosis can be difficult. Differentiating classic PD from a variety of parkinsonian syndromes characterized by motor decline and/or dementia can be challenging.[170] Anatomic and functional brain imaging, CSF evaluation, and laboratory testing are often necessary to exclude other diagnoses.

Treatment

At present there is no cure for PD, but a variety of medications and procedures provide dramatic relief from the symptoms.[165,170,185,187] Therapies are based on symptoms, side effects, cost, and disease severity, along with the patient's age, functionality, values, and personal preferences.[188]

Dopamine replacement therapy using levodopa (used by neurons to synthesize dopamine), combined with carbidopa (delays the conversion of levodopa into dopamine until it reaches the brain), remains the initial gold standard.[177] Levodopa initially helps about 75% of patients, but not all symptoms respond equally to the drug; bradykinesia and rigidity respond best, whereas tremor may be only marginally reduced and impaired balance and other symptoms may not be alleviated at all. It is the best initial therapy in symptomatic patients over the age of 65.[188] Additionally, levodopa often has the unwanted side effect of increasing dyskinesias, which may occur more frequently as levodopa levels fall between dosings, so-called off periods. Levodopa/carbidopa has a half-life of about 1.5 hours, while longer-acting formulations of levodopa that are available may alleviate some of these off periods. The use of levodopa does not result in disease progression.[189]

Dopamine agonists such as bromocriptine, rotigotine, pramipexole, and ropinirole, alone or in combination with levodopa, may control PD symptoms and improve daily functioning better than treatment with levodopa alone. Dopamine agonists directly stimulate dopamine receptors and have longer half-lives. They unfortunately have a higher incidence of psychiatric side effects, including hallucinations and impulse control, as well as sleep disturbances, particularly in the elderly. Medical management can become challenging, as it commonly occurs that a medication that improves one symptom may worsen another.

Monoamine oxidase inhibitors (selegiline, rasagiline, and safinamide) have a modest effect on motor function, but are well tolerated and may be considered as an initial therapeutic option in those with mild disease.[190]

Amantadine is another well-tolerated medication that can be considered as an initial treatment with moderate efficacy for the motor symptoms of PD, particularly tremor. It can also be used for the treatment of "off-time" dyskinesias seen with levodopa therapy.[191]

Treatment of dementia, depression, and other psychiatric symptoms in PD can be challenging.[166] Rivastigmine, a cholinesterase inhibitor, is effective in treating PD dementia.[192] Clozapine, quetiapine, and primavanserin are effective for treating PD psychosis, but may worsen motor function.[193] Tricyclic antidepressants are typically avoided for treating depression due to their anticholinergic effects, but serotonin-norepinephrine reuptake inhibitors (SNRIs) or SSRIs are preferred for this common comorbidity.[193,194] Similarly, benzodiazepine medications often used to treat anxiety may worsen motor performance and confusion, while buspirone, SSRIs, and SNRIs are again preferred.[193,194] Alternative therapy, particularly exercise, has demonstrated significant benefit in physical conditioning, gait, balance, leg strength, and walking speed, with fewer falls.[195,196]

Surgical management of PD by DBS has shown excellent efficacy in patients who fail levodopa treatment or have refractory tremor, and has largely replaced lesioning procedures.[197] DBS is more often selected in younger patients with advanced PD or intolerable medication side effects. Embryonic stem cell research to provide transplantation, implantation, and gene therapy is an area of active investigation.[198]

Oral Health Considerations

Patients with PD present several challenges to the dental healthcare team and to the patient related to both the illness and its treatment, but the importance of maintaining optimal oral hygiene must be emphasized.[37,90] Patients with PD must often be treated in a relatively upright position, making complex dental procedures in the maxillary arch or posterior oral cavity a challenge. Resting tremors and drug-related dyskinesia can complicate procedures, and behavioral techniques to reduce anxiety as well as gentle cradling techniques can help. Dysphagia and impaired gag reflex increase the risk for aspiration of oral and irrigation fluids, and high-speed evacuation of fluids is important in reducing the risk for aspiration pneumonia. Some patients experience sialorrhea, making maintenance of a dry field difficult for some operative and surgical procedures.

Pharmacologic treatment for PD has implications of importance to dentistry. Levodopa and dopamine agonists can lead to both orthostatic hypertension and, rarely, severe hypertension; other side effects of particular importance to the dental team include mandibular and facial dyskinesia, xerostomia, arrhythmia, and blood dyscrasias.[90] Recent evidence suggests that PD patients managed with levodopa may experience impaired masticatory function.[115,199] Limiting use of local anesthetic with 1:100,000 epinephrine to two carpules in PD patients using catechol-O-methyltransferase (COMT) inhibitors for disease management is recommended, due to the potential for an exaggerated and prolonged pressor response to epinephrine.[37] Careful consideration and management include (1) monitoring of blood pressure; (2) correct positioning and repositioning during and after treatment; (3) xerostomia and caries risk reduction through hygiene; (4) sealants and fluorides when indicated; (5) impact of oro-mandibular dyskinesia on the design of dental prostheses, with strong consideration given to implant-supported fixed or removable prostheses to improve chewing and quality of life;[200] and (6) periodic evaluation of the complete blood count to detect drug-related hematologic adverse effects (see Table 23-5).

Table 23-5 Orofacial findings associated with parkinson's disease.

Extraoral	Intraoral
• Tremors • Involuntary mandibular and/or lip movement (dyskinesia) • Muscle stiffness/rigidity – Facial muscles – Masticatory muscles • Impaired masticatory function	• Gag reflex impairment • Dysphagia • Sialorrhea • Involuntary lip and/or tongue movement (dyskinesia) • Medication-induced reactions/side effects – Involuntary lip and/or tongue movement (dyskinesia)—levodopa and dopamine agonists – Xerostomia—levodopa and dopamine agonists ○ Increased risk of periodontal disease ○ Increased risk of dental caries ○ Increased risk of oral candidiasis

MYASTHENIA GRAVIS

Epidemiology and Etiology

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that causes fatiguing weakness in ocular, bulbar, and skeletal muscles that increases during periods of activity and improves after periods of rest.[201] It can progress to involve the function of respiratory muscles in some patients during

severe exacerbations, resulting in respiratory failure requiring intubation and respiratory support. These severe episodes are termed myasthenic crises. The disease results from antibody-mediated, T cell–dependent attack of the postsynaptic neuromuscular membrane, resulting in loss and downregulation of acetylcholine receptor (AChR) along with damage and morphologic changes of the postsynaptic membrane.[202] This process results in impaired neurotransmission and fatiguing muscle weakness. Prior to effective therapy, death commonly resulted from respiratory failure and pneumonia.[203] Ocular weakness, presenting as fluctuating ptosis and/or diplopia, is the most common initial presentation of MG. Muscles of facial expression, as well as masticatory and swallowing muscles, are also affected early, resulting in facial asymmetry, dysarthria, and dysphagia.[203]

Several clinical MG subtypes are defined by clinical presentation, age at onset, autoantibody profile, and presence or absence of thymus pathology.[204] Discrimination among subtypes is important: clinical presentation and disease progression vary significantly, and recent evidence suggests differential treatment effectiveness.[204] Antibodies against the postsynaptic alpha-subunit of AChR are the most common mechanism of injury and result in AChR endplate destruction through complement activation.[205,206] In approximately one-third of MG patients without AChR antibodies, muscle-specific receptor tyrosine kinase (MuSK) antibodies are present.[207] The pathophysiology of MuSK, an autoantigen, is unclear in MG, but it has a role in the clustering of postsynaptic AChRs and their maintenance in the postsynaptic endplate is likely involved.[208] A seronegative MG subtype has also been recognized, but recent findings suggest this may represent a distinct subset with low-affinity IgG antibodies to AChR.[209] The AChR-related autoantibodies in MG are a T cell–dependent process and the thymus is felt to have a role in the pathogenesis of MG, although the exact mechanism remains unclear.[205,206] Thymic hyperplasia is common and approximately 10%–15% of MG patients have a thymic tumor (thymoma), which occurs equally in men and women, typically over age 50, tends to have a more severe clinical presentation, and exhibits high anti-AChR titers.[201]

The biologic and clinical heterogeneity of MG is reflected in a widely accepted classification system: generalized with early (under age 40) and late-onset disease or ocular disease only.[204] Generalized early onset tends to be female, with anti-AChR antibodies and thymic hyperplasia. Late onset tends to be male, with normal thymus glands. As the name implies, ocular MG is limited to the ocular muscles and tends not to generalize if weakness remains limited to ocular muscles for more than 2 years, regardless of anti-AChR titer.[204]

The estimated prevalence rate for MG is 15–20 cases per 100,000 population, with an estimated 60,000 affected patients in the United States.[203] However, the rate of MG diagnoses has increased every year for the past 50 years and probably remains underdiagnosed and underreported.[210–213] The most common age at onset is the second and third decades in women and the seventh and eighth decades in men, and as the population ages, males are more often affected than females, and the onset of symptoms is usually after age 50.[207,214] Pediatric MG is very rare.

Clinical Manifestations

The core clinical feature of MG is muscle weakness that worsens with exercise and improves with rest. Neck flexion weakness is more pronounced than extension and proximal musculature is often significantly affected. Severity of weakness typically fluctuates on a daily basis, but tends to worsen as the day progresses. A majority of MG patients present with ocular symptoms characterized by diplopia and/or ptosis.[201] Oropharyngeal, facial, and masticatory muscle weakness is common and results in dysphagia, asymmetry, and dysarthria, which are the initial symptoms in one-sixth of patients.[203] The clinical course of disease is variable, but usually progressive.[212] By 1 year after onset, 86% of ocular MG patients have gone on to generalized weakness.[215] Weakness limited to the ocular muscles for more than 1 year was unlikely to generalize in the future.[203] In general, MG patients experience an initial period of 1–2 years during which the disease reaches a maximum level of severity, followed by improvement for the majority.[215] Clinical exacerbations or crises may be triggered by several factors, including medications (antibiotics, magnesium, botulinum toxin, interferon alfa, penicillamine, quinine, beta-blockers, calcium-channel blockers, anesthetics, neuromuscular blocking agents), surgery, pregnancy, stress, heat, and viral infections.[216]

Diagnosis

The clinical examination and history are highly suggestive of MG. The most commonly used immunologic test to establish a diagnosis of MG quantifies serum anti-AChR, with a reported sensitivity of 80% for generalized MG and 50% for ocular MG.[206] The presence of other muscle cytoplasmic antibodies may raise the suspicion for thymoma[217] and CT/MRI imaging of the chest is highly accurate in detecting thymoma.

Diagnosis is confirmed by a variety of bedside, electrophysiologic, and immunologic tests. Administration of a Tensilon (edrophonium) challenge (rapid, resulting in immediate elevation of available Ach) is highly reliable in patients with ocular weakness and results in a brief increase in clinical function for a few minutes.[218] Electrodiagnostic testing is very helpful, particularly in antibody-negative cases. Abnormal decrementing compound muscle action potential following repetitive

nerve stimulation is present in 83% of generalized and 54% of ocular MG patients.[219] A special neurophysiologic test called single-fiber electromyography (EMG) can identify jitter (a neurophysiologic finding) in almost 100% of MG patients if performed on a weak muscle; its sensitivity is less given jitter presence in other neuromuscular disorders.[220]

Treatment

The goal of treatment in MG is to achieve remission or minimal symptoms with medications that result in minimal side effects. As with many autoimmune illnesses, treatment is directed at several levels, including reduction of pathologic antibody production or presence, and/or replacement/preservation of the pathologic antibody target (AChR). Anticholinesterase drugs, such as neostigmine and pyridostigmine bromide, increase acetylcholine availability and receptor binding and provide symptomatic benefit without influencing the course of the disease.[207] Anti-AChR-positive MG patients with thymus tumors may have dramatic improvement following thymectomy. MG patients have been shown to benefit clinically from thymectomy and it is recommended that all patients who develop MG are offered the procedure.[221] Plasma exchange and high-dose IV immunoglobulin can rapidly and temporarily reduce circulating antibodies and are very effective in crisis management.[222,223]

Patients with more severe symptoms or poor response to treatment have treatment using corticosteroids and nonsteroid immune suppressants to reduce antibody production and/or B-cell/T-cell lymphocyte activation/proliferation.[224] Corticosteroids, because of their rapid onset of action, are almost always used initially, particularly in patients who are resistant. Prednisone (60 mg/d) is typically started, paying special attention to the acute bulbar weakness associated with the medicine. Prednisone is slowly tapered over time to avoid long-term side effects, as other slower-acting but better-tolerated immunosuppressants such mycophenolate or azathioprine are added. Rituximab, a monoclonal antibody directed against the B-cell surface marker CD20, as in several other autoimmune disorders, has been shown to reduce B-cell counts, disease activity, and even result in remission.[225] Several reports have described its benefit for treatment of anti-MuSK MG.[203] Eculizumab, a complement inhibitor, has received FDA approval for AChR-positive MG that is refractory to other treatments.[226]

Oral Health Considerations

Orofacial signs and symptoms are prominent presenting features of MG, and dental clinicians are frequently in a position to recognize them and refer for diagnosis. Difficulty with prolonged opening and swallowing presents challenges in dental treatment delivery and the ability to tolerate treatment, and difficulty in chewing can affect diet and the design of prostheses. Implant-retained removable or fixed prosthesis may be preferable to tissue-supported prosthesis for improved chewing efficacy. Appropriate oral hygiene measures should be discussed and demonstrated to patients with MG to optimize oral health (see Table 23-6).[227]

Table 23-6 Orofacial findings associated with myasthenia gravis.

Extraoral	Intraoral
• Ocular symptoms – Diplopia – Ptosis • Muscle weakness – Ocular muscles – Facial muscles – Masticatory muscles – Neck muscles • Facial asymmetry • Dysarthria	• Muscle weakness – Oropharyngeal muscles • Dysphagia • Increased risk of opportunistic infections (bacterial/viral/fungal) due to immunosuppressants

Aspiration risks can be high and are often reduced by adequate suction, the use of a rubber dam, and avoiding bilateral mandibular anesthetic block. The MG patient may also be at risk for a respiratory crisis from the disease itself or from overmedication; if this is a substantial risk and dental treatment is necessary, dental treatment in a hospital should be considered where endotracheal intubation can be performed.[228] Emotional stress can precipitate myasthenic crisis, so dental professionals should make every attempt to minimize stress associated with dental visits.[227] Avoid prescribing drugs that may affect the neuromuscular junction, such as narcotics, tranquilizers, and barbiturates. Certain antibiotics, including tetracycline, aminoglycosides, and erythromycin, can affect neuromuscular activity and should be avoided.[227,228] Myasthenic crisis has been documented with use of fluoroquinolones in patients with MG and must be avoided.[227,228] Esther anesthetics that are metabolized by plasma cholinesterase should be avoided in MG patients on anticholinesterase therapy.

OROFACIAL DYSKINESIA/ DYSTONIA

Dyskinesia consists of involuntary movements with wide-ranging clinical features, including myoclonic jerks and tics, which can affect any part of the body.[229] Orofacial dyskinesia (ODk) is characterized by abnormal, involuntary, stereotypical movements of the tongue, lips, and jaw. ODk may be a factor contributing to muscle stiffness, TMJ degenerative changes, orofacial pain, mucosal lesions, damage to

teeth, and dental prostheses. Three types of ODk are recognized clinically: (1) tardive dyskinesia, (2) edentulous dyskinesia, and (3) spontaneous dyskinesia.[230]

Tardive Dyskinesia

The term tardive dyskinesia (TD) was introduced in 1964 to describe dyskinesia associated with antipsychotic medication.[231] The prevalence of TD in patients treated chronically with conventional antipsychotic medication is estimated to be approximately 20%.[232] Other classes of medications associated with TD include atypical antipsychotics, antiemetics, tricyclic antidepressants, and SSRIs.[230,233] Diagnosis of TD requires a minimum of 3 months of cumulative exposure to the offending drug and must persist for 3 months after withdrawal of the medication.[233] Striatal dopamine D2 receptor supersensitivity has been associated with the development of TD.[233] Clinically, patients with TD may present with tongue protrusion and twisting, lip puckering, and smacking and/or chewing movements.[233]

Edentulous Dyskinesia

Complete loss of teeth is associated with the development of edentulous dyskinesia (ED). Partial or complete loss of sensory receptors associated with dental and/or perioral structures, contributing to disruption of central proprioceptive function, is thought to be the cause of ED.[234] The general prevalence of ED is difficult to estimate due to lack of reported data.[230] Evidence suggests that patients with ED exhibit mild masticatory and labial movements compared to patients with TD.[230] Lack of denture replacements may also initiate this condition.[235] Intensity of movement and overall clinical improvement of disease may be observed in ED patients who wear properly fitted dentures.[230,234]

Spontaneous Dyskinesia

Spontaneous dyskinesia (SD) typically affects approximately 3% of the healthy elderly, with a higher prevalence in the elderly living in retirement homes.[233] A higher prevalence of SD has been reported in women and clinical presentation is typically mild, with combinations of tongue, lip, and jaw movements.[233] SD is associated with ill-fitting removable prostheses and also occurs in association with several CNS conditions, including AD, chronic schizophrenia, and autism.[233]

The emphasis in the management of ODk is on prevention, because no one treatment is predictably effective and safe. A dentist observing ODk in a patient taking drugs associated with this condition should inform the physician managing the medication. Palliative treatment using tetrabenazine, a central monoamine depleter, clonazepam, and baclofen has been tried.[235] Fabrication of dentures or replacement of ill-fitting dentures may be of benefit to patients with ODk.[230]

Oromandibular Dystonia

Dystonia is characterized by muscle contraction that may present in acute (transient contracture) or tardive (persistent contracture) forms.[229] Oromandibular dystonia (OMD) is a focal disorder characterized by involuntary and excessive contractions of tongue, lip, and jaw muscles. Primary (idiopathic) OMD is more common than the secondary form, which may be associated with medications, illicit drugs, CNS injury and/or neurodegenerative conditions.[233,236] The incidence of OMD is estimated at 7 per 100,000 persons in the United States, is more common among women, and the mean age of symptom onset is between 31 and 58 years.[233,236] Etiopathogenesis is thought to be related to dysfunction in the basal ganglia, abnormalities with signaling pathways, aberrant dopamine signaling, and/or modified brainstem and spinal cord inhibition.[236] Compared to ODk, OMDs are intermittent and observed as short, sustained muscular contractions resulting in abnormal movements.[233] In addition to typical clinical features, OMD may also be associated with dysarthria, dysphagia, and temporomandibular disorders.[236] Conservative treatment of OMD consists of physical and speech therapy, acupuncture, and biofeedback. Evidence suggests benefit with botulinum toxin A injections to affected musculature for the management of OMD, while central pharmacologic therapy appears to have a more limited role.[236] Limited evidence supports peripheral and/or central surgical interventions in the management of OMD.[236] Dental professionals should be able to identify patients with signs and symptoms suggestive of OMD and refer those individuals to appropriate healthcare providers for further evaluation and management. Occlusal appliance therapy for OMD patients with severe bruxism may be considered to mitigate tooth wear in appropriate cases.

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24

Psychological and Psychiatric Aspects of Oral Health

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Patients seen in oral medicine departments commonly have conditions with features that can be challenging to live with and can be associated with distress. Examples of such features include pain or other unpleasant sensations, fatigue, chronicity, and altered facial appearance. Healthcare professionals working in this specialty have a vital role to play in taking a holistic approach to assessment and treatment. This chapter has five sections. In the first, the psychological management of patients with chronic orofacial pain is discussed in detail. Patients in pain (such as those with chronic orofacial pain and with burning mouth syndrome [BMS]) are among the most common presentations in dentistry and oral medicine. An understanding of the psychological processes involved in patients' interpretation of their pain, as well as the impact of chronic pain on mood and behavior, is critical to the care of these patients. The second section will outline psychological approaches applicable to people with orofacial pain, as well as to other long-term orofacial conditions commonly seen in oral medicine. The next section describes the psychological impact of changes in appearance, such as can occur in conditions including orofacial granulomatosis (OFG). The penultimate section deals with communicating difficult news to the patient (such as a diagnosis of oral cancer). The final section will provide an overview of those psychiatric conditions likely to present among the population of patients with orofacial conditions and the implications of each diagnosis for patient management.

PSYCHOLOGICAL ASSESSMENT AND MANAGEMENT OF INDIVIDUALS WITH OROFACIAL PAIN

The Biopsychosocial Model and Relationship to the Gate Control Theory of Pain

The biopsychosocial model is the most useful in clinical dentistry. The model suggests that the development and experience of illness are the result of the interplay of three broad groups of factors: biologic, psychological, and social (Table 24-1).[1] The biologic grouping includes genetic predispositions, evolutionary vulnerabilities, infective agents, and other biologic processes. The psychological factors include both behaviors and thoughts (cognitions) that

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

Table 24-1 The biological, psychological and social factors that need to be taken into account in assessing a patient's clinical response to pain (the biopsychosocial model).

Biologic	Psychological	Social
Genetic predispositions	Behaviors	Living circumstances
Evolutionary vulnerabilities	Thoughts (cognitions)	Economic factors
Infective agents	Experience of psychosocial stress	Interpersonal factors
Other biologic processes	Beliefs about disease	Social support
	Symptom interpretation	

influence the onset of disease (for example health-related behaviors, the experience of psychosocial stress, beliefs about disease, and symptom interpretation) and the course of the disease.

Examples of thoughts that would have an impact on disease perceptions include beliefs about the ability to control symptoms, the extent to which symptoms are perceived as "normal" or "abnormal," coping strategies, and so on. Social factors cover living circumstances, economic factors, but also interpersonal factors that operate at the level of the person's immediate social group, including social support and engagement with the "sick role." Most illness is socially distributed—that is, related to the social gradient in society—with the experience of illness being more common in those who are most economically deprived, who may also have the fewest resources to address their illness. Furthermore, social support may ameliorate the impact of biologic disease processes.

The *gate control theory of pain* was proposed over 50 years ago by Melzack and Wall,[2] but has stood the test of time. The theory incorporates the biopsychosocial approach just detailed, with the assumption that the experience of pain is the result of a combination of physical, emotional, and cognitive components. The gate control theory is underpinned by an essentially physiological model of pain experience through the interaction of the peripheral and central nervous systems.

Melzack and Wall proposed that the dorsal horn on the spinal cord acts as a "gate" between the peripheral fibers and communication with the pain centers of the brain via the spinal cord. When the gate is open, the nerve fibers can transmit messages to the brain and thus pain is experienced. When the gate is closed, these pain messages are blocked. The gate can be opened and closed both locally and centrally; small fibers at the location of injury may inhibit or excite the gate, which can also be modulated by descending signals from the brainstem. As the brainstem is affected by cortical activity, then cortical activity can indirectly open and close the gate.[3]

Concordant with the biopsychosocial model, the gate control theory identifies three components of the pain experience. First, there is the sensory–discriminative component that gives information about the location, type, and intensity of the pain stimuli. The second is that the affective–motivational component characterizes the emotional responses to pain (such as anxiety, fear, or distress). Finally there is the cognitive–evaluative component, which refers to the interpretation or meaning that the individual ascribes to the sensory experience, and which is related to their characteristic pattern of thinking about their pain, their beliefs, expectations, and other cognitions concerning the pain, as well as the presence of psychological comorbidities such as depression. Together these interact to determine the individual experience of pain. Figure 24-1 summarizes the interaction of the sensory–discriminative component, the affective–motivational component, and the cognitive–evaluative component to form the experience of pain.

Assessments of the different dimensions have found that pain of different origins can be distinguished according to these dimensions. Melzack et al.[2] report that the pattern of reporting of the pain experience using the McGill Pain Questionnaire (MPQ; see later) was different for patients presenting with atypical facial pain compared with those with trigeminal neuralgia. Similarly, while the sensory component of toothache and the pain of BMS were reported to be similar, the affective–motivational and cognitive–evaluative components were different according to the two sources of pain.[4]

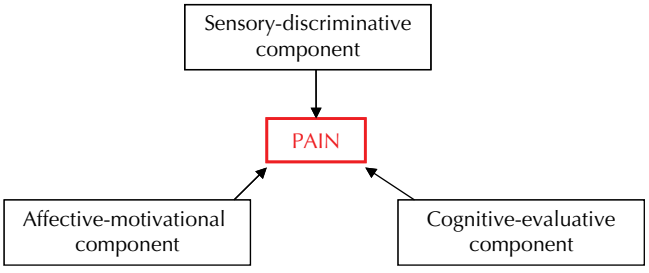

Figure 24-1 The components of pain as identified by gate control theory.

Psychological Assessment of Individuals with Chronic Orofacial Pain

The initial assessment of an individual with chronic pain should encompass the following areas:

- The pain experience.
- Psychological wellbeing (including the most common manifestations of psychological disturbance: depression and anxiety, as well as significant risks such as suicidal ideation).
- The impact of pain on functioning and wellbeing.

The Experience of Pain

The three broad components of pain as identified in gate control theory have implications for the comprehensive assessment and management of chronic pain. The McGill Pain Questionnaire was designed to assess all three components of the pain experience.[5] Patients are asked to select from a list of 78 pain-related adjectives (arranged in 20 groups) those that most accurately reflect their pain experience. Sections 1–10 explore the sensory component of the pain, sections 11–15 the affective component, and the evaluative dimensions are covered in section 16. There is also a miscellaneous set of sections (16–20). A single Pain Intensity item asks the patient to rate their pain on a six-point Likert scale (Present Pain Index, PPI), and finally there is a picture of a human figure facing forward and backward, and the patient is asked to shade those areas where they experience pain. The full MPQ takes approximately 15 minutes to complete. A short form is available that takes approximately 5 minutes to complete. The short form comprises 15 descriptive words taken from the MPQ, each of which is scored on a four point Likert scale, as well as the PPI and a Visual Analogue Scale to assess pain intensity. The short form correlates highly with the full McGill Pain Scale.

Psychological Wellbeing

The identification of coexisting negative impacts on psychological wellbeing, such as low mood or anxiety, is important in the assessment of an individual with chronic orofacial pain, since such issues may have an impact on adherence to medical advice, as well as exacerbating the negative impact of pain on everyday functioning and pursuit of valued goals by the patient. An impact on psychological wellbeing, although not inevitable, has been found to be increased above general population rates in orofacial pain, including temporomandibular dysfunction (TMD)[6] and BMS.[7]

Depression and Suicidal Ideation

Depression and depressive disorders are characterized by a disturbance in mood that is marked and of prolonged duration. It differs from the regular changes in mood that are experienced every day by duration and intensity. The disturbance in mood may take the form of sadness, flat mood, or an unusual degree of irritability. Depression is often accompanied by the experience of changes in the way in which the body is experienced: those affected may report increased aches and pains or a feeling of slowness, excessive sleep, and poor quality of sleep. Depression is accompanied by distinctive changes in the way the person thinks (cognitions), which are often characterized as being negative thoughts about themselves or their situation, and are perceived to be personal (the result of their own actions or character, rather than the situation in which they find themselves) and fixed (not susceptible to change).

The lifetime prevalence of depression and depressive symptoms is about 25% for women and 12% for men, though at any one time it is estimated that approximately 7% of the population will be experiencing marked symptoms of depression.[8] There are many questionnaire measures of depression available, and in considering which measure to adopt a key factor should be consideration of the extent to which the measure includes items relating to the somatic aspects of depression (aches, pains, difficulty sleeping, etc.). Such items may overlap with the individual's experience of pain and as such give an elevated score for the "depression" construct.

The most useful is the Patient Health Questionnaire (PHQ-9),[9] which is a brief measure that assesses nine diagnostic features of depression as identified in the Diagnostic and Statistical Manual of Diseases (DSM-5). The nine items also include a single item relating to suicidal ideation, which is an important risk to assess as part of the identification and management of depression. The scale can be administered over the phone and takes only a few minutes for the patient to self-complete. Scores range from 0 to 27, with higher scores indicating a greater severity of depressive symptoms. Where mild or moderate depressive illness is identified, the patient should be referred to psychological and/or psychiatric services for management. If suicidal ideation is identified during the risk assessment (i.e., the score for the single item on suicidal ideation is "more than half the time"), then an urgent referral should be made for assessment by a psychiatric team.

Anxiety

A patient faced with the uncertainty of the diagnosis of a chronic condition will inevitably be concerned for their future wellbeing and the impact socially in terms of family, friends, and work. Where the degree of anxiety becomes debilitating, this may have an impact on the individual's wellbeing and functioning. Anxiety disorders are manifest when the anxiety experienced is such as to have an impact on the individual's wellbeing; they are associated with high levels of autonomic arousal, hypervigilance, and avoidance behaviors, such as withdrawal from activities that might increase

the person's anxiety level. *Panic attacks* are a particular manifestation of anxiety whereby the physiologic and cognitive response to the fear becomes overwhelming.

A range of questionnaire measures of anxiety exist. The authors recommend the use of the Generalized Anxiety Disorder Assessment (GAD-7[10]). Developed by the same team as the PHQ-9, the GAD-7 is easy and quick to complete and gives a score in the range of 0–21, with higher scores indicating higher levels of anxiety. The scale has high levels of sensitivity and specificity in detecting anxiety disorders presenting in nonpsychiatric populations.[11] Where a moderate or marked level of anxiety is identified, the patient should be referred for psychological and/or psychiatric assessment.

Impact of Pain on Functioning and Wellbeing

An assessment of the impact of pain and any associated psychological changes on the individual's functioning is an essential part of the evaluation of chronic pain. People experiencing chronic pain conditions will often make adjustments to their lifestyle in order to incorporate their perceived limitations as a result of the pain experience. Some patients may benefit from a referral to a multidisciplinary pain rehabilitation program. A primary goal of any pain rehabilitation program is the recovery of physical and social functioning and psychological wellbeing, even in the absence of change in the sensory experience of pain. Measures of quality of life, health-related quality of life, and specific assessments of oral health-related quality of life are all available. The West Haven-Yale Multidimensional Pain Inventory (WHYMPI[12]) is a 52-item, 12-scale measure of three dimensions of the experience of chronic pain. Part I assesses the perceived interference of pain in vocational, social/recreational, and family/marital functioning; support or concern from spouse or significant other; pain severity; perceived life control; and affective distress. Part II assesses patients' perceptions of the degree to which spouses or significant others display solicitous, distracting, or negative responses to their pain behavior. Part III explores patients' report of the frequency of common everyday activities: household chores; outdoor work; activities away from home; and social activities. The WHYMPI provides a comprehensive assessment of the social and psychological impact of the individual's chronic pain, together with an identification of the thoughts, behaviors, and contingencies that may be maintaining the pain behavior.

As part of the overall clinical evaluation, it is important to explore any valued activities that the patient may have decreased or ceased as a result of their pain, since these can form the target of psychological interventions in the pain rehabilitation program.

PSYCHOLOGICAL INTERVENTIONS IN CHRONIC OROFACIAL PAIN AND OTHER LONG-TERM CONDITIONS

Psychological approaches are widely recommended for long-term health conditions, including chronic pain, in order to help people live with their condition more effectively. These approaches combine techniques to address the cognitive and behavioral manifestations associated with long-term health conditions. Appreciation of psychological techniques will help oral medicine clinicians to better manage these patients. Examples of common presentations in which it is helpful to have an appreciation of psychological techniques include those in which there is:

- Anxiety about the condition and/or its progression.
- Avoidance of activity, leading to reduced quality of life.
- Continued requests for further investigations or a cure, despite the condition being chronic and/or further investigations not being indicated.

Some patients may additionally benefit from referral to a psychologist for further assessment and a course of psychological therapy to address these issues in more depth.

Cognitive behavioral therapy (CBT) is an example of a brief psychological therapy with proven effectiveness. It uses both behavior modification techniques and cognitive restructuring procedures to change maladaptive beliefs and behaviors. Behavioral aspects of CBT include learning relaxation skills, conducting mini-experiments, pacing (building an awareness of cycles of energy and fatigue and arranging activity around those cycles), and behavioral activation (encouraging patients to engage in activities that they have previously avoided).

Cognitive aspects of the approach are based primarily in the analysis of people's cognitions (e.g., thoughts, beliefs, interpretations). The central concept is that the way people think about events plays a central role in their emotions (e.g., anxiety) and physiological responses and paves the way to establishing and maintaining unhelpful behaviors such as avoidance. Cognitive therapy therefore aims to facilitate a new understanding (cognitive restructuring) by the patient.

An important principle underlying CBT is its focus on the "here and now," as the origin of any behavior may differ from the factors that maintain it. For example, while pain may have originally arisen in response to a physical trauma, pain-related behavior such as avoiding housework or social isolation may be maintained by a fear of increased pain or by the secondary gain of avoiding an unpleasant activity. In contrast to other psychotherapies, CBT is a short-term therapy, with treatment typically lasting 6–10 sessions. Other

characteristics of CBT that set it apart from other therapies include the collaborative nature and structured approach of therapeutic sessions, and asking clients to spend time each day working on specific tasks in order to practice and establish the skills they have learned in their CBT sessions. The cognitive components of a CBT approach may include psychoeducation: learning more about the nature of their health condition and ways to manage it, challenging beliefs about their health condition (such as that the chronic pain they experience is not an indication of ongoing damage), and small-scale experiments to test beliefs, for example the patient testing for themselves in a small and systematic way whether increased activity would result in increased pain.

Acceptance and commitment therapy (ACT) is an advanced form of CBT that has been used successfully with patients with various long-term health conditions. Central to this form of therapy is the notion of "psychological flexibility," which is a concept that explores how flexible our thoughts and actions are in relation to the demands of the current situation. For many people everyday behavior is habitual and unreflective. This allows many of the day-to-day decisions about what to do to be made easily, without too much thought. However, when faced with an unusual situation or challenge (such as the experience of a long-term health condition), habitual and established patterns of thoughts and behavior may not be helpful. ACT uses notions of acceptance and mindfulness strategies, together with commitment and behavior change strategies, to increase psychological flexibility. Rather than concentrate on trying to change their situation, patients are encouraged to accept the current state of things and seek flexible strategies to move toward their valued goals. The great benefit of ACT for patients with long-term health conditions is acceptance of the current situation and an emphasis on return to activities that may have been suspended or avoided.

APPEARANCE-RELATED ISSUES

Psychosocial Issues Experienced by People with a Visible Difference

Some conditions such as oral cancer and OFG can be associated with changes in appearance, also commonly termed visible difference. Rumsey and Harcourt[13,14] give a detailed account of the psychosocial issues related to visible difference. In summary, visible difference can be associated with:

- Anxiety and depression.
- Negative self-perceptions and self-esteem.
- Challenging encounters with other people (e.g., staring), which can contribute to distress.
- Behaviors such as avoiding social situations. In the longer term, avoidance can compound distress.

Importantly, the level of psychosocial distress experienced by an individual is *not* related to the severity of the visible difference.[15] Factors that are associated with more positive psychosocial outcomes in people with visible difference include having good social support and effective communication skills.[13]

It should also be noted that the treatments for some of the conditions in which visible difference occurs can be demanding. Furthermore, physical functioning can be affected and the patient may be in pain. These factors can present additional challenges and sources of distress, alongside a visible difference.

Identification and Management of Psychosocial Issues

It is important for oral medicine clinicians to include assessment of psychosocial concerns as part of their consultation. Since clinicians' judgment of the severity of the visible difference is not an accurate predictor of psychosocial adjustment, it is important that clinicians do not make assumptions based on this; for example, referring somebody for psychological support simply because they have an objectively large visible difference. Example questions that can be used to identify patients' psychosocial needs are included in Box 24-1. Including questions about how patients feel about their appearance is an important part of normalizing their concerns, as well as recognizing when further support may be required. Organizations such as the UK charity Changing Faces can provide training and resources for health professionals in this regard.

As part of the consultation, questionnaires such as the PHQ-9 and GAD-7 can be used to screen for psychological distress. More specifically, the Derriford Appearance Scale-24 (DAS24[16]) is a widely used measure that assesses distress and

Box 24-1 Useful Questions to Aid in Identification of Psychosocial Needs

- Do you think your medical condition has affected your appearance?
- Have you stopped doing anything because of how you feel about your appearance?
- Are there any situations you avoid because of how you feel about your appearance?
- Has how you feel about your appearance affected your relationships with others? In what ways?
- What helps you cope? Have you got a supportive network of family and/or friends?
- What do you say or do if somebody asks you about your appearance?

dysfunction related to visible difference (such as distress at one's reflection and avoidance of social situations). The information from the questionnaires, in conjunction with discussion with the patient, can inform recommendations about psychosocial interventions (Bessell and Moss offer a review of psychosocial interventions for visible difference[17]). Self-help resources and support groups are among the interventions to which the clinician may direct patients. A smaller proportion of patients may require referral for psychological therapy, including CBT, and/or social interaction skills training. Social interaction skills training involves helping patients to feel more confident when interacting with others. For example, patients with facial alterations due to surgery or OFG learn ways to prepare for challenging social situations, such as when a stranger asks "What's wrong with your face?"

It is helpful if there is ready access to psychology professionals in Oral Medicine departments, both to provide consultation to the team and to see those patients who may need more support (such as CBT or social interaction skills training). Including a psychologist in multidisciplinary clinics is an effective and nonstigmatizing way to achieve this.

COMMUNICATING WITH PATIENTS

Effective Communication in Medical/Dental Settings

The way healthcare professionals communicate with patients can have a significant influence on patients' adjustment to their condition, their satisfaction with their care, health outcomes, and adherence to treatment. Riedl and Schüßler provide a systematic review of the influence of doctor–patient communication on health outcomes[18] and Newton reviews dentist–patient communication.[19] Useful models to aid communication in dental and medical settings have been developed and include the Calgary-Cambridge communication guide[20,21] and Scambler and Asimakopoulou's model of patient-centered care.[22]

Some principles of effective communication in dental/medical settings include the following:

- Avoid jargon, or make sure to explain it when its use is necessary.
- Include open-ended questions such as "What problem brought you to the hospital today?" to allow the patient to tell their story.
- Elicit and explore the patient's perspective. For example, ask about the patient's understanding of their health condition and about their perspective on the costs and benefits of the proposed treatment.
- Collaborate with the patient when discussing treatment choices.
- Demonstrate empathy. For example, let the patient know that it is understandable that they might be nervous about a potential treatment.
- Give opportunities for the patient and their family to ask questions.
- Summarize key information at regular interviews.
- Check that the patient has understood key messages by asking them to recap what has been said.

Breaking Difficult News

The oral medicine clinician will at times have to inform patients of difficult news, including diagnoses of chronic conditions (such as HIV) or of conditions with poor or uncertain prognoses (such as in some cases of oral cancer). The SPIKES protocol is a helpful framework to consider when breaking difficult news and has been shown to increase clinicians' confidence in doing so (Table 24-2).[23]

PSYCHIATRIC CONDITIONS IN ORAL MEDICINE

Individuals living with psychiatric disorders in general experience poorer oral health than those who do not have psychiatric disorders.[24] Those with three particular disorders (somatic symptom disorder, body dysmorphic disorder, and the eating disorders anorexia nervosa and bulimia nervosa) are especially prone to present with oral and dental symptoms and are discussed in detail here.

Somatic Symptom Disorders

The somatic symptom disorders are a group of psychiatric disorders where the patient presents with a physical symptom that cannot be explained or explained adequately by the individual's medical condition or the use of a substance, or another psychiatric disorder. The term "somatic symptom disorder" replaces the earlier term "somatoform disorder." Three broad criteria must be met for the diagnosis: there should be no medical or physical explanation for the severity of the symptom(s); the patient's concern in relation to the symptom(s) is out of proportion to the severity of the symptom; and the condition must have lasted in excess of 6 months (Box 24-2).[25] The group includes body dysmorphic disorder (BDD), which is discussed separately later.

Patients may present in oral healthcare settings with unexplained symptoms of this sort, including pain of unidentifiable origin. Diagnosis of somatic symptom disorder is achieved through the gradual and systematic refutation of alternative diagnoses. Management approaches typically include CBT, occasionally with the adjunctive use of pain-relieving medication.[26,27]

Table 24-2 The SPIKES framework.

Step	Details and Example Phrases
1 SETTING up the interview	• What? Make sure you have checked all the available information and have test results. Decide general terminology to be used • Where? Arrange for some privacy • Who? Who should break the news, should other staff be there or significant others? • Starting off. Introductions and appropriate opening
2 Assessing the patient's PERCEPTION	• Determine the patient's current perception of the situation, particularly of the seriousness of the condition • "What have you made of the illness so far?" • "What did your doctor/doctor X tell you when s/he sent you here?" • Note the language the patient uses and aim to use the same language in your responses
3 Obtaining the patient's INVITATION	• Ascertain how much information the patient would like at this time • "How much information would you like me to give you about your diagnosis and treatment today?" • "Are you someone who prefers to know *all* the details about what is happening?"
4 Giving KNOWLEDGE and information to the patient	• Give the patient some warning that difficult news is coming: "Unfortunately, I've got some difficult news to share with you" • Use the same language the patient uses • Give information in small chunks and check regularly that it has been understood: "Is this making sense so far?" • Modify the rate at which you provide the information
5 Addressing the patient's EMOTIONS with empathic responses	• Allow expression of emotion: "How does hearing this make you feel?" • Show empathy: "I understand that this news is distressing for you" • Allow silence • Do not argue
6 STRATEGY and summary	• Summarize the main points of the discussion • Make a plan or strategy and explain it • Identify the patient's coping strategies and reinforce them • Identify other sources of support for the patient and incorporate them • Invite questions • Tell the patient what happens next. Plan follow-up

Source: Adapted from Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES – a six-step protocol for delivering bad news: application to the patient with cancer. *Oncologist*. 2000;5:302–311.

Box 24-2 Criteria for Diagnosis of Somatic Symptom Disorder

- There should be no medical or physical explanation for the severity of the symptom(s).
- The patient's concern in relation to the symptom(s) is out of proportion to the severity of the symptom.
- The condition must have lasted in excess of six months.

Body Dysmorphic Disorder

BDD is a condition that falls within the scope of somatoform disorders in the DSM-5. It is manifest as a disproportionate concern about the appearance of a particular body part, or appearance in general. People with BDD are likely to present for cosmetic treatments. Among sufferers, the body part causing the most distress varies from person to person. However, there are certain areas that are more frequently cited as troublesome than others. These include nose, eyes, ears, balding, genitals, and breasts, and it is not uncommon for a patient to have an issue with more than one of these body parts at any one time.[28] Veale and colleagues report that 86% of patients diagnosed with BDD perceived themselves to have a facial defect, with 12% reporting specific dental defects,[29] while Phillips reports that 20% of sufferers had concerns about their teeth.[28]

The high levels of distress experienced by sufferers of BDD can sometimes lead to patients attempting to take their own life. In a study conducted by Phillips, it was found that about 80% of 185 subjects had experienced suicidal

ideation and 28% had a history of a suicide attempt, which was 45 times higher than levels experienced by the general population.[30] These extremely high rates indicate the necessity for dental professionals to screen for potential instances of BDD and to refer those experiencing such issues for psychiatric help immediately, rather than carrying out further medical or surgical treatment.

Guidelines on the treatment of BDD identify that any attempt to address the concerns about appearance through surgical care is contraindicated. Treatment options include the use of selective serotonin uptake inhibitors and CBT.[31] The clinician suspecting that a patient has presented with issues related to BDD should make a referral for psychiatric assessment.

Anorexia Nervosa and Bulimia Nervosa

Anorexia nervosa and bulimia nervosa are two psychiatric diagnoses that fall within the grouping of feeding and eating disorders within the DSM-5 classification. This group includes a variety of problems around food and eating, as well as some disorders with a marked similarity to anorexia nervosa or bulimia nervosa where the individual does not fulfill all the criteria for one of those diagnoses (Box 24-3).

All the criteria must be met for a diagnosis. The persistent behaviors referred to may include self-induced vomiting, laxative abuse, excessive exercise, and a variety of other behaviors alone or in combination.

For a diagnosis of bulimia nervosa, the criteria are:

- Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
  - Eating in a discrete period of time (e.g., within any two-hour period) an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances.
  - A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).
- Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.

Box 24-3 Criteria for Diagnosis of Anorexia Nervosa

- Restriction of energy intake relative to requirements leading to a low body weight.
- Intense fear of gaining weight or persistent behaviors that interfere with gaining weight.
- Disturbance in the way a person's weight or body shape is experienced or a lack of recognition about the risks of the low body weight.
- Binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for three months.
- Self-evaluation is unduly influenced by body shape and weight.
- The disturbance does not occur exclusively during episodes of anorexia nervosa.

Note that self-induced vomiting in the presence of low weight is given a diagnosis of anorexia nervosa.

Among individuals who regularly induce vomiting, the most common oral manifestations are dental erosion, dental caries, and reduced salivary secretions leading to xerostomia.

Dental erosion is a frequent oral finding among bulimics. It is accepted that patients who self-induce vomiting are 5.5 times more likely to experience dental erosion than healthy controls.[32] Clinicians noting erosions in their clinical examination therefore need to have bulimia in mind as a possible diagnosis. While the primary factor leading to dental erosion is frequent vomiting, food choices may also have an impact on dental erosion. Bulimics are more likely to consume herb tea, soft drinks, and apple vinegar than healthy controls. Carbonated drinks are also frequently consumed, often to decrease the reflex stimulus for hunger.[33]

Self-induced vomiting may result in enlarged salivary glands, particularly the parotid glands. Prevalence estimates ranged between 0 and 80% of bulimia sufferers, but is very rare in age-matched control subjects.[34] Although they are commonly associated with vomiting, the precise causes of enlarged parotid glands among bulimics are unclear, though it is apparent that when present, their effect is to cause a reduced salivary flow rate, not an enhanced rate.

Data concerning the relationship between bulimia nervosa and caries experience are equivocal. Vomiting may have an effect on the risk of caries, both directly and as a result of reduced salivary flow rate. In addition, the food choices made by bulimics during a binge, which are largely carbohydrate based, will increase caries risk. In a young adult with reduced saliva flow and parotid enlargement, the presence of self-induced vomiting as a causative factor should be considered. Referral for a psychiatric opinion should be made if anorexia nervosa or bulimia nervosa is suspected.

CONCLUSIONS

Patients living with chronic orofacial conditions may experience elevated levels of psychological distress. The assessment of such distress together with the impact of chronic pain and other orofacial conditions on the patient's health and wellbeing is central to a holistic

biopsychosocial model of care. Psychological approaches can have great value in helping the patient return to valued activities. Certain psychological conditions may manifest as orofacial conditions—an awareness of these will help the clinician to direct the patient to appropriate sources of care and support.

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25

Pediatric Oral Medicine

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A wide spectrum of soft tissue lesions of the oral maxillofacial region may occur in children and adolescents. Fortunately, the majority of pediatric pathologies are benign and the management of these conditions is relatively straightforward. As many of these conditions also occur in adults, the aim of this chapter is to focus on those that are more prevalent in children and to highlight the considerations specific to this population.

CONSIDERATIONS IN CHILDREN

According to the American Academy of Pediatrics (AAP), the upper age limit of "pediatric care" is 21 years, though exceptions may be made, particularly in an individual with special healthcare needs. Childhood development is grouped into early childhood (0–8 years), middle childhood (8–12 years), and adolescence (12–18 years).[1] The early and middle childhood stages may be further categorized into newborn (0–1 month), infant (1 month–1 year), toddler (1–3 years), preschool (3–5 years), and school-age (6–12 years) children. Stratifying childhood into stages is clinically relevant because the needs of patients in this group are constantly changing due to their rapid physical and cognitive development within a relatively short period. As such, certain unique considerations with regard to eliciting history, patient examination, and treatment may arise in this age group that are not relevant in adults.

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

Eliciting History

There is pertinent content in a pediatric medical history that is not required for an adult. In addition, the value of certain aspects of the history changes in significance as the child transitions through the various developmental stages. For instance, prenatal history is an essential component of the history in an infant, but diminishes in importance in older children and adolescents.

History-taking is another aspect that is different in children and adolescents. For an infant and toddler, the history is obtained exclusively from the parent/caregiver; while for older children, the history is usually elicited from both the parent and the patient. The history-taker should be cognizant that parents and caregivers may be influenced by their frame of mind, emotional state, presumptions, and expectations, which may compromise the reliability of the history. Children above the age of 4 years are often able to supplement their parent's description with their own account. School-age children and adolescents can assume a larger role in being the main historian and the reliance on parents is further reduced. This is potentially a delicate situation and the history-taker needs to negotiate the process tactfully to avoid offending the parents or embarrassing older children/adolescents when sensitive topics are being discussed. Involving the child/adolescent in the interview process builds rapport and is the foundation for a successful and long-term patient–doctor relationship.

Patient Examination

It is recommended to gather as much information as possible from the parent, and through observation and interaction with the child prior to the examination. The factors that influence the child's compliance include past experiences, temperament, approachability, adaptability to the environment, and stage of cognitive development. There are several theories on how children evolve as they mature; the best known is Piaget's theory of cognitive development. The four stages of Piaget's theory correspond with age: sensorimotor (0–2 years), preoperational (2–7 years), concrete operational (7–11 years), and formal operational stage (11 years to adulthood). Behavioral management strategies are generally based on these theories. To maximize compliance for an examination, the practitioner should utilize the most appropriate behavioral management technique (Table 25-1) based on the child's developmental age, temperament, and past experiences.

Generally, children under the age of 3 years are pre-cooperative and behavioral management strategies have limited benefit. The goal then is to perform an examination in a gentle and time-efficient manner. For newborns and infants, clinical examination may be done on a flat surface or in the parent's arms. For older infants and toddlers, a "knee to knee" examination is commonly performed. The infant/toddler lays flat on both the examiner's and parent's laps, with the head on the examiner's lap and the lower half of the body on the parent. The child's legs hang loose or looped around the parent's waist. Children between the ages of 3 and 7 years are potentially cooperative and behavioral management strategies should always be employed. Children of these ages may be able to sit on the dental operatory chair independently for an examination. If the child is apprehensive, the parent may be invited to sit with the child on the dental chair.

Table 25-1 Behavioral management techniques and appropriateness by age.

Behavioral Management Techniques	Neonate/ Infant	Toddler/ Preschool	School-age
Nonverbal communication, e.g., appropriate contact, posture, facial expression, and body language	√	√	√
Voice control: controlled alteration of voice volume, tone, and/or pace	–	√	√
Tell–show–do: verbal explanations, demonstrations, and completion of the procedure	–	√	√
Modeling: direct observation of a video or another cooperative child undergoing the procedure	–	√	√
Positive reinforcement: praising desired behaviors	√	√	√
Distraction	√	√	√

Diagnostic Investigations

Ordering of diagnostic investigations is less straightforward in younger children for numerous reasons. In general, any investigation that rely on subjective response (e.g., pain on palpation or percussion) is less reliable in children. The ability to comply with an investigation is another consideration unique to this population. If a young child is unable to remain still for a radiographic imaging or will not allow blood to be drawn for a hematologic test, the practitioner then needs to decide whether the investigation is sufficiently critical to justify sedating the child (and exposing the child to the risk of sedation or general anesthesia) to complete the investigation. Another frequent parental concern is the risk of radiation exposure. The radiation exposure from dental radiographs is small and dental radiographs should be taken if the image finding will impact treatment. Although the radiation doses are higher with medical-grade imaging, the same principle will apply.

Treatment

As with adults, symptomatic, aggressive, potentially malignant, or malignant conditions in children should be managed immediately. The decision to treat asymptomatic, slow-growing, and likely benign lesions is less clear in a young child, especially when sedation or general anesthesia is needed. With a recent flurry of reports of potentially negative impact of repeated general anesthetics on the brain development of children under the age of 3 years,[2] the practitioner needs to weigh the pros and cons of performing the procedure under sedation, versus monitoring and delaying intervention until the child is able to comply for the procedure under local anesthesia.

Medications for oral medicine conditions are often prescribed "off-label" due to a lack of clinical trials.[3] Of the limited studies available, most are in the adult population. The effectiveness, safety, and adverse reactions of a particular drug in an adult may differ in a child, especially in those under the age of 2 years. As such, practitioners must exercise caution when prescribing a medication for a child, even if the same medication may have been found beneficial in an adult. Other considerations include the impact of the medication on growth and development, the need for dose adjustments in overweight and obese children as well as in newborns and infants due to immature metabolic processes, the potential for miscalculated doses, as well as the ability and the compliance of the child to adhere to the route and frequency of the prescribed regimen. A general guide to ascertain whether an off-label medication should be used in a child may be guided by these principles: (1) moderate- or high-quality evidence supporting the off-label use; and (2) obtaining informed consent whereby the rationale of using the medication, side effects, and alternative treatments are explained to the parent and the patient.

Consent

The consent process varies between countries. Practitioners should be familiar with and must abide by the local laws and regulations where they practice. In the United States, both the 1976 and 1995 AAP policies on informed consent stipulate that permission must be obtained from the parent or legal guardian prior to medical interventions for patients under 18 years of age.[4] The 1995 policy also states that older children and adolescents should participate in the medical decision-making process and provide assent to their care whenever reasonable.[5] Although assent is only mandatory for enrollment in research studies, the value of involving young patients in their own medical decision-making is increasingly being acknowledged. Assent may be obtained from children as young as 6–7 years of age. Assent involves explaining to the child in a language that they can understand as to what to expect with investigations and treatment, and encouraging questions to ensure that the child understands the situation. This process will help them become more involved in their medical care. While involving children and adolescents in medical decision-making is desired, they are vulnerable decision-makers. This is attributed to their neuropsychologic immaturity (e.g., adolescent behaviors such as sensation-seeking and risk-taking), influences from peers, and inexperience with decision-making, especially in complex and stressful situations. Thus, it is imperative that the parent/legal guardian remains the final decision-maker. When a treatment or intervention is deemed essential, assent should not be sought. Instead, the pediatric patient should be informed of the decision. Dissent by the pediatric patient will carry more weight for elective interventions or interventions that can be deferred without substantial risks or complications.

DEVELOPMENTAL CONDITIONS

Developmental Oral Cysts of the Newborn

Developmental oral cysts are common in newborns, with no gender predisposition. It is difficult to provide an estimate of the prevalence because of reporting bias as well as differences in study design, diagnostic criteria, and sample population between studies. Fromm classified developmental oral cysts based on their etiology and location.[6] Epstein pearls are located on the mid-palatal raphe, Bohn's nodules may be found at the junction of the hard and soft

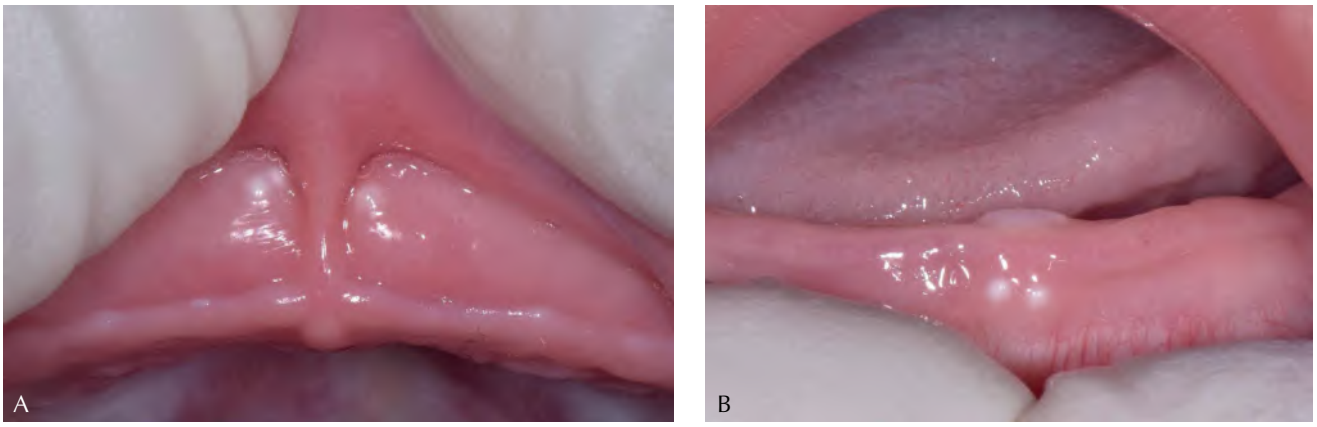

Figure 25-1 A, B. Developmental cysts of the newborn.

palate or at the vestibular region (rare), and dental lamina (gingival) cysts are found on the alveolar ridge crest. An Epstein pearl is thought to be a result of epithelium entrapment between the palatal shelves when they fuse in the midline in utero to form the secondary palate. Bohn's nodule is thought to be derived from the epithelial remnants of minor salivary glands.[7] Unlike Epstein pearl and Bohn's nodule, dental lamina (gingival) cyst (Figure 25-1) is odontogenic in origin and arises from the cell rests of Serres (remnants of dental lamina epithelium).[8] Of note is that these three terms are often used interchangeably, although the term "developmental oral cyst of the newborn" is preferable. Regardless of the origin and location, developmental oral cysts typically present as a single or multiple painless, small nodules filled with keratin, which imparts a white/yellowish appearance. The diagnosis is made clinically based on the presentation, location, and age. Developmental oral cysts of the newborn are benign and resolve spontaneously within the first few months of life, thus no treatment is needed.

Lymphangioma of the Alveolar Ridge

Lymphangiomas of the alveolar ridges (Figure 25-2) in infants were first described in 1976 and present as a single or multiple, fluid-filled, sessile, dome-shaped, bluish lesions on the maxillary or mandibular posterior dentoalveolar ridges.[9] The condition usually occurs bilaterally.[10] Lymphangiomas of the alveolar ridges have only been reported in infants of African descent, with a male predilection. The histologic examination reveals a proliferation of endothelial-lined lymphatic spaces. The diagnosis is often made clinically based on the presentation and ethnic predilection. No treatment is needed, as the lesions are benign and all cases have been reported to resolve spontaneously.[11]

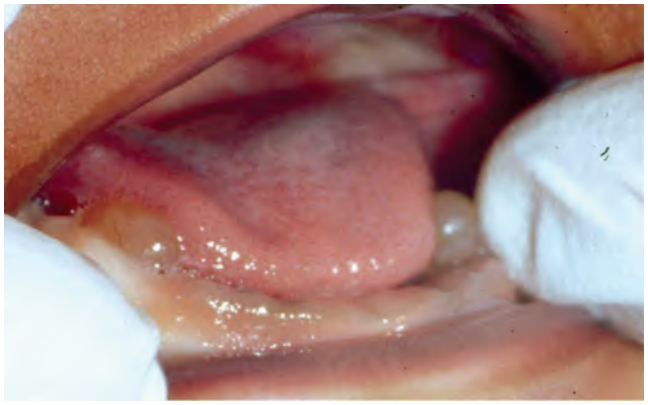

Figure 25-2 Lymphangioma of the alveolar ridge.

Eruption Cyst

An eruption cyst is a benign odontogenic cyst that is considered to be a soft tissue variant of the dentigerous cyst. It is recognized as a separate clinical entity from a dentigerous cyst and is proposed to develop from the separation of the reduced enamel epithelium from the crown of the tooth.[12] The eruption cyst usually presents in the first decade of life and is commonly associated with the eruption of the permanent first molars and maxillary incisors. Clinically, the cyst appears as a soft, fluctuant, sessile, dome-shaped, translucent swelling overlying the crown of an erupting tooth. Occasionally, the swelling may appear blue or blue-black when it is filled with blood (eruption hematoma), likely attributed to trauma during function. The diagnosis is made clinically based on the presentation and temporal relationship with the eruption of a tooth. Radiographs are generally not necessary, as there are no characteristic findings. Furthermore, the cystic space cannot be visualized, as the cyst is entirely in soft tissue. The majority of eruption cysts are asymptomatic and rarely

require intervention. The cyst naturally marsupializes as the tooth erupts into the cystic space and through the gingiva. In individuals who complain of discomfort during mastication and in situations whereby the cyst continues to enlarge to cause discomfort, simple surgical removal of the roof of the cyst to expose the crown of the tooth under local anesthesia may be performed.

Congenital Epulis of the Newborn (Congenital Granular Cell Tumor)

The congenital epulis (CE) is a rare, soft tissue benign tumor (0.0006%) that occurs almost exclusively in newborns (Figure 25-3). The tumor occurs 8–10 times more often in females than in males.[13] The etiology is unknown, but there are several hypotheses regarding the origin of CE. The most popular ones are those that favor gingival and odontogenic epithelial origins.[14] Clinically, CE appears as a single, firm, smooth-surfaced, sessile or pedunculated, round, pink or reddish mass commonly occurring on the anterior maxillary alveolar ridge. Multiple tumors have been reported in a minority of cases.[15] CE does not appear to grow after birth and the majority are less than 2 cm, though tumors as large as 10 cm have been reported.[16] Large CE may interfere with feeding and cause airway obstruction. The granular cells in CE resemble the cells in granular cell tumor histologically (i.e., large round cells with abundant granular, eosinophilic cytoplasm, and round basophilic nuclei) and thus it is also known as congenital granular cell tumor. However, unlike granular cell tumor, CE does not display a strong reactivity to S100 protein.[17,18] A clinical diagnosis of CE is not difficult to make because of its presence at birth, appearance, and location. Nevertheless, histology is needed to confirm diagnosis. Spontaneous regression is rare.[17] Surgical excision is the treatment of choice and recurrence is unlikely even when the removal is incomplete.

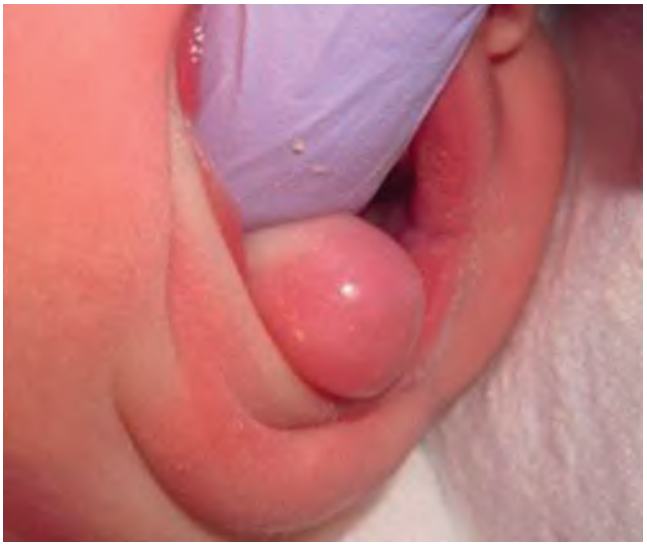

Figure 25-3 Congenital epulis of the newborn.

Lingual Thyroid

Lingual thyroid is an ectopic thyroid gland found at the base of the tongue. This occurs as a result of the thyroid gland failing to descend to its normal anatomic site in utero. The incidence is approximately 1 in 100,000 to 1 in 300,000 live births and is 4–7 times more common in females.[19] Lingual thyroid may present as small asymptomatic nodules or a single large mass. The diagnosis is made by radionuclide imaging, ultrasonography, computed tomography, and magnetic resonance imaging. Most affected individuals do not require treatment.[19] Some individuals may be hypothyroid and require thyroid hormone replacement.[20] Over 70% of cases have no other functional thyroid tissue, thus surgical removal is contraindicated unless the structure is causing airway obstruction, bleeding, or shows cystic degeneration. The potential for malignant change appears to be similar to that of orthotropic thyroid tissues.[21]

Melanotic Neuroectodermal Tumor of Infancy

Melanotic neuroectodermal tumor of infancy (MNTI) is rare and only about 350 cases have been reported in the literature.[22] The tumor commonly occurs in children under 1 year of age. The majority of MNTI are benign, but a few malignant cases have been reported.[23,24] The high urinary levels of vanillylmandelic acid in individuals with MNTI support the neural crest origin of MNTI. Clinically, the tumor typically presents as a painless, nonulcerative, firm, smooth-surfaced, sessile swelling on the anterior maxillary alveolar ridge. The color varies greatly, ranging from mucosal colored with a bluish hue to a reddish-brown lesion. Although benign, MNTI grows rapidly and can infiltrate and destroy the adjacent bone and soft tissue. The histologic examination reveals two distinct cell types that form sheets, nests, or cords within a dense collagenous stroma.[25] The first cell type is a larger, cuboidal epithelioid cell containing melanin granules, generally found at the periphery of the tumor. The other cell type is smaller and round, with a hyperchromatic nuclei and scant cytoplasm. These cells tend to grow in nests and are surrounded by the larger cuboidal cells. The diagnosis is made based on the clinical presentation, high urinary vanillylmandelic acid, and histology. Surgical intervention is the treatment of choice. Recurrence ranges greatly, between 10% to 60%.[22,26] Younger age and surgical curettage were associated with the highest recurrence, while segmental resection was associated with the lowest recurrence.[26]

Vascular Anomalies

Vascular anomalies are common in newborns and the majority are benign and self-limiting. They are broadly categorized into vascular tumors and malformations. Vascular tumors are true neoplasms of endothelial cells, while vascular malformations are abnormalities of the vessel structure. Historically, the term "hemangioma" was used to describe any vascular tumor-like lesion; however, this definition should not be used when referring to vascular malformations.

Vascular Tumors

Infantile hemangioma (IH) is the most common benign vascular tumor in infancy. IH occurs in approximately 5%–10% of the population and is more common in low-birthweight (less than 1 kg) premature infants, females, and Caucasians.[27,28] The majority are on the skin and 60% occur in the head and neck region. Intraoral IHs are uncommon, but have been reported to occur on the tongue, buccal, and palatal mucosa as well as the gingiva.[29] The exact pathogenesis is unclear; the proposed origin of IH is thought to arise from the proliferation of endothelial cells or angioblasts, which is influenced by internal (e.g., dysregulation of vasculogenesis and angiogenesis) and external factors (e.g., tissue hypoxia). The behavior of IH is distinctive and is characterized by a proliferative phase followed by an involution phase. At birth, the majority of IHs are not evident, but they become apparent within the first few days or months of life. The proliferation is rapid for the first few months and slows down between the 6th and 12th months of life. Spontaneous involution typically begins after 1 year of age and approximately 90% of IHs completely involute by 9 years of age.[30] The rate and extent of involution vary greatly between cases. Complete involution does not always result in normal-appearing skin. About 50% will experience permanent changes such as scarring, atrophy, wrinkling, discoloration, and telangiectasia.

IH usually presents as a solitary lesion and the size ranges from a few millimeters to several centimeters. The clinical appearance varies based on the depth of involvement.[28] Superficial IH involves only the skin and is the most common. The lesion presents as a firm, rubbery, bright red papule, nodule, or plaque surrounded by normal skin that does not blanch on pressure. Superficial IH has been called "strawberry" hemangioma, but this term is discouraged as not all superficial IHs have the "strawberry" appearance. Deep IH involves only the subcutaneous tissue and appears as a raised, skin-colored nodule with a bluish hue. Combined IH typically displays features of both superficial and deep IH, as the lesion involves both the skin and the underlying subcutaneous tissue. The initial clinical sign of involution for a superficial IH is a color change from bright red to dark or violaceous red to gray, often beginning at the center of the lesion. For deep IH, the lesion becomes less blue and feels less warm. These descriptions are for skin lesions. To date, intraoral IHs are poorly described due to their rare occurrences and the inconsistency of how they are defined in the literature. Based on the available reports, intraoral IH appears as a soft, fluctuant, sessile, dome-shaped, erythematous mass that blanches slightly with pressure.[29,31] As with cutaneous IH, intraoral IH appears to involute; however, the changes during involution for intraoral IH are not well described.[29] The diagnosis of IH is often made clinically based on history and presentation. Imaging studies may be needed for deeper lesions. The majority of cutaneous IHs do not require treatment unless they are deemed to be unlikely to involute or are located in areas associated with significant morbidity (e.g., visual impairment in periorbital IHs). Intraoral IH may require intervention, especially if the lesion is on the tongue, which may interfere with mastication and speech.[29] In cases where intervention is indicated, the treatment modalities include topical (for superficial lesions) or systemic (for large lesions) propranolol, corticosteroids (intralesional or systemic depending on extent of lesion), laser treatment, and surgical removal.[28,32,33] PHACE syndrome (**p**osterior fossa anomalies, **h**emangioma, **a**rterial anomalies, **c**ardiac anomalies, and **e**ye anomalies) is an uncommon sporadic disorder that should be considered in an infant presenting with a large (>5 cm) segmental hemangioma, especially on the face, scalp, or posterior neck. The management of PHACE syndrome is based on the severity of the clinical manifestations and the risks associated with the arterial abnormalities.

Congenital hemangioma (CH), tufted angioma (TA), and Kaposiform hemangioendothelioma (KH) are other rare vascular tumors that occur in infancy and early childhood. Although these tumors look similar to IH, they behave differently clinically and are histologically and immunophenotypically distinct. Unlike IH, CH is fully developed at birth.[34] There are two variants of CH: rapidly involuting congenital hemangioma (RICH) and noninvoluting congenital hemangioma (NICH). RICH involutes within a few days to a few weeks after birth and usually completely disappears by 14 months of age. NICH does not regress and grows in proportion with general physical growth. A thorough history as to whether the lesion presented as a palpable mass (suggesting CH) or a flat/subtle area of discoloration at birth with a history of rapid postnatal growth will help to differentiate IH from CH. If a definitive diagnosis is needed, a histologic examination demonstrating a positive (IH) or negative (CH) immunohistochemical stain for glucose transporter protein-1 will differentiate the two entities. TA and KH are discussed together as they are believed to be part of the same spectrum. Unlike IH, they tend to be located on the extremities

or on the trunk. Both TA and KH typically appear as an indurated, reddish or purplish lesion with ill-defined borders. TA is absent or barely evident at birth, but will manifest over time. KH may be present at birth or develop during early childhood. KH is more locally aggressive than TA. Kasabach-Merritt phenomenon (KMP) is associated with 70% of KHs and 10% of TAs. KMP is a life-threatening condition characterized by severe thrombocytopenia and the consumption of fibrinogen and other coagulation factors.[35] There are case reports of TAs occurring in the oral cavity (e.g., tongue, floor of mouth), with the majority being located on the lip.[36–38] The diagnoses of KH and TA are made based on clinical, radiographic (magnetic resonance imaging), histologic, and laboratory findings (to rule out KMP). The management of TA and KH vary based on the size, location, symptoms, and whether the conditions are associated with KMP. The current treatment modalities are largely based on limited evidence and include observation for asymptomatic tumors, pulsed dye laser, surgical excision, and use of single- or multiple-agent chemotherapeutics (e.g., vincristine, sirolimus).

Vascular Malformations

Vascular malformations (VMs) are categorized by the International Society for the Study of Vascular Anomalies into (1) simple malformation consisting of only one type of vessel; (2) combined malformation defined as ≥2 VMs in a single lesion; (3) anomalies of major named vessels; and (4) VM associated with other anomalies (Table 25-2).[39] VMs are further divided based on the type of involved vessels and flow characteristics: low flow (capillary, venous, lymphatic, or combination) and high flow (arterial, arteriovenous). The diagnosis for small localized or superficial lesions is often based on history and clinical presentation. The use of imaging such as Doppler ultrasonography and magnetic resonance imaging may be needed to confirm the diagnosis of extensive and deeper lesions.

Approximately 50% of VMs occur in the head and neck region, with a slight female predisposition.[40] All VMs are present at birth, but may be clinically subtle. They become more apparent over time and grow proportionately with the infant's overall growth. VMs generally do not involute (with the exception of nevus simplex), and their growth may be influenced by trauma, infection, and hormonal changes.

Lymphatic Malformations

Lymphatic malformations (traditionally known as "lymphangiomas") are benign, low-flow lesions consisting of malformed, dilated lymphatic channels or cysts of varying sizes. These abnormal structures do not communicate with the rest of the lymphatic or venous systems, resulting in lymphedema, lymphangiectasia, and proliferation in the affected area. The majority of the lymphatic malformations are congenital and are due to the abnormal development of lymphatic jugular sacs. Acquired lesions are thought to arise as a result of trauma or respiratory infection. The reported incidence ranges from 1 in 500 to 1 in 4000 live births.[41] Lymphatic malformations are usually diagnosed at birth or before 2 years of age.[42] Two-thirds of the cases occur in the head and neck region.[43,44]

Table 25-2 Classifications of vascular malformations.

Vascular Malformations			
Simple	**Combined**	**Anomalies of Major Named Vessels**	**Associated with Other Anomalies (Not Exhaustive)**
1) Low flow • Lymphatic malformation • Capillary malformation • Venous malformation 2) High flow • Arteriovenous malformation (development)* • Arteriovenous fistula (acquired)*	Any combination of the four types of vessels (lymphatic, capillary, venous, or arteriovenous) or ≥2 vascular malformations in a single lesion, e.g., capillary–venous malformation, capillary–arteriovenous malformations	Affecting veins, arteries, or lymphatics of large caliber	1) Sturge–Weber syndrome 2) Klippel–Trenaunay syndrome 3) Capillary malformation–arteriovenous malformation syndrome 4) Cutis marmorata telangiectatica congenita 5) Macrocephaly–capillary malformation syndrome 6) Maffucci syndrome 7) Phakomatosis pigmentovascularis 8) Proteus syndrome 9) CLOVES (**c**ongenital **l**ipomatous **o**vergrowth, **v**ascular malformations, **e**pidermal nevi and **s**coliosis/skeletal/spinal anomalies) syndrome

*Although arteriovenous malformations/fistulas contain arteries, veins, and capillaries, they are not considered a combined venous malformation with an arterial malformation, but an entity involving several types of vessels.

Lymphatic malformations are classified into three types: microcystic, macrocystic (cysts >2 cm, formerly known as cystic hygroma), and mixed type. Microcystic lesions are commonly found above the level of the mylohyoid muscle, while macrocystic lesions are typically located below the level of the mylohyoid muscle and involve the anterior and posterior cervical triangles.[43,44] An intraoral lymphatic malformation is usually of the microcystic type and commonly presents on the anterior portion of the tongue. The condition presents as a cluster of multiple, small, firm, clear vesicles ("pebbly" or "frog's eggs" appearance) that may infiltrate the underlying subcutaneous tissues and muscles (Figure 25-4A). The vesicles sometimes appear red or purplish due to secondary bleeding from trauma. A macrocystic lymphatic malformation appears as a smooth, compressible swelling under normal or bluish skin (Figure 25-4B). The symptoms and the severity of complications vary based on the type, size, depth, and location(s) of the malformation. Fortunately, medically significant lymphatic malformations are rare. The main treatment objectives are restoration and preservation of function and esthetics. The treatment modalities range from observation, drug therapy (e.g., sirolimus), sclerotherapy, laser therapy, and radiofrequency ablation to surgical excision.[45,46] Small lesions that do not affect function and do not cause cosmetic disfigurement are managed conservatively. Large head and neck lymphatic malformations often require intervention, as they may obstruct the airway. Such lesions are extremely difficult to manage (e.g., high risk of complications, incomplete resection) due to their close proximity with adjacent vital structures.

Capillary Malformations

Capillary malformations are low-flow malformations of the dermal capillaries and postcapillary venules. There are two types of capillary malformations: nevus simplex (macular stain) and nevus flammeus (port-wine stain).[47]

Nevus simplex is a common condition affecting 40%–60% of newborns and presents as single or multiple, blanchable, pale pink to red patches with indistinct borders. The patch becomes more visible when the infant is crying. Nevus simplex typically occurs on the midline, commonly affecting the eyelid, glabella, and midline of the nape of the neck. Nevus simplex generally fades without treatment within 1–2 years.

Nevus flammeus affects 0.1%–0.3% of newborns and presents as a flat, pink or purple macule with variable blanchability that is most common on the face. The affected area typically has a unilateral distribution that does not cross the midline and frequently follows the distribution of the trigeminal nerve. Nevus flammeus does not regress and grows in proportion to the infant's growth, becoming darker and nodular ("cobblestone" appearance) with age. Nevus flammeus is usually an isolated condition, but may be associated with other abnormalities (e.g., glaucoma, central nervous system [CNS] involvement) or be part of a syndrome such as in Sturge–Weber syndrome. There are several reports of accompanying oral findings in individuals with facial port-wine stains and Sturge–Weber syndrome.[48,49] These manifest as unilateral hemangiomatous lesions occurring on the gingiva, lips, tongue, and palate. In a case series of 30 individuals with facial port-wine stains and corresponding oral lesions, hemorrhage after dental procedures appeared to be low.[50] The treatment objectives are esthetic improvement and prevention of complications. Pulsed dye laser is considered to be the standard of care for the treatment of nevus flammeus.

Venous Malformations

Venous malformations are the most common low-flow VMs. The malformation can affect any tissue, but primarily develops in cutaneous, subcutaneous, or mucosal tissues. Approximately 40% occur in the head and neck region.

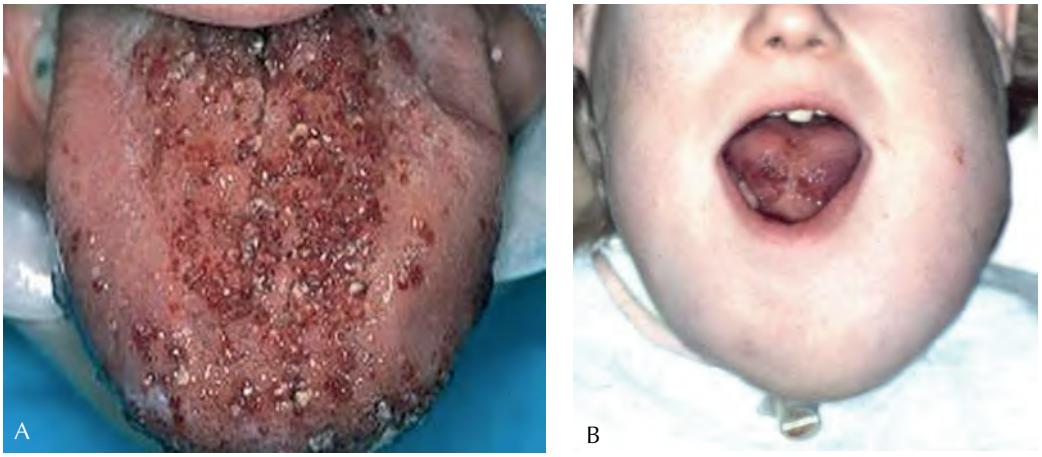

Figure 25-4 Lymphatic malformations. (A) Microcystic type. (B) Macrocystic type.

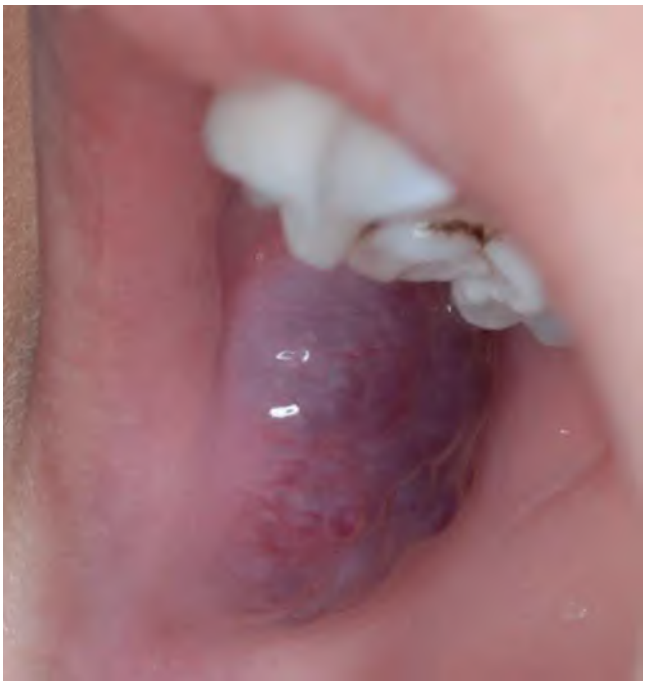

Figure 25-5 Venous malformation.

Intraoral venous malformation appears as a slow-growing, soft, compressible, bluish lesion that may swell with the Valsalva maneuver (Figure 25-5). Occasionally, phlebolith formation within a venous malformation may occur, thought to be due to trauma or venous stasis.[51,52] Intraoral venous malformations may cause speech and masticatory difficulties if they are on the tongue. Some may be life-threatening if they are close to vital structures. Venous malformation is frequently misdiagnosed as IH; a detailed history of the presentation at birth and the behavior in the first few months of life will help distinguish the two entities. The treatment modalities include sclerotherapy, laser therapy, compression therapy, and surgical resection.[53] The choice of treatment is based on the location and extent of the malformation as well as the individual's preference.

Arteriovenous Malformations

Arteriovenous malformations (AVMs) are high-flow VMs that occur due to the abnormal connections of arteries, veins, and capillaries, resulting in a direct arterial and venous communication. AVMs commonly occur in the head and neck region, but overall they are rare.[54] They are the most dangerous among all the vascular anomalies because they are associated with life-threatening complications. In the oral cavity, AVMs have been reported to occur on the tongue (most common), floor of the mouth, and palate, as well as the gingival and buccal mucosa.[55,56] An intraoral AVM appears as a soft, blanchable, red to bluish swelling, usually with a palpable thrill or audible bruit. Other oral findings include warmth, tissue expansion and destruction, ulceration, disfigurement, bleeding and pain. Clinically, AVM may be differentiated from IH by the continuous expansile growth after birth and from capillary malformation by the high-flow rate. The treatment objectives are to control the shunting effect and minimize clinical manifestations and complications. The treatment modalities include embolization and surgical management.[57]

Intraosseous Vascular Malformations

Intraosseous VMs are extremely rare. Fortunately, the majority of intraosseous VMs are predominantly venous malformations and AVMs are uncommon.[58–60] Intraosseous AVM is the more serious condition because of the risk for catastrophic hemorrhage after a dental extraction or a routine biopsy.[61–63] Affected individuals frequently present with pain, facial swelling and asymmetry, skin discoloration, loose teeth, bleeding from the gingival sulcus or associated with erupting teeth, and audible or palpable pulsations. Intraosseous venous malformation is a slow-growing, indolent mass with variable intraoral presentations depending on the location and extent. The condition may be totally asymptomatic or present with signs and symptoms similar but milder than that observed in an intraosseous AVM. Radiographically, intraosseous VM commonly appears as a unilocular or multilocular radiolucency, with each locule having a "soap bubble" or "honeycomb" appearance. A "sunburst" radiographic pattern may be observed with larger malformations. Teeth in the affected area may show root resorption. In addition to the treatment modalities for mucosal VMs, partial or total jaw resections may be indicated.[63,64]

Lip Anomalies

Cleft Lip and Palate

The incidence of cleft lip (CL) with or without cleft palate (CP) is approximately 1 in 700 live births.[65] About a quarter of cases are isolated CL (25%), 45% are CL with CP, and 30% are isolated CP. CL arises due to the failure of the medial nasal process to fuse with the maxillary process, while CP arises due to the failure of the palatal shelves to fuse. About 70% of CL with CP and 50% of CP cases occur as isolated entities, while the rest occur as part of a syndrome.[66] Hundreds of syndromes have been associated with CL with or without CP; the notable ones are van der Woude syndrome, Stickler syndrome, chromosome 22q11 deletion, oral–facial–digital syndrome type 1, and Treacher Collins syndrome. Nonsyndromic CL with or without CP is most frequent in males, while isolated CP is most typical in females. The risk of nonsyndromic CL with or without CP is associated with several maternal risk factors

such as tobacco and alcohol use, folate deficiency, obesity, stress, viral infections, and medications.[66] The clinical phenotype varies widely and is dependent on the number of structures affected, complete or incomplete presentation, and unilateral or bilateral involvement. The teeth near or within the cleft are often missing or malformed (typically the maxillary incisors). Early management include feeding and airway management, as well as surgical repair of lip and palate at 3 and 6 months of age, respectively. Additional surgery, speech therapy, and orthodontic treatment are often needed in later years.

Lip Pits

Commissural lip pits are small, unilateral or bilateral invaginations at the corners of the mouth on the vermillion border. They may extend up to a depth of 1–4 mm. Although considered developmental, they are often incidentally discovered in adulthood during a routine examination. No treatment is needed.

Paramedian lip pits (Figure 25-6) are rare congenital, bilateral symmetric depressions in the vermillion border of the lower lip. The most significant finding of paramedian lip pits is their autosomal dominant inheritance and their association with syndromes, most commonly van der Woude syndrome (characterized by lower lip pits, CL with or without CP, and congenitally missing premolars).[67] The treatment is directed toward problems associated with the congenital defects (e.g., CL, CP) or for esthetic reasons.

Tongue Anomalies

Ankyloglossia

Ankyloglossia or tongue tie is a developmental abnormality characterized by a short lingual frenum or a frenum attachment at or near the tongue tip, resulting in restricted tongue movement. Posterior ankyloglossia is a widely used term to specifically refer to a frenulum attachment at the middle to posterior aspect of the undersurface of the tongue. The use of the term "posterior ankyloglossia" is discouraged, because the frenulum attachment may be normal in these cases and the associated feeding difficulties are likely caused by other factors. The term "symptomatic ankyloglossia" is thus more appropriate. The reported prevalence of ankyloglossia ranges widely from <1% to 12%, with a male predilection.[68,69] The diagnosis has increased significantly in the past two decades due to the increased advocacy of breastfeeding coupled with the awareness of the impact of ankyloglossia on breastfeeding.[70]

There are generally two classification systems used to grade ankyloglossia severity: those that utilize anatomic criteria such as point of tongue attachment and length of frenulum (e.g., Coryllos system, Kotlow system) and those that incorporate function in addition to anatomic criteria (e.g., Hazelbaker Assessment Tool for Lingual Frenulum Function, Bristol Tongue Assessment Tool).[68] Classification systems that incorporate function are generally preferred, but so far none is universally accepted. The clinical examination often reveals the presence of a heart-shaped tongue on protrusion or the inability of the tongue to touch or protrude beyond the vermillion border. Infants with ankyloglossia are reported to experience more difficulty with breastfeeding. In such cases, frenotomy, which involves elevating the tongue, isolating the frenulum with a retractor/gloved fingers, and cutting of the frenulum with scissors, may be performed. Hemostasis is easily achieved with the application of pressure with gauze. Frenotomy may also be carried out with a laser or electrocautery. A randomized clinical trial concluded that topical anesthesia is not beneficial for pain relief. Instead, 24% sucrose solution given orally before the procedure accompanied by postprocedure nonnutritive sucking can help reduce discomfort.[71] Complications are rare, but may include bleeding (most common), pain, injury to the Wharton ducts, infection, and recurrence. The association between ankyloglossia and articulation problems, malocclusion, gingival recession, and mandibular growth is not clearly defined. A recent systematic review concluded that there was insufficient evidence to support frenotomy for these conditions.[72,73]

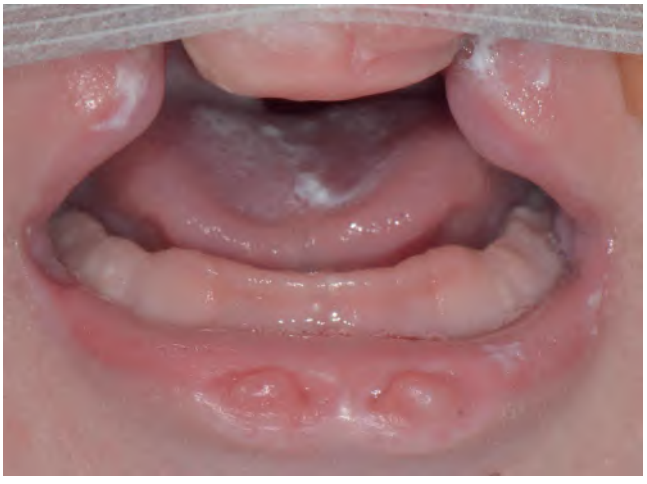

Figure 25-6 Paramedian lip pits and bilateral cleft lip and palate in a patient with van der Woude syndrome. *Source*: Courtesy of Dr. Chng CK.

Tongue Size Anomalies

Macroglossia is characterized by an abnormally large tongue. Pseudomacroglossia is a condition in which the tongue size is normal, but appears large in relation to adjacent structures. Microglossia is a rare condition characterized by an abnormally small tongue with an unknown etiology. There are only approximately 50 cases reported in the literature. Microglossia is often associated with a small

Table 25-3 Congenital causes of abnormal tongue size.

Macroglossia	Microglossia
Beckwith Widerman syndrome	Oromandibular limb hypogenesis syndromes
Congenital hypothyroidism	• Charlie M syndrome
Congenital idiopathic macroglossia	• Hypoglossia–hypodactylia syndrome
Trisomy 21* (Down syndrome)	• Mobius syndrome
Glycogen storage disease type 2	
Mucopolysaccharidosis	
Multiple endocrine neoplasia type 2B	
Neurofibromatosis	
Vascular malformations	

*There is debate with regard to whether a protruding tongue in children with Trisomy 21 is caused by true macroglossia or poor muscular tone.
Refer to Online Mendelian Inheritance in Man for complete lists: https://www.ncbi.nlm.nih.gov/omim/?term=macroglossia; https://www.ncbi.nlm.nih.gov/omim/?term=microglossia.

mandible, atrophic mandibular ridge, and missing incisors. The common developmental causes for both conditions are listed in Table 25-3. The need for intervention depends on the etiology and severity of the condition.[74] Treatment is warranted for a grossly enlarged tongue if there is ulceration and necrosis of the tip of tongue, airway obstruction, and swallowing difficulties. The treatment modalities include orthodontics and/or surgery (i.e., glossectomy).

Fissured Tongue

Fissured tongue is characterized by shallow or deep grooves or fissures on the dorsum of the tongue. The prevalence ranges greatly between 0.6% to as high as 30% in some parts of the world.[75,76] Although considered a developmental condition, it is observed more frequently in adults. The condition is generally asymptomatic and does not require treatment. Deep fissures can trap food debris and individuals may complain of slight discomfort due to inflammation or secondary fungal infections. Affected individuals are encouraged to gently brush their tongue daily to prevent the recurrence of symptoms. Antifungals may be prescribed if needed. Fissured tongue has been associated with benign migratory glossitis (geographic tongue), Trisomy 21 (Down syndrome), and Melkersson–Rosenthal syndrome.[77–79]

Retrocuspid Papillae

The retrocuspid papilla is a small (2–3 mm), moderately firm, smooth-surfaced, sessile, round, pink (normal gingival color) to red papule located on the attached lingual gingiva of the mandibular canine. They often occur bilaterally and are observed more frequently in children and females. The reported prevalence ranges from 25% to 80%. The histologic examination reveals large, stellate-shaped, multinucleated fibroblasts that are similar to those observed in giant cell fibroma.[80] The diagnosis is made clinically based on the bilateral presentation and location. Retrocuspid papillae are asymptomatic and spontaneously resolve with age. No treatment is needed.

Café-au-Lait Pigmentation

Café-au-lait pigmentation appears as well-circumscribed, uniformly light to dark brown skin macules that are typically two to three shades darker than the normal skin color. They vary from a few millimeters to ≥10 cm and can occur anywhere on the body. Café-au-lait pigmentation is often present at birth or appears in the first months of life. Isolated macules are common and usually have no clinical significance. However, multiple café-au-lait spots or macules should prompt evaluation for underlying genetic disorders such as Peutz–Jeghers syndrome, McCune–Albright syndrome, or neurofibromatosis type 1.[81,82] The outline of the café-au-lait spots may provide a clue as to the underlying genetic disorder. Café-au-lait spots in McCune–Albright syndrome have characteristic irregular borders analogous to the coast of Maine, unlike the smooth borders of the hyperpigmentation in neurofibromatosis, which is analogous to the coast of California. Multiple mucosal pigmentations on the lips and buccal mucosa have also been observed in these genetic disorders.[83] Of these disorders, perioral pigmentation is a prominent feature in Peutz–Jeghers syndrome. The intraoral pigmentation associated with genetic conditions, especially those on the buccal mucosa, do not fade and tend to persist with age.[81] Another case report suggested that intraoral pigmentations associated with genetic disorders appeared to develop later in life compared to the cutaneous café-au-lait pigmentation.[84]

Congenital Lingual Melanotic Macule

Congenital lingual melanotic macule (CLMM) is a rare benign condition that was first described in 2003.[85] The prevalence is unknown. CLMM (Figure 25-7) is present at birth and appears as a homogeneous or heterogeneous, 2–5 mm brown or black macule on the midline or the lateral border of the tongue. The size appears to increase with the infant's

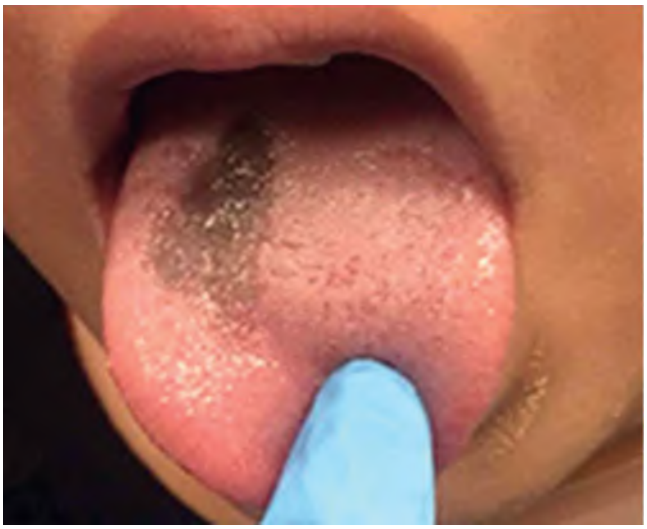

Figure 25-7 Congenital lingual melanotic macule.

growth. The histologic examination reveals increased melanin deposition in the basal cell layer and varying degrees of hyperkeratosis.[86] The diagnosis is often made clinically based on the characteristic appearance and the presence at birth. No treatment is required other than routine reviews to ensure that the macule has not rapidly increased in size or demonstrated any signs of induration or ulceration. A biopsy is indicated if the macule displays these signs and symptoms.

Physiologic Pigmentation

Physiologic pigmentation is common among darker-skinned individuals and results from an increase in melanin production. The attached gingiva is the most common location, where it appears as a homogeneous, ribbon-like band of light brown to almost black pigmentation. Physiologic pigmentation may be observed elsewhere in the oral cavity, including the tips of the fungiform papillae. The color appears to darken with age. The diagnosis is made clinically and no treatment is required.

Genetic Disorders with Significant Oral Mucosal Findings

Hereditary Gingival Fibromatosis

Hereditary gingival fibromatosis (HGF) is a rare condition characterized by a slow, progressive gingival enlargement due to the collagenous overgrowth of connective tissue. The incidence ranges greatly between 1 in 175,000 to 1 in 750,000 live births. HGF may be an isolated disorder with an autosomal dominant or recessive mode of inheritance (less common), or may occur as part of a syndrome (Table 25-4).[87] The gingival enlargement is asymptomatic and the enlarged gingival tissue is firm, fibrotic, and pink in color (normal mucosal color). There is minimal inflammation. The location of the gingival enlargement may be generalized or localized to either a quadrant or the interdental papillary area. The condition is rarely present at birth and the onset appears to correlate with the eruption of the permanent dentition, though there have been reports of earlier onset coinciding with the eruption of the deciduous dentition. The gingival enlargement worsens during adolescence, suggesting a hormonal influence. The complications include mastication and speech difficulties as well as teeth displacement. The diagnosis is usually made clinically based on presentation, family history, and exclusion of drug-induced causes of gingival enlargement. For minimal gingival enlargement, regular professional dental cleaning and a good oral hygiene home-care program are often adequate. Gingivectomy may be carried out for more extensive involvement, but repeated interventions are needed due to recurrence.

Multiple Neuroendocrine Neoplasia Type 2B

Multiple endocrine neoplasia syndromes (MENs) are a group of rare autosomal dominant disorders classified into types 1, 2A, 2B (formerly type 3), and 4 based on the genetic mutations and phenotypic features. The estimated prevalence of MEN type 2 is 1 in 30,000 and the disorder is due to a mutation in the *RET* proto-oncogene. This mutation causes a gain of function, resulting in increased cell proliferation and abnormal division in tissues where the *RET* proto-oncogene is expressed (i.e., thyroid, parathyroid, adrenal glands). Oral findings are prominent features in MEN type 2B, typically occurring in the first decade of life, and are often the first signs of the syndrome. The oral findings present as multiple asymptomatic, pink or mucosal-colored nodules or papules ("oral neuromas").[92] They are frequently located on the labial mucosa or anterior tongue,[93,94] but may also be observed on the buccal mucosa, gingiva, or palate. The presence of bilateral neuromas on the commissures of the lips is characteristic for MEN type 2B.[95] The histologic examination of the neuroma reveals an encapsulated mass of myelinated and unmyelinated nerves in a connective tissue background.[96] Other clinical features include full lips, thickened eyelids, high-arched palate, and a marfanoid body habitus. A serious complication in all individuals with MEN type 2B is the early development of aggressive medullary thyroid carcinoma (MTC).[97] Approximately 50% will also develop pheochromocytoma. A preliminary diagnosis of MEN type 2B is made based on the clinical presentation and confirmed with genetic testing. The treatment objectives are early diagnosis and prophylactic thyroidectomy at an early age (usually during the first year of life). Those who do not undergo thyroidectomy are likely to develop metastatic MTC. No treatment is necessitated for the oral neuromas as they are benign. They may be surgically excised if they interfere with function or for esthetic reasons.

Table 25-4 Syndromes associated with hereditary gingival fibromatosis.

Syndrome[87]	Inheritance	Features Apart from Gingival Enlargement
Costello syndrome[88]	Autosomal dominant	• Coarse facial features including relative macrocephaly, high forehead, bi-temporal narrowing, hypertelorism, short nose with depressed nasal bridge, large mouth with thick upper lip vermillion, low-set ears • Nasal and perioral papillomas • Redundant skin on neck, hands, and feet • Short stature
Cross syndrome	Autosomal recessive	• Athetosis • Hypopigmentation • Intellectual disability
Amelogenesis imperfecta, type Ig (Enamel–renal–gingival syndrome)[89]	Autosomal recessive	• Amelogenesis imperfecta • Nephrocalcinosis
Gingival fibromatosis with hypertrichosis	Autosomal dominant	• Hypertrichosis • Intellectual disability
Hyaline fibromatosis syndrome[90] (Figure 25-8)	Autosomal recessive	• Joint stiffness and contractures • Osteopenia • Pink papules on chin, nasolabial folds, forehead, ears, and back of neck • Subcutaneous nodules • Systemic manifestations, e.g., failure to thrive, persistent diarrhea, recurrent infections
Jones syndrome	Autosomal dominant	• Progressive sensorineural hearing loss
Ramon syndrome	Autosomal recessive	• Cherubism • Epilepsy • Hypertrichosis • Intellectual disability • Juvenile rheumatoid arthritis • Ocular abnormalities • Stunted growth
Rutherford syndrome	Autosomal dominant	• Corneal dystrophy • Delayed tooth eruption
Zimmermann–Laband syndrome[91]	Autosomal dominant	• Dysplastic or absent nails • Ear and nose defects • Hepatosplenomegaly • Hirsutism • Hypoplasia of distal phalanges • Joint hyperextensibility • Scoliosis

Sources: Refer to Online Mendelian Inheritance in Man for a complete list of syndromes: https://www.ncbi.nlm.nih.gov/omim/?term=hereditary+gingival+fibromatosis

Sources: Coletta RD, Graner E. Hereditary gingival fibromatosis: a systematic review. *J Periodontol.* 2006;77(5):753–764; Poulopoulos A, Kittas D, Sarigelou A. Current concepts on gingival fibromatosis-related syndromes. *J Investig Clin Dent.* 2011;2(3):156–161; Martelli-Junior H, Bonan PR, Dos Santos LA, et al. Case reports of a new syndrome associating gingival fibromatosis and dental abnormalities in a consanguineous family. *J Periodontol.* 2008;79(7):1287–1296; Bedford CD, Sills JA, Sommelet-Olive D, et al. Juvenile hyaline fibromatosis: a report of two severe cases. *J Pediatr.* 1991;119(3):404–410; Castori M, Valiante M, Pascolini G, et al. Clinical and genetic study of two patients with Zimmermann-Laband syndrome and literature review. *Eur J Med Genet.* 2013;56(10):570–576.

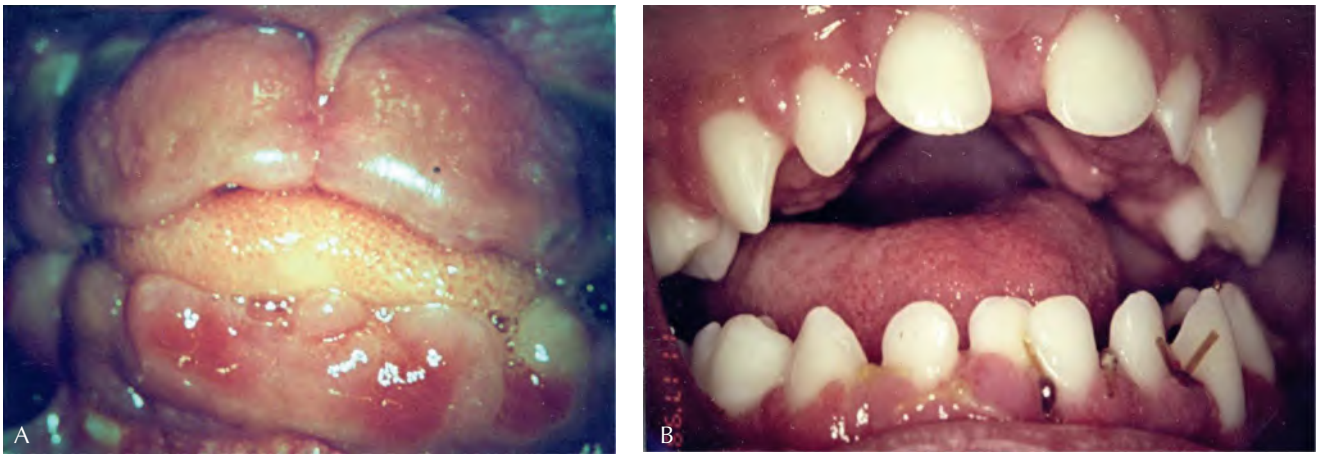

Figure 25-8 Gingival enlargement associated with hyaline fibromatosis syndrome. A. Preoperative. B. Postoperative.

Genodermatoses

Genodermatoses are a large group of inherited skin disorders. Many of these disorders have accompanying oral findings, which are discussed in this section.

Cowden Syndrome (Multiple Hamartoma Syndrome)

Cowden syndrome is an autosomal dominant disorder characterized by the distinctive mucocutaneous findings of trichilemmomas, acral keratosis, as well as facial and oral papillomatous papules. The estimated prevalence is 1 in 200,000 to 1 in 250,000. The majority of cases are due to a mutation in the *PTEN* gene. The *PTEN* gene is considered to be a tumor suppressor gene and the loss of function results in uncontrolled cell proliferation. The age of onset of the skin and oral findings ranges from 4 to 75 years of age, but is most commonly noticed in the second decade of life. The oral findings present as multiple asymptomatic papules on the gingiva, buccal mucosa, and tongue in up to 80% of affected individuals and impart a "cobblestone" appearance to the affected surfaces. This oral presentation has been termed "oral papillomatosis" or "fibropapillomatosis."[83,98] A recent study suggested that the etiology of the oral papillomatous papules may be related to the human papilloma virus.[99] Other dental findings include high-arched palate, increased risk of periodontal disease, and dental caries.[100] The systemic presentations include hamartomas in multiple organ systems, gastric and intestinal polyps, increased risk for breast (most common), thyroid, endometrial, and renal carcinomas, macrocephaly, and cognitive delay. The National Comprehensive Cancer Network clinical criteria are often used to obtain a preliminary diagnosis of Cowden syndrome.[101,102] Follow-up genetic testing should be performed to confirm diagnosis if the individual fulfills the criteria. The treatment objectives include close cancer surveillance and genetic counseling. No treatment is usually needed for the mucocutaneous lesions as they are benign. Surgical excision may be carried out for esthetic reasons or if the lesions interfere with function.

Dyskeratosis Congenita (Zinsser–Engman–Cole Syndrome)

Dyskeratosis congenita (DC) is a rare inherited disorder characterized by the classic triad of mucocutaneous features: dystrophic nails, oral leukoplakias, and reticular skin hyperpigmentation. Three modes of inheritance are recognized: X-linked recessive, autosomal dominant, and autosomal recessive. The estimated incidence is 1 in 1,000,000 live births. DC is caused by a defect in the telomere complex resulting in genomic instability and premature cell death. Several genetic mutations have been reported, including *ACD*, *CTC1*, *DKC1*, *NHP2*, *NOP10*, *PARN*, *RTEL1*, *TERC*, *TERT*, *TINF2*, and *WRAP53*.[103] The oral lesions in DC present as bullae on the tongue or buccal mucosa that rupture to form erosions or ulcers (Figure 25-9). The chronic cycle of mucosal breakdown and healing eventually results in the development of generalized intraoral white plaques (oral leukoplakia).[83,104] The tongue is the most frequently affected site. Oral leukoplakias are present in 65%–80% of individuals with DC, including those younger than 15 years of age. One-third of the oral leukoplakias will become malignant within a 10–30-year period.[83] In addition to the increased risk for head and neck squamous cell carcinoma, individuals with DC are at an increased risk for hematologic (e.g., leukemia, myelodysplastic syndrome)[105] and solid organ malignancies (e.g., lung, stomach). Other reported oral/dental findings include complete loss of papillae on the tongue, spontaneous oral bleeding, intraoral pigmentation, oral lichenoid changes, aggressive periodontitis, decreased crown-to-root ratio, increased risk of dental caries, hypodontia, and taurodontism.[106–108] DC is usually diagnosed between the ages of 5 and 12 years and is made based on the classic mucocutaneous

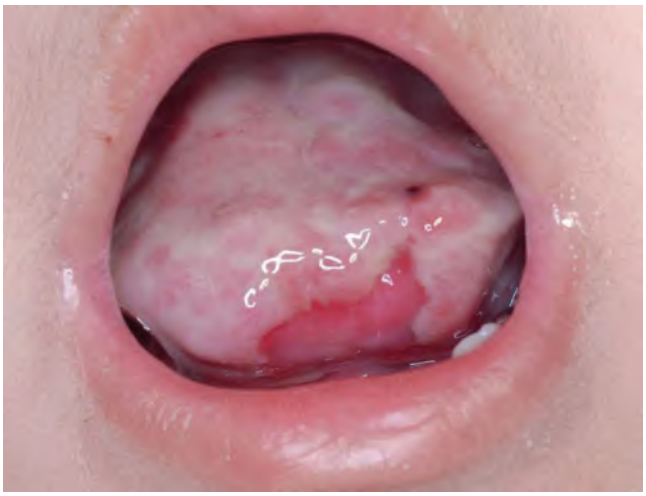

Figure 25-9 Dyskeratosis congenita with widespread ulceration and microstomia.

features. Reticulate hypopigmentation involving the chest and neck, and small thin nails with longitudinal ridges that fade with age, are the typical initial findings. The management of DC is based on the involved organ systems. Early diagnosis and referral to a hematologist are essential because of the risk of bone marrow failure. Hematopoietic cell transplantation is the definitive treatment for bone marrow failure associated with DC, but this does not resolve the oral lesions. The use of topical corticosteroids and thalidomide for oral ulcers in both children and adults has been reported with variable effectiveness.[105] As the oral leukoplakias in individuals with DC have a 1000-fold increased risk of malignant transformation compared to the general population, a comprehensive oral mucosal examination should be performed every 6 months.[109] Biopsy is indicated if the oral leukoplakic areas demonstrate clinical features suspicious for malignant changes (i.e., thickening surface, granular or verruciform surface, erythroplakia).

Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a genetically diverse group of disorders characterized by epithelial fragility resulting in blisters and ulcers after minor trauma. The estimated incidence is 1 in 50,000 live births. EB is classified into four main types based on the level of blister formation: EB simplex (most common; Figure 25-10), junctional EB, dystrophic EB, and Kindler syndrome.[110] Within each type, there are various subtypes that are further classified based on the inheritance pattern, the defective protein, and phenotypic features.[111] Table 25-5 summarizes the key findings of the various EB subtypes. The diagnosis of EB is confirmed by skin biopsy with immunofluorescence microscopy. Some cases may require transmission electron microscopy or mutational analysis to identify the level of cleavage and subtype. There is no cure for EB and the treatment strategies are largely supportive (e.g., pain control, wound care, prevention of secondary infections). Oral healthcare is an integral component of the multidisciplinary care needed for individuals with EB because of their increased risk for dental caries (due to difficulty in maintaining adequate oral hygiene) and oral malignancies. The general dental management includes emphasis

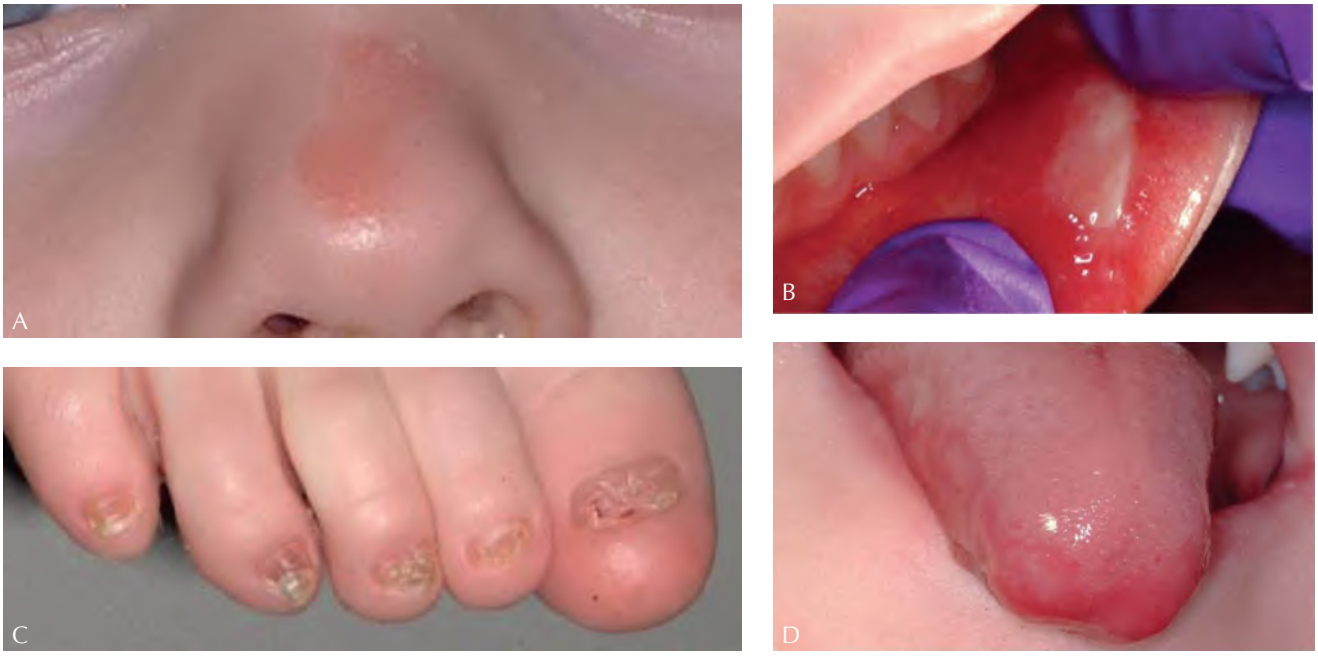

Figure 25-10 A–D. Epidermolysis bullosa simplex

Table 25-5 Epidermolysis bullosa types, mutations, and presentations.

Type/ Inheritance	Gene	Defect and Level of Bullae/ Blister Formation	Common Subtypes	Key Findings	Oral Findings				
					Blister/ Ulcer (Severity)	Scarring	Microstomia	Enamel Defects	Oral SCCA
EB Simplex/ mostly AD	Common • *KRT5* • *KRT14* Rare • *DSP* • *DYS* • *DST* • *EXPH5* • *ITGA6* • *JUP* • *KLHL24* • *PKP1* • *PLEC1* • *TGM5*	Mostly caused by keratin defects, which result in a cleavage at the intraepidermal level	• Localized • Generalized intermediate • Generalized severe	• Onset at birth or early infancy for generalized types, may be later for localized type • Bullae in areas of trauma (e.g., hands, elbows, and feet), which usually heal without scarring for milder types • Generalized severe type may have nail and hair abnormalities • Usually normal life span	Yes, severity depends on type (Localized: + Generalized: ++)	Localized: No Generalized severe: Yes	No	No	No
EB Junctional/ AR[116]	Common • *LAMA3* • *LAMB3* • *LAMC2* Others • *COL7A1* • *ITG6A* • *ITGB4*	Mostly caused by a lack of laminin-332, which results in a structural defect of the anchoring filament, causing a cleavage at the intralamina lucida level	• Localized • Generalized intermediate • Generalized severe	• Onset at birth or early infancy for all types, though milder for localized type • Localized type: mild with blistering localized to hands, feet, knees, and elbows that heal without scarring • Generalized types: severe widespread mucocutaneous blistering that heals with scarring • Generalized severe type is associated with mortality before 1 year of age	Yes, severity depends on type (Localized: ++ Generalized: +++)	Yes	Localized: No Generalized: Yes	Yes	No

EB Dystrophic/ AD or AR[117]	*COL7A1*	Mostly caused by collagen type VII defect (main constituent of anchoring fibrils), which results in a cleavage at the sublamina densa level	• AD generalized • AR generalized intermediate • AR generalized severe	• Onset at birth • Generalized bullae that heal with scarring • Contraction flexures at elbows and fusion of digits of hands and feet due to scarring • Nail dystrophy • AR types more severe than AD type and are associated with shortened life expectancy due to infection and severe malnutrition	Yes, severity depends on type (AD: + AR: ++/+++)	Yes, but less severe in AD	AD: No AR: Yes	No	AD: No AR: Yes
Kindler syndrome/ AR[118]	*FERMT1*	Caused by a defect in kindlin-1 that results in cleavages at multiple levels (Intraepidermal, intralamina lucida, sublamina densa)	Not applicable	• Skin bullae usually present at birth and may be severe, but appear to decrease with age • Nail dystrophy • Photosensitivity • Progressive poikiloderma • Skin atrophy • Sparse hair	Yes (++), though blisters/ ulcers appear to decrease with age	Yes	Variably present or absent	No (but periodontal disease is common)	Yes

AR, autosomal recessive; AD, autosomal dominant; SCCA, squamous cell carcinoma; +, mild if present; ++, present and moderately severe; +++, always present and severe.

on preventive care (e.g., diet counseling, placement of fissure sealants, alcohol-free fluoride rinses, fluoride varnish) and regular professional oral examinations. Special precautions are needed during dental visits to minimize injury to the oral mucosa. Copious lubrication of the oral tissues, gloves, radiographic films, and instruments as well as contact avoidance of suction tips on mucosal tissues should be routinely carried out. If blisters form during dental treatment, they may be drained with a sterile needle to limit blister growth.[112] The management of the oral ulcers is largely symptomatic (e.g., sucralfate, bland mouth rinses).[113,114] A recent pilot study evaluated the use of cord blood platelet gel with or without low-level laser therapy and found them safe and effective for the treatment of oral lesions in individuals (mean age: 19 years, range: 9 to 34 years) with EB.[115]

Hereditary Benign Intraepithelial Dyskeratosis (Witkop-von-Sallman Syndrome)

Hereditary benign intraepithelial dyskeratosis (HBID) is a rare autosomal dominant disorder of the conjunctiva and oral mucosa with a prevalence of <1 in 1,000,000.[119] This condition was first described in descendants of the Haliwa-Saponi Native American tribe in North Carolina. Sporadic cases have been reported. The genetic defect is not well characterized, though de novo duplication of 4q35 has been reported in some cases.[120] The oral findings present as asymptomatic white plaques of varying thickness on the buccal and labial mucosa.[121,122] They are occasionally observed on the floor of the mouth or lateral border of the tongue. Clinically, they appear similar to white sponge nevus. The histology examination reveals prominent parakeratin production and marked acanthosis. In addition, an unusual feature whereby an epithelial cell appears to be surrounded by another epithelial cell ("cell-within-cell" pattern) is present.[123] The ocular lesions initiate early in life and are present in almost all individuals with HBID by 1 year of age. The conjunctival plaques are usually bilateral and often associated with dilated hyperemic epibulbar blood vessels, giving rise to the appearance of eye redness. The ocular signs and symptoms vary based on the extent and severity of involvement. Preliminary diagnosis is made based on the ocular and oral presentations, and diagnosis is confirmed with histology. There is no cure for HBID and the treatment is symptomatic. The oral lesions are often asymptomatic and thus do not require treatment. Furthermore, no cases of malignant transformation have been reported.[83] For ocular lesions, surgical excision is indicated for patients with impaired vision; however, the lesions tend to recur after excision.

Neurofibromatosis Type 1 (Von Recklinghausen's Disease)

Neurofibromatosis (NF) type 1 is the most common form of neurofibromatosis and is characterized by multiple café-au-lait macules and neurofibromas. The incidence is 1 in 2500 to 1 in 3000 live births. About half of the cases are inherited (autosomal dominant inheritance), while the rest are a result of sporadic mutations. NF type 1 is caused by a mutation of the *NF1* gene, which results in the lack of production or reduced function of the tumor suppressor protein neurofibromin.[124] More than 70% of affected individuals with NF type 1 present with intraoral neurofibromas and enlargement of the fungiform papillae.[125,126] Another common oral finding is the enlargement of the attached gingiva. Dental radiographic examination may reveal enlargement of the mandibular foramen. The most serious complication of NF type 1 is the development of malignant peripheral nerve sheath tumors and other cancers such as rhabdomyosarcoma, Wilms tumor, leukemia, and tumors of the CNS.[127] The diagnosis is made clinically based on the presence of ≥2 characteristic clinical features (Table 25-6). There is no cure for NF. The management objectives are early detection through regular reviews and treatment (e.g., surgical intervention, pain control) when complications (e.g., interference with function, compression of vital structures, esthetic concerns) arise. Treatment is not routinely needed for intraoral neurofibromas as they are mostly benign, though there have been reports of malignant transformation.[128,129]

Table 25-6 Diagnostic criteria for neurofibromatosis type 1.

≥6 cafe au-lait macules of >5 mm (greatest diameter) in prepubertal individuals, and >15 mm (greatest diameter) in postpubertal individuals
≥2 neurofibromas or one plexiform neurofibroma
Axillary or inguinal freckling
Optic glioma
≥2 iris hamartomas (Lisch nodules)
Distinctive bony lesion, such as sphenoid dysplasia, or medullary narrowing and cortical thickening of the long bone cortex with or without pseudarthrosis
A first-degree relative with neurofibromatosis type 1 diagnosed based on the above criteria

Keratosis Follicularis (Darier–White Disease, Dyskeratosis Follicularis)

Keratosis follicularis is a rare autosomal dominant disorder characterized by skin, nail, as well as oral and other mucosal changes (i.e., esophageal, vaginal, anal, rectal). The condition has a prevalence of 1 in 30,000 to 1 in 100,000 and affects both males and females. Keratosis follicularis is caused by a mutation in the *ATP2A2* gene, which codes for the calcium pump of the endoplastic reticulum of the epithelial cells. The mutation results in abnormal cell adhesion. Oral findings are present in approximately 13%–50% of cases and appear as white papules of varying sizes with a central

depression. The papules may coalesce and impart a "cobblestone" appearance to the affected surfaces.[104,130] The skin lesions are characterized by red-brown keratotic papules following a seborrheic distribution. The nail changes are characterized by white and red bands along the longitudinal length of the nails with a V-shaped notch at the free nail border. The diagnosis is made based on the mucocutaneous presentations and histology of skin lesions. There is no cure for keratosis follicularis. The treatment objectives are to improve the skin appearance, prevent or treat infectious complications, and provide symptomatic relief. Treatment for the oral lesions is usually not needed as they are asymptomatic.

Pachyonychia Congenita (Jadassohn–Lewandowsky syndrome)

Pachyonychia congenita is a rare autosomal dominant disorder characterized by plantar keratoderma and hypertrophic nail dystrophy. As of June 2019, there were 907 individuals registered on the International Pachyonychia Congenita Research Registry[131] The condition is caused by mutations in five keratin genes, *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, or *KRT17*.[132] The consequence is a weakened keratin cytoskeleton, resulting in epithelial fragility. Up to 50% of affected individuals present with oral leukokeratosis, which appears as thick, whitish gray plaques on the dorsum of the tongue, gingival, buccal, and palatal mucosa.[104,132,133] The lesions may be painful. The presence of natal or neonatal teeth has been reported in some individuals.[132,133] A diagnosis is made based on the mucocutaneous presentations and confirmed with genetic testing. There is no cure for pachyonychia congenita. The treatment objectives are to reduce the nail and skin changes as well as offer pain control.

Tuberous Sclerosis Tuberous sclerosis is an autosomal dominant hamartoneoplastic disorder affecting multiple organ systems, including the brain, heart, skin, kidneys, and lungs. The reported incidence is 1 in 6000 to 1 in 10,000 live births. Tuberous sclerosis is caused by a mutation in either the *TSC1* or, more frequently, the *TSC2* gene.[134] The *TSC* genes function as tumor suppressor genes; thus, their mutations result in the abnormal production of hamartin (*TSC1*) and tuberin (*TSC2*), which regulate cell growth and size. The characteristic oral finding is the presence of fibromas, commonly occurring on the anterior gingiva.[135,136] They may also be present on the buccal and palatal mucosa, lips, tongue, and intraosseously.[104,137] A prominent dental finding is the enamel pitting on the facial surfaces of anterior teeth. Other reported dental/oral findings include diffuse gingival overgrowth not associated with drug therapy, mucosal and intraosseous vascular anomalies, CL, CP, high-arched palate, bifid uvula, and delayed dental eruption. In addition to the features in Table 25-7, other systemic findings include seizures, cognitive deficits, autism spectrum disorder, and the increased risk of renal cell carcinoma, rhabdomyosarcoma, and malignant tumors of the CNS. The disorder is usually diagnosed by 4–10 years of age and is based on the clinical criteria with or without genetic testing. The clinical diagnosis is made based on the presence of 2 major features or 1 major feature with ≥2 minor features (Table 25-7). Those who fulfill the criteria do not need to undergo genetic testing for diagnosis. The management of the oral fibromas includes regular reviews and surgical excision if they interfere with function or for esthetic reasons. However, they are likely to recur.

Table 25-7 Tuberous sclerosis diagnostic criteria.

Major Features	Minor Features
Hypomelanotic macules (≥3, >5 mm)	"Confetti" skin lesions (1–3 mm hypopigmented macules on the extremities)
Angiofibromas (≥3) or fibrous cephalic plaque	Enamel pits (≥3, up to 3 mm)
Angiomyolipomas (≥2)	Intraoral fibromas (≥2)
Cardiac rhabdomyoma	Multiple renal cysts
Cortical dysplasia (includes tubers and cerebral white matter radial migration lines)	Nonrenal hamartomas
Lymphangioleiomyomas	Retinal achromic patch
Multiple retinal hamartomas	
Shagreen patch	
Subependymal giant cell astrocytoma	
Subependymal nodules	
Ungual fibromas (≥2)	

White Sponge Nevus White sponge nevus (WSN) is a rare autosomal dominant disorder with high penetrance but variable expression. The prevalence is estimated to be <1 in 200,000. The condition is caused by a mutation in genes encoding for keratin (e.g., *KRT4*, *KRT13*).[138] WSN typically presents at birth or in early childhood and is characterized by bilateral, diffuse, corrugated or velvety, white plaques commonly affecting the buccal mucosa and tongue.[83] Other mucosal surfaces such as the nasal, esophageal, and anogenital mucosa may be involved. The skin is not involved. The histologic examination reveals prominent hyperkeratosis, marked acanthosis, and intracellular edema of the spinous cells, which is similar to HBID (differentiated by ocular involvement in HBID). The diagnosis is made based on the clinical presentation and histology. Most individuals do not report any discomfort, but some may complain of an altered mucosal texture. No treatment is needed as this is a benign condition.

Natal and Neonatal Teeth

Natal teeth are teeth present at birth, while "neonatal" teeth refer to teeth that erupt within the first month of life. Natal teeth occurs three times more frequently than neonatal teeth.[139] The majority of natal and neonatal teeth are a result of the early eruption of teeth of the deciduous dentition, most commonly the lower central incisors.[139] The precise etiology for the natal and neonatal teeth is unknown. Most are isolated occurrences, though natal teeth have been associated with several syndromes such as chondroectodermal dysplasia, pachyonychia congenita, and oculomandibulofacial syndrome with hypotrichosis.[140] Clinically, the shapes of natal and neonatal teeth often resemble normal teeth but are smaller in size. Some may appear yellowish-brown due to enamel hypoplasia or hypomineralization. Natal and neonatal teeth are frequently mobile due to incomplete or defective root development. The complications include maternal discomfort during breastfeeding, sublingual ulceration, and tooth aspiration. The diagnosis is made clinically based on the time of eruption of the tooth and appearance. The management is directed by signs and symptoms.[141] No treatment is needed if there is no maternal or infant discomfort. When there is maternal/infant discomfort, smoothening the incisal edges of the tooth may alleviate symptoms.[142] In situations where the tooth is excessively mobile (only held by soft tissue) and is at significant risk for aspiration, extraction is indicated. Socket curettage after extraction should be performed to prevent continued development of the dental papilla cells, which may result in eruption of tooth-like structures later on.

Developmental Alterations in Number, Size, Shape, and Structure of Teeth

Alterations in number, size, shape, and structure of teeth typically occur as an isolated trait, but may be part of a syndrome. The associated problems are largely related to esthetics (e.g., malocclusion, ectopic eruption), aberrant eruption pattern/sequence, and dental sensitivity/pain. Table 25-8 provides a brief summary on common developmental dental abnormalities and the associated syndromes.

ACQUIRED CONDITIONS

Infectious Conditions

Herpes Simplex Virus Infections

Primary Herpetic Gingivostomatitis

Approximately 30% of herpes simplex virus (HSV) infections are symptomatic. The most common symptomatic presentation of an initial HSV infection is primary herpetic gingivostomatitis. The infection typically afflicts children between the age of 6 months and 5 years, and transmits mainly by direct contact with infected oral secretions or lesions. In young children, the presence of clusters of pin-head vesicles together with painful, edematous, and erythematous marginal gingiva that bleed easily are characteristic initial findings. The vesicles eventually rupture and coalesce to form larger ulcers. The ulcers occur on both the keratinized (most common on the gingiva, other sites tongue, hard palate) and nonkeratinized (most common on the buccal and labial mucosa) tissues. The lesions may also be present on the pharynx and perioral skin. Fever above 100.4 °F and malaise generally precede the oral findings. Most ulcers heal without scarring in 7–10 days. In severe cases, healing may take up to 14 days. In older children and adolescents, severe pharyngitis may be the main presenting symptom. The diagnosis is generally made clinically based on the history and clinical presentation. The main treatment objectives are pain control with either acetaminophen or ibuprofen and maintenance of adequate fluid intake. The use of "magic mouthwash" and other topical anesthetics such as topical benzocaine or lidocaine is not recommended in young children due to safety concerns and lack of evidence to demonstrate efficacy.[148] Topical antiviral therapy is not recommended for immunocompetent children. In immunocompromised individuals, topical antiviral therapy may accelerate resolution of the lesions, but parenteral therapy is generally preferred. Oral acyclovir (15 mg/kg/dose, 5 doses/day, 5–7 days) may be prescribed for immunocompetent children who present within 72–96 hours of disease onset and/or are in great pain or are unable to eat or drink.[149,150] For immunocompromised children, oral (children ≥2 years: 1000 mg/day divided in 3–5 doses, 10–14 days) or intravenous (children of all ages: 30 mg/kg/day divided in 3 doses, 10–14 days) acyclovir should be given regardless of time of onset. The refusal to drink may lead to dehydration, warranting hospitalization for parenteral fluid replacement.

Table 25-8 Dental abnormalities and associated syndromes.

Dental Abnormality and Type		Commonly Associated Syndromes
Number of teeth	• Hypodontia[143] – Most are isolated occurrences where only 1 or 2 teeth are congenitally missing. Permanent second premolars and maxillary lateral incisors are most likely to be missing – Anodontia (congenitally missing all teeth) and oligodontia (congenitally missing ≥6 teeth) are rare and more likely to be associated with syndromes	• Charcot–Marie–Tooth disease type 2E • Cleft lip/palate including associated syndromes with cleft lip/palate • Coffin–Lowry syndrome • Ectodermal dysplasias* • Rubinstein–Taybi syndrome • Trisomy 21 (Down syndrome)
	• Hyperdontia[140,144] – Most are isolated occurrences, commonly occurring at the anterior midline region (i.e., mesioden) – Extra teeth are known as supernumerary teeth	• Cleft lip/palate • Cleidocranial dysplasia • Familial adenomatous polyposis • Oculo-facial-cardio-dental syndrome • Oral–facial–digital syndrome types I and III • Rubinstein–Taybi syndrome • Trisomy 21 (Down syndrome)
Tooth size	• Microdontia – Most are isolated occurrences, often affecting the maxillary lateral incisor (peg lateral)	• Hemifacial microsomia • Pituitary dwarfism • Trisomy 21 (Down syndrome)
	• Macrodontia	• Hemifacial hyperplasia • Pituitary gigantism
Tooth shape	Most are isolated occurrences • Accessory cusps (e.g., cusp of Carabelli, dens evaginatus, Talons' cusp) • Concrescence • Ectopic enamel ("enamel pearl") • Fusion • Germination • Hypercementosis • Taurodontism	• Associated with hypercementosis – Paget's disease of bone[145] • Associated with taurodontism[146] – Amelogenesis imperfecta- taurodontism type IV – Klinefelter syndrome – Oral–facial–digital syndrome type II – Tricho-dento-osseous syndrome – Trisomy 21 (Down syndrome)
Tooth structure[147]	• Amelogenesis imperfecta • Dentinogenesis imperfecta • Dentine dysplasia • Regional odontodysplasia	• Associated with dentinogenesis imperfecta type 1 – Osteogenesis imperfecta

* Ectodermal dysplasias are a large group of inherited disorders characterized by abnormal structures (i.e., skin, nails, sweat glands, and teeth) derived from the embryonic ectoderm. Many of them are associated with hypodontia.

Sources: De Coster PJ, Marks LA, Martens LC, Huysseune A. Dental agenesis: genetic and clinical perspectives. *J Oral Pathol Med.* 2009;38(1):1–17; Lubinsky M, Kantaputra PN. Syndromes with supernumerary teeth. *Am J Med Genet A.* 2016;170(10):2611–2616; Yague-Garcia J, Berini-Aytes L, Gay-Escoda C. Multiple supernumerary teeth not associated with complex syndromes: a retrospective study. *Med Oral Patol Oral Cir Bucal.* 2009;14(7):E331–E336; Rao VM, Karasick D. Hypercementosis—an important clue to Paget disease of the maxilla. *Skeletal Radiol.* 1982;9(2): 126–128; Jaspers MT, Witkop CJ Jr. Taurodontism, an isolated trait associated with syndromes and X-chromosomal aneuploidy. *Am J Hum Genet.* 1980;32(3):396–413; refer to Online Mendelian Inheritance in Man for a complete list of syndromes: https://www.ncbi.nlm.nih.gov/omim.

Neonatal Herpes Simplex Virus Infection

Neonatal HSV infection is a serious and potentially fatal condition that occurs in 1 in 3000 to 1 in 10,000 live births.[151] The incidence appears to correlate with the seroprevalence of HSV-2 in the general population. Neonatal HSV infection may be transmitted in utero (5%), during intrapartum (85%), or postnatally (10%) and is grouped into three categories; localized skin, eye, and mouth (SEM) disease, CNS disease with or without involvement of SEM, and disseminated disease. SEM disease accounts for 45% of neonatal HSV infections.[152] Initially asymptomatic, the oral presentation eventually manifests as localized ulcers involving the oral mucosa, tongue, and palate. Eye involvement presents as excessive watering of the eye and conjunctival erythema. Skin lesions appear as clusters of coalescing vesicles with erythematous bases. The diagnosis is made by scraping of the

vesicles on the skin or oral mucosa and isolating the HSV virus by culture or detecting HSV DNA with polymerase chain reaction assays from these samples. Serology is not indicated, as it is only useful for determining past exposure. The treatment objectives are early intravenous antiviral therapy (at the time of suspected diagnosis) and supportive measures (e.g., fluid and electrolyte maintenance, antimicrobial therapy for secondary infections).[153] Fortunately, mortality is rare in HSV SEM disease. However, these patients should still be evaluated for CNS involvement and disseminated disease.

Varicella Zoster Virus Infection

The characteristic presentation of primary varicella zoster virus (VZV) infection is the vesicular and often pruritic skin rash on the face, trunk, and extremities. The main routes of transmission are via contact with aerosolized droplets from an infected individual or from direct contact with the vesicle fluid from the skin lesion. A prodrome of fever, malaise, pharyngitis, and loss of appetite usually presents 24 hours before the skin rash. Oral findings are common in VZV infections and may precede the skin rash. The oral lesions begin as small, white opaque vesicles, which eventually rupture to form small ulcers on the palate and buccal mucosa. They resemble the ulcers in primary herpetic gingivostomatitis, but are less painful.[154] The diagnosis is frequently made clinically from the history and typical skin presentation. Varicella zoster infections are self-limiting in immunocompetent individuals and the management is primarily symptomatic. Oral acyclovir (children ≥2 years: 20–30 mg/kg/dose, 4 doses/day, 5–10 days; longer for immunocompromised children, maximum dose 800 mg) or valacyclovir (20 mg/kg/dose, 3 doses/day, 5–10 days, longer for immunocompromised children, maximum dose 1000 mg) should be initiated for immunocompromised children and may be initiated for immunocompetent children who are at increased risk for complications (e.g., unvaccinated individuals, intermittent oral or inhaled steroid therapy, chronic salicylate therapy).[155]

Coxsackievirus Infections

The majority of herpangina and hand–foot–mouth disease (HFMD) cases occur in infants and children. The causative viruses for both conditions belong to the enterovirus family (Table 25-9) and the main route of transmission is through the fecal–oral route. The diagnosis for herpangina and HFMD is usually made clinically based on the history and oral (and skin for HFMD) presentation(s).

Herpangina

The onset of herpangina (Figure 25-11) is acute, with high fever, sore throat, and dysphagia. Prodrome is usually absent or very short (a few hours). Other associated symptoms include headache, nausea, and anorexia. The oral lesions begin as papules at the anterior pillars of the fauces, soft palate, tonsils, and uvula that eventually form vesicles, which rupture to form 3–4 mm aphthous-like ulcerations. The number of ulcers varies, but there is usually fewer than 10.

Table 25-9 Causative virus of hand–foot–mouth disease and herpangina.

Herpangina	Hand–Foot–Mouth Disease
Coxsackievirus **A1–A6**, A7, **A8**, A9, **A10**, A16, A22, B1 to B5	Coxsackievirus A2, A4–A10, **A16**, B2, B3, B5
Echovirus 6, 9, 16, 19	Echovirus 1, 4, 7, 19
Enterovirus A71	**Enterovirus A71**

Bold: common causes

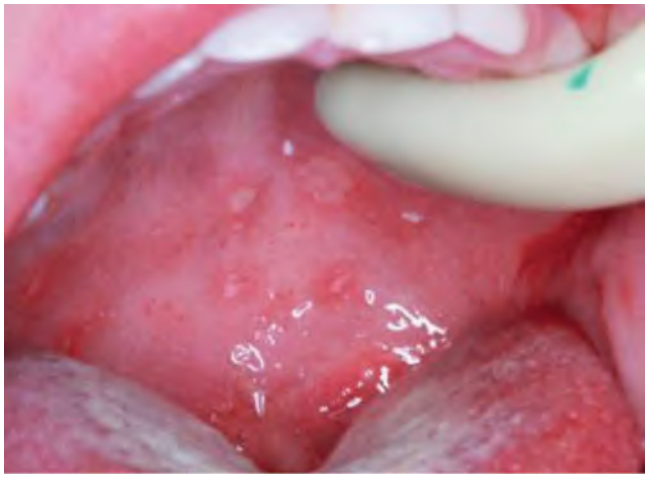

Figure 25-11 Herpangina.

Hand–Foot–and–Mouth Disease

Individuals with HMFD present with oral pain, often with accompanying fever and flu-like symptoms (e.g., malaise, myalgia). As with herpangina, prodrome is usually absent. The oral ulcers resemble herpangina ulcers, but are more numerous. The location of the oral ulcers in HFMD also differs from herpangina and they are located anterior to the faucial pillars, most commonly on the tongue, labial, and buccal mucosa. The hand lesions are located on the dorsum of the fingers, interdigital spaces, and palms. The foot lesions are typically on the dorsum of the toes, sole, heel, and lateral borders of the foot. In infants, toddlers, and preschool children, lesions may occur on the buttocks. The skin lesions may be macular, maculopapular, or vesicular. The skin vesicles contain a clear or turbid fluid surrounded by a halo of erythema. HFMD caused by enterovirus A71 and a novel coxsackievirus A6 genotype are associated with more severe disease patterns (Enterovirus 71: CNS disease, heart failure; Coxsackievirus A6: wider distribution, longer duration).[156–158]

The management for both herpangina and HMFD is usually symptomatic, as the majority of the infections are mild and resolve within 1–2 weeks. Topical oral anesthetics are not routinely prescribed due to safety concerns and lack of evidence to demonstrate efficacy in children. Antiviral therapy is also not recommended, as there is no specific drug against coxsackieviruses. Hospitalization may be needed for severe forms of HFMD due to the difficulty of maintaining adequate hydration and the potential for neurologic or cardiovascular complications.

Measles

Measles is an infection caused by the morbilli (rubeola) virus belonging to the *Paramyxovirus* virus family. The infection is transmitted through direct contact and the average incubation period is 14 days. The prodrome consists of fever, malaise, conjunctivitis, and cough. In addition, over 70% of cases present with a characteristic oral finding known as Koplick spots.[159] Koplick spots are 1–3 mm white spots surrounded by erythema, usually observed on the buccal mucosa. They are thought to represent foci of epithelial necrosis. Koplick spots appear 1–2 days before the characteristic skin rash (often beginning on the face and spreading downward) and typically last for 12–72 hours before sloughing off. Enamel pitting on the permanent teeth has been reported in children who develop measles in early childhood. The approaches to diagnosis differ depending on the prevalence of measles in the region. In general, measles should be considered in an unvaccinated individual presenting with the corresponding clinical signs (e.g., skin rash) and symptoms (e.g., fever, malaise), as well as a recent travel history to an area of high measles prevalence. Definitive diagnosis is made by one of the following investigations: detection of serum measles immunoglobulin (Ig) M antibody, a substantial rise in measles IgG antibody titers between acute and convalescent states, isolation of measles virus from culture, or detection of measles RNA by polymerase chain reaction. The treatment is supportive, as there is no specific antiviral therapy for measles. Early recognition is essential for infants due to their increased risk for complications, the most serious being respiratory tract complications and encephalitis.

Human Immunodeficiency Virus–Associated Lesions

Oral lesions associated with human immunodeficiency virus (HIV) infections are common in both adults and children. However, some are more common in children, while others are seldom observed in children (Table 25-10).[160,161] Recent studies suggest that HIV-associated oral lesions have significantly reduced in the post–highly active antiretroviral therapy era, with the exception of salivary gland disease and oral papillomas.[161]

Oral Findings in Other Acute Viral Infections

Oral and dental findings do occur in other viral infections not already mentioned so far in this chapter; however, they may not be consistently observed in all individuals. Table 25-11 summarizes these other viral infections and the associated findings.

Human Papillomavirus Infections

Human papillomavirus (HPV) is a double-stranded DNA virus that is epidermotropic and affects both mucosa and skin. To date, more than 130 types have been identified. The types are classified as either low or high risk based on their role in the pathogenesis of potentially malignant and malignant conditions. HPV types 16 and 18 have been associated with cervical, anal, oropharyngeal, laryngeal, and esophageal carcinomas.[162] HPV infection is transmitted by vertical or horizontal transmission (e.g., sharing utensils and toys) and/or self-inoculation from skin, genital, or anal lesions. The common HPV oral infections in children are squamous papilloma, verruca vulgaris (common wart), condyloma acumina-

Table 25-10 Pediatric human immunodeficiency virus (HIV)-associated oral lesions.

Group 1 Lesions Commonly Associated with Pediatric HIV Infection	Group 2 Lesions Less Commonly Associated with Pediatric HIV Infection	Group 3 Lesions Strongly Associated with HIV Infection But Rare in Children
Angular cheilitis	Cytomegalovirus infections	Kaposi's sarcoma
Erythematous and pseudomembranous candidiasis	Human papilloma virus infections	Non-Hodgkin lymphoma
Herpes simplex virus infections	Necrotizing ulcerative stomatitis	Oral hairy leukoplakia
Linear gingival erythema	Molluscum contagiosum	Tuberculosis-related ulcers
Parotid enlargement	Seborrheic dermatitis	
Recurrent aphthous ulcers	Varicella zoster virus infections	
	Xerostomia	

Table 25-11 Other viruses and the associated oral and dental findings.

Virus	Oral and Dental Findings
Cytomegalovirus	1) Most cases are asymptomatic 2) If symptomatic: • Pharyngitis is common in immunocompetent individuals • Chronic oral ulceration may be present in immunocompromised individuals • Congenital and neonatal infections result in developmental tooth defects
Epstein–Barr virus	1) Most cases are asymptomatic 2) Acute infectious mononucleosis is the most common symptomatic presentation of acute infection, typically affecting young adults: • Pharyngitis, tonsillitis, secondary tonsillar abscesses, palatal petechiae 3) Delayed complications usually associated with immunocompromised states: • Oral hairy leukoplakia • Lymphoproliferative disorder 4) Association with certain malignancies: • Burkitt lymphoma • Hodgkin lymphoma • In human immunodeficiency virus patients: non-Hodgkin lymphoma and smooth muscle tumors (specific in children: leiomyomas and leiomyosarcomas) • Nasopharyngeal carcinoma • T-cell lymphoma
Mumps	• 90% of cases present with bilateral parotid swelling • Orifice of Stensen's duct may be erythematous and enlarged
Rubella	• Forchheimer spots, which present as transient nonspecific red spots on the soft palate, may be observed in some individuals

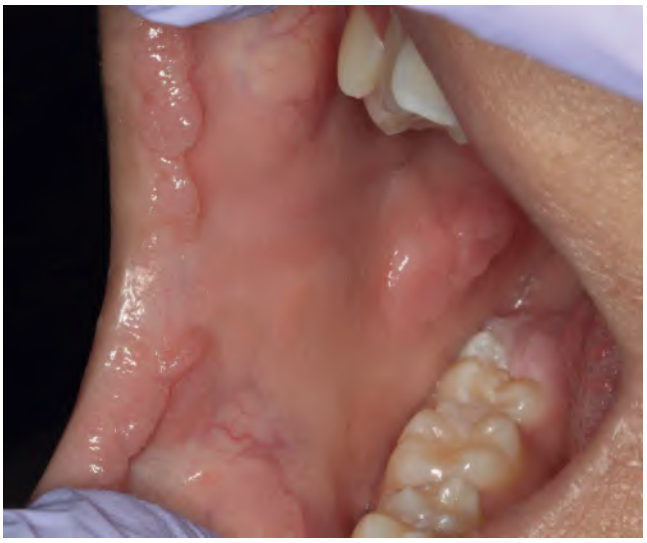

Figure 25-12 Multifocal epithelial hyperplasia (Heck's disease).

tum, and multifocal epithelial hyperplasia (Heck's disease; Figure 25-12). Table 25-12 summarizes the clinical presentations and treatments for these conditions.[163,164] Notably, HPV may be present in the oral mucosa without any observable clinical lesion.[165] The diagnosis is made based on the clinical presentation and histology. Several vaccines are available, including the bivalent vaccine targeting HPV 16 and 18, a quadrivalent vaccine for HPV 6, 11, 16, and 18, and the 9-valent vaccine for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. Currently, only the 9-valent vaccine is available in the United States. The Centers for Disease Control and Prevention recommend HPV vaccination for children 11–12 years of age. The recommendation for girls is for the prevention of cervical, anal, vaginal, and vulvar cancers, as well as anogenital warts. In boys, the vaccine is recommended for the prevention of anal and penile cancers, as well as for anogenital warts. There is evidence that vaccination protects against oropharyngeal HPV infections, but the evidence with regard to protection against HPV-associated oropharyngeal cancer is unclear.[166]

Superficial Candida Infections

Most superficial fungal infections are caused by *Candida albicans*. Pseudomembranous or erythematous candidiasis, angular cheilitis, and central papillary atrophy (CPA) are common superficial fungal infections in children.[170] Most of the causes and clinical presentations of these conditions are similar to adults and their descriptions are covered elsewhere in this textbook. Pseudomembranous candidiasis is relatively common in newborns (5%–10%) and is likely attributed to their immature immune system. Mild cases of

Table 25-12 Human papilloma virus (HPV)-associated oral lesions.

HPV Lesion	Causative HPV Type	Location	Presentation	Management	Recurrence/ Prognosis
Verruca vulgaris	2	• Labial mucosa • Anterior dorsum of tongue • Vermillion border of lip	• <5 mm papule • Pedunculated or sessile • Papillary projections or pebbly surface • Usually white color	• Surgical excision • Laser ablation (may produce HPV plume) • Electrosurgery	• May resolve spontaneously • Recurrence is low • No malignant transformation reported
Squamous papilloma	6, 11	• Labial mucosa • Tongue • Soft palate	• 5–10 mm papule • Usually pedunculated • Exophytic surface projections • Red, white, or normal mucosal color		• Recurrence is unlikely • No malignant transformation reported
Condyloma acuminatum	6, 11, 16, 18	• Labial mucosa • Lingual frenum • Soft palate	• 10–15 mm papule • Sessile • Blunt papillary projections • Pink color		• No malignant transformation reported even when caused by HPV subtypes 16 and 18[167] • This is considered a sexually transmitted lesion. If sexual abuse is suspected, a report to the appropriate authorities is warranted
Multifocal epithelial hyperplasia (Heck's disease) (Figure 25-12)	13, 32	• Labial, buccal, and lingual mucosa • Gingiva • Palate • Floor of mouth • Tonsillar mucosa	• Primarily seen in children • Papulonodular variant: multiple smooth-surfaced pink papules of varying sizes between 1 and 10 mm • Papillomatous variant: pebbly-surfaced white or pink papules of varying sizes between 1 and 10 mm	• Surgical excision • Laser ablation (may produce HPV plume) • Electrosurgery • Topical agents,* e.g., Imiquimod 5% cream, interferon-β cream168 • Others: intramuscular interferon-α injection[169]	• May resolve spontaneously • May recur after excision • No malignant transformation reported

*Data in children limited and mostly based on case reports.

pseudomembranous candidiasis in neonates may resolve without treatment. Angular cheilitis in children is often associated with chronic lip licking and thumb sucking. Occasionally, there is involvement of the perioral skin secondary to chronic lip licking known as cheilocandidosis. CPA (previously median rhomboid glossitis) is a form of erythematous candidiasis formerly thought to be a developmental defect.[171] However, studies have demonstrated that the prevalence of CPA is not higher in children, dispelling the belief that CPA is developmental in etiology.[172] Table 25-13 summarizes the various antifungal agents commonly prescribed for children and the treatment considerations specific to them.[173]

Impetigo

Impetigo is a contagious superficial skin infection caused by either *Staphylococcus aureus* (majority of cases) or group A *Streptococcus* (e.g., *Streptococcus pyogenes*). The infection is commonly observed among children 2–5 years of age. The transmission is by direct contact with the bacteria. Predisposing factors include poor hygiene, crowded living conditions, and hot, humid climates. There are three variants of impetigo: nonbullous impetigo, bullous impetigo, and ecthyma. Although there are no intraoral lesions, the nonbullous variant, which is the most common form, presents with significant perioral skin lesions. The lesions begin as papules and progress to vesicles, which break down to

Table 25-13 Antifungal therapy in children.

Condition	Medication	Specific Considerations
General Considerations • Topical treatment with nystatin is generally the first-line therapy for immunocompetent children • Nystatin suspension contains high sucrose content, which may increase the risk of dental caries when used chronically • Antifungal treatment should be continued 48 hours after resolution of lesions to reduce recurrence of infection • Bottle nipples and pacifiers should be sterilize (e.g., by boiling) before each use		
Pseudomembranous/ erythematous candidiasis	Nystatin suspension 100,000 U/mL • Neonates up to 1 month: 1 mL, 4 times/day, duration 5–10 days • Immunocompetent infants 1 month–11 months: 2 mL, 4 times/day, duration 7–14 days • Immunocompetent children ≥12 months: 4–6 mL, 4 times/day, maximum dose 2.4 million U/day, duration 7–14 days	• Applied with gauze or cotton swab • Should be administered after feeds • Avoid feeding for 5–10 minutes after application • For neonates and infants, split each dose into two portions, one for each side of the mouth • If able to swish, rinse for several minutes and swallow or spit
	Clotrimazole 10 mg troche • Children ≥4 years: suck 5 times/day, duration 14 days	• Choking hazard for children <4 years
	Fluconazole oral suspension 10 mg/mL, 40 mg/mL • Neonates up to 1 month: 3 mg/kg/day, single dose/ day, duration 7 days • Infants 1 month–11 months: 3–6 mg/kg/day, single dose/day, maximum dose 200 mg/day, duration 7–14 days • Children ≥12 months: day 1: 6 mg/kg/day, single dose/day; day 2 onward: 3 mg/kg/day, single dose, maximum dose 200 mg/day; duration 7–14 days	• Used only for widespread infections, in immunosuppressed children, or if topical treatment fails to resolve infection • If symptoms do not improve in 7 days, fungal culture and susceptibility testing recommended • Adverse effects include nausea, vomiting, headaches, rash, abdominal pain, and diarrhea • Hepatic toxicity, including fatalities, has been reported rarely • Contraindicated use with drugs metabolized by CYP3A4 and those known to prolong QT interval
Angular cheilitis or cheilocandidosis	Nystatin ointment or cream 100,000 U/g • Infants >2 months: apply a thin layer to affected area, 3–4 times/day	
	Nystatin suspension 100,000 U/mL and triamcinolone acetonide 0.1% • Infants >2 months: apply a thin layer to affected area, 3–4 times/day	• Not Food and Drug Administration (FDA) approved for this use
	Miconazole 2% ointment or cream • Children >2 years: apply to affected area, 3–4 times/ day	• Not as first-line therapy • Off-label use, as not FDA approved for children

form thick, adherent lesions with a gold, crusty appearance. The majority of the cases are diagnosed clinically by the characteristic skin presentation. In cases when the diagnosis cannot be made from the clinical presentation, isolation of the bacteria by gram stain and culture may be performed. Acute glomerulonephritis and rheumatic fever are significant postinfectious complications of impetigo infections caused by group A *Streptococcus*. Thus, the treatment objectives are to reduce the spread of infection and risk of complications.[174] Topical treatment with mupirocin, retapamulin, or fusidic acid is preferred for limited disease. Other over-the-counter antibiotic ointments may not be as effective. For extensive disease, systemic antibiotics, typically cephalexin or dicloxacillin, for 7 days are recommended.

Scarlet Fever

Scarlet fever is a complication of group A streptococcal tonsillopharyngitis common in children. It is due to a delayed reaction to the exotoxin most often produced by *Streptococcus pyogenes*. Enanthem of the tonsils, pharynx, or soft palate

may be present, but these findings are of the tonsillopharyngitis and not specific for scarlet fever. "Strawberry tongue" is the characteristic oral finding in scarlet fever. The tongue initially appears white. The white tongue coating eventually sheds to reveal an erythematous dorsal surface of the tongue, with inflamed and hyperplastic fungiform papillae. A diffuse papular erythematous skin rash is also present. The diagnosis is made clinically based on the mucocutaneous presentations. If the diagnosis cannot be made clinically, a throat culture or a rapid streptococcal test may be performed. The main treatment objective is to treat the primary infection (i.e., streptococcal tonsillopharyngitis) so as to reduce the risk of scarlet fever and other poststreptococcal complications (e.g., acute glomerulonephritis, rheumatic fever, poststreptococcal reactive arthritis). The antimicrobial of choice is either penicillin or amoxicillin for 10 days.

Noninfectious Conditions

Benign Migratory Glossitis (Also Known as Geographic Tongue or Erythema Migrans)

Benign migratory glossitis (BMG) is a benign, chronic, recurring inflammatory condition of unclear etiology. In children, the prevalence ranges between 0.4% and 14.3%. BMG is characterized by multiple well-demarcated areas of erythema (due to the atrophy of filiform papillae) that are surrounded partially or completely by slightly elevated, yellow to white scalloped borders. The condition is frequently observed on the anterior two-thirds of the dorsum of the tongue, but may be seen less commonly in other oral mucosal locations, such as the buccal and labial mucosa, or floor of the mouth. The location, size, and shape of the erythematous areas change with time. The diagnosis is made clinically based on the history and characteristic presentation. BMG is usually asymptomatic and often noted as an incidental finding. Some individuals may report a burning sensation when inflamed. A myriad of treatment modalities, ranging from topical corticosteroids, analgesics, and diphenhydramine with or without topical anesthetics, have been reported in the literature. A recent systematic review concluded that there was insufficient evidence to support any specific treatment for symptomatic BMG.[175] Thus, the current recommended treatment is largely conservative and includes reassurance and avoidance of acidic foods when symptomatic. BMG has been associated with fissured tongue, psoriasis, and atopic dermatitis.[176,177]

Frictional Keratosis

Both linea alba and morsicatio (Figure 25-13) are variants of frictional keratosis that are common in children. Linea alba is usually bilateral and presents as an asymptomatic, nonulcerated, white hyperkeratotic line coinciding with the level of the occlusal plane. It is associated with low-grade trauma caused by friction, or sucking trauma from the buccal surfaces of the teeth. Morsicatio appears as white plaques on the oral mucosa, with surface shredding and occasionally with areas of erythema or ulceration. The condition occurs as a result of chronic nibbling or chewing of the mucosa and is most frequently observed on the buccal mucosa (morsicatio buccarum), followed by the labial mucosa and lateral borders (morsicatio linguarum) of the tongue. The diagnosis is usually made clinically based on the history and clinical presentation. No treatment is necessary for either condition and cessation of habit will result in spontaneous regression.

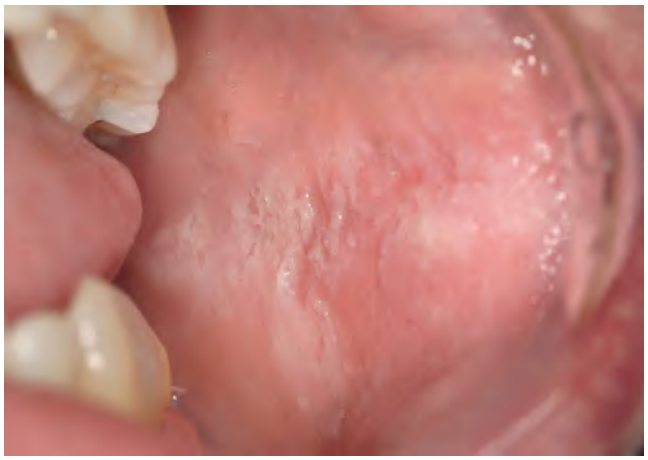

Figure 25-13 Morsicatio.

Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis (RAS) is also referred to as aphthous ulcers or "canker sores." RAS is a common condition that often initiates in childhood and affects up to 40% of the population. Similar presentations of recurrent aphthous-like oral ulceration may occur in association with systemic diseases such as autoimmune conditions (e.g., periodic fever-aphthous stomatitis-pharyngitis-adenitis syndrome [PFAPA], Behcet syndrome), immunodeficiency states (e.g., cyclic neutropenia), nutritional deficiency (e.g., iron/folate/vitamin B_{12} deficiencies), and gastrointestinal disorders (e.g., celiac disease). Therefore, the term RAS should be reserved for oral ulcers that are not associated with systemic diseases. The clinical presentation, subtypes, triggers, diagnosis, and management in children are similar to adults, which are described elsewhere in this textbook. The use of topical corticosteroids is the treatment of choice for RAS, which may be concerning for parents when prescribed for a child. Currently, there is no study specifically evaluating the safety of topical corticosteroid use for RAS in children. Extrapolation from pediatric dermatologic studies suggest that low- to medium-potency topical corticosteroids (Groups 4–7) for short durations are generally safe.[178,179] However, the frequent and routine use of mild corticosteroids has been reported to cause hypothalamic–pituitary axis (HPA) suppression in children. In a meta-analysis of 522 children

aged 3 months–18 years on topical corticosteroids for atopic dermatitis for 2–4 weeks, the HPA suppression rates using low-, medium-, or high-potency corticosteroids were 2%, 3.1%, and 6.6%, respectively.[180] Triamcinolone acetonide 0.1% (Kenalog orabase) is a medium-potency corticosteroid that is often used for minor RAS. Unlike in atopic dermatitis, corticosteroid use in RAS is intermittent and limited to a small area for a short period of time; thus, adverse effects are unlikely.

Riga–Fede Disease

Of the various types of traumatic ulcers, Riga–Fede disease and ulcerations arising from self-injurious behaviors (e.g., trauma from lip biting after local anesthesia) are unique to the pediatric population. These types of ulcerations are more common in individuals with cognitive impairment. Riga–Fede disease is an ulcerative condition that occurs in infants and is observed on the ventral surface of the tongue (Figure 25-14). The ulcer is caused by persistent trauma to the tongue by the lower incisors. The lesion may be extensive and/or present as a large fibrous indurated mass, whereby the possibility of malignancy is raised. The diagnosis is usually made clinically based on the temporal relationship as well as the location of the ulcer with the eruption of the lower incisors (or parafunctional/self-injurious habit). The treatment is challenging, because the infant's compliance often limits the treatment options. Smoothening of the incisor edges and good wound care are recommended. Extraction of the incisors may be needed in severe, nonhealing ulcers.

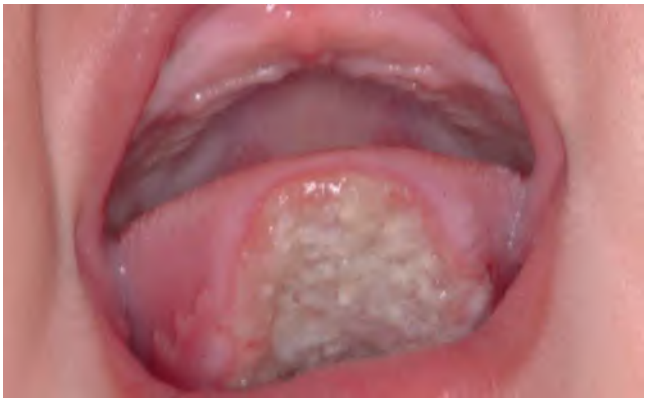

Figure 25-14 Riga–Fede disease.

Pigmented Lesions

Pigmented lesions are caused either by increased melanin deposition or a deposition of endogenous or exogenous pigments in the epithelium and underlying connective tissue.[181] The lesion color depends on the quantity, location, and depth of the pigment. Intraorally, oral melanotic macule (frequently found on the labial and buccal mucosa, gingiva, and palate) and amalgam tattoo are the most likely encountered pigmented lesions in the pediatric population. The detailed descriptions of these lesions are covered elsewhere in this textbook. As mucosal melanomas are exceedingly rare in children, a biopsy is generally not routinely performed for diagnosis. The management of these lesions is largely observational. A biopsy should be considered if the lesion is located on the maxillary alveolus, gingiva, or palate and displays worrisome characteristics suspicious of a melanoma. The ABCDE acronym (marked **a**symmetry; **b**order irregularity; **c**olor variegation, e.g., shades of black, brown, tan, red, or pink; **d**iameter >6 mm; change in surface **e**levation, e.g., nodule formation) is a common checklist used to evaluate the malignant risk of pigmented lesions.[182]

Localized Juvenile Spongiotic Gingival Hyperplasia

Localized juvenile spongiotic gingival hyperplasia (LJSGH; Figure 25-15) is a recently described lesion of unknown etiology. This condition occurs most frequently in children, with a mean age of 12 years. The lesion is commonly observed on the facial free gingiva margins (may extend to

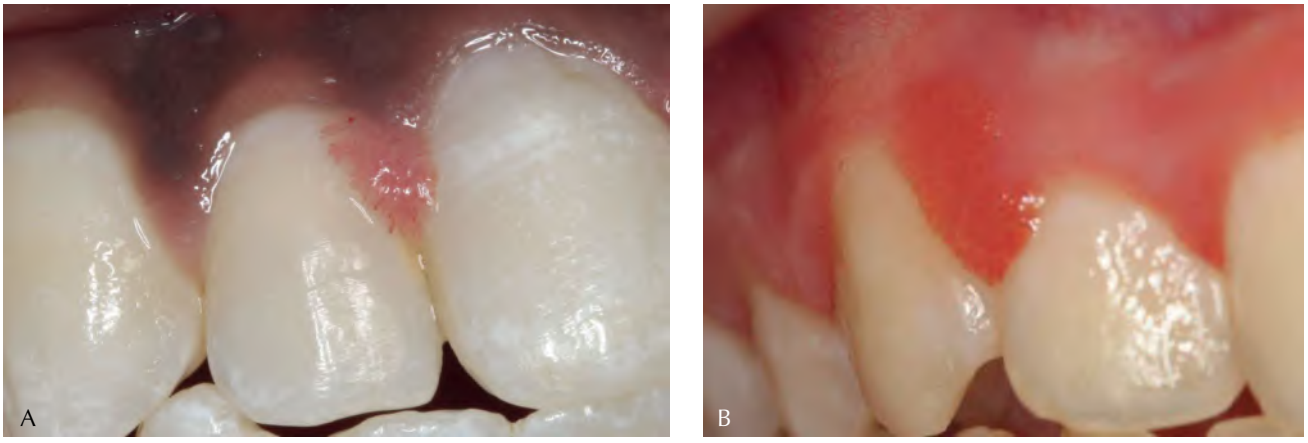

Figure 25-15 A, B. Localized juvenile spongiotic gingival hyperplasia.

the mucogingival junction) at the anterior maxillary region. LJSGH usually occurs in solitary cases, but multifocal cases have been reported. Two clinical presentations have been described: a bright red plaque with a granular or velvety surface or a nodule with a papillary surface. The lesion is painless, but tends to bleed easily.[183] The histologic examination reveals areas of nonkeratinized, acanthotic stratified squamous epithelium, exhibiting spongiosis. Rete pegs elongation, atrophy of the epithelium overlying long connective tissue papillae, and a neutrophilic infiltrate are also present. The diagnosis is frequently made clinically based on the location and distinctive clinical presentation, and thus does not always require histologic confirmation. As LJSGH is not related to local plaque accumulation, conventional plaque control measures are not effective. The most frequently reported treatment is surgical or laser excision, with recurrence rates ranging from 6% to 16%.[184] Treatment with topical corticosteroids has been found to have mixed results.[184]

Pyogenic Granuloma

Pyogenic granuloma (Figure 25-16) is a reactive oral mucosal lesion common in children and adolescents, with a female predisposition. The etiology is thought to be due to an exaggerated soft tissue response to local irritation or trauma. Notably, pyogenic granulomas have recently been classified under vascular tumors and termed lobular capillary hemangiomas by the International Society for the Study of Vascular Anomalies.[39] This was based on the difficulty in definitively ascertaining whether pyogenic granulomas were reactive or neoplastic in origin.[39,185] Clinically, pyogenic granuloma presents as a painless, rapidly growing, pedunculated, erythematous soft tissue mass, with or without an ulcerated surface. The lesion is usually located on the maxillary gingiva, but has been observed on other sites such as the labial and buccal mucosa, or the tongue. The diagnosis is made based on the

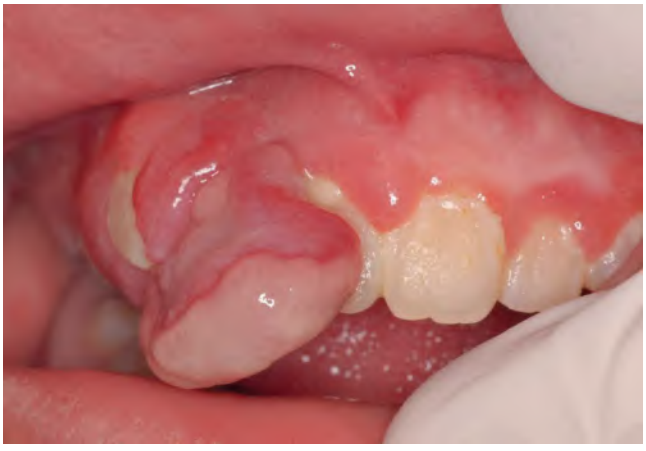

Figure 25-16 Pyogenic granuloma.

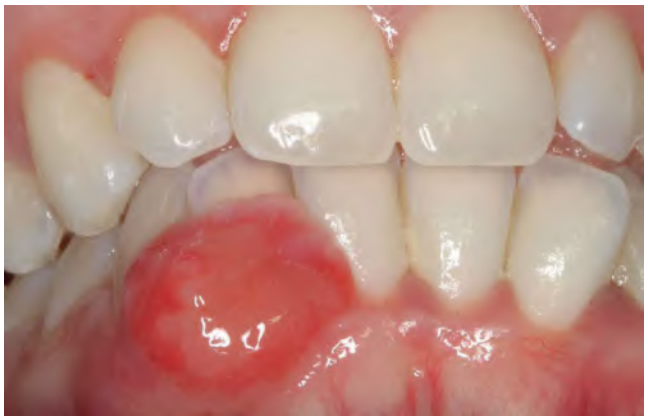

Figure 25-17 Peripheral ossifying fibroma.

clinical presentation and histology. The treatment is surgical excision, with a reported recurrence rate of 3%–5%.

Peripheral Ossifying Fibroma

Peripheral ossifying fibroma (Figure 25-17) is a reactive oral mucosal lesion common in adolescents and young adults, with a female predisposition. The exact etiology of peripheral ossifying fibroma is unclear and the lesion is unrelated to central ossifying fibroma.[186] Peripheral ossifying fibroma presents as a firm, smooth-surfaced or ulcerated, pedunculated or sessile, pink or red, gingival mass, often arising from the interdental papilla. They are usually <2 cm in size and are most commonly observed at the incisor/canine region. The histologic examination reveals a cellular fibrous proliferation associated with the presence of mineralized products such as bone, cementum-like, or dystrophic calcifications. The diagnosis is made based on the clinical presentation and histology. The treatment is surgical excision, with a recurrence rate of 8%–16%.

Peripheral Giant Cell Granuloma

Peripheral giant cell granuloma is a reactive lesion thought to occur secondary to local irritation or trauma. Approximately 20%–33% occur in the first two decades of life, with a female predisposition. Peripheral giant cell granuloma presents as a smooth-surfaced or ulcerated, pedunculated or sessile, red or reddish-purple mass on the gingiva. The most common location is at the anterior mandibular area. A periapical radiograph may occasionally show superficial resorption or "cupping" of the underlying alveolar bone caused by the lesion.[187] The radiograph also aids in determining the origin of the lesion, as some central giant cell granulomas can erode through the cortical bone and present as gingival masses. Histologically, peripheral giant cell granuloma is similar to central giant cell granuloma, and is considered to be the soft tissue counterpart. There is a proliferation of multinucleated giant cells in a stroma of spindle

cells and abundant hemorrhage. The diagnosis is made based on the clinical presentation and histology. The treatment of choice is surgical excision, with a recurrence rate of 10%–18%.

Oral Mucocele: Extravasation Type (Mucus Extravasation Phenomenon)

Mucus extravasation phenomenon (Figure 25-18) occurs due to the rupture of the minor salivary glands, often from local trauma, resulting in mucous extravasation into the surrounding soft tissues. The phenomenon is common in children and presents as a soft, fluctuant, smooth-surfaced, dome-shaped bluish swelling. The size ranges from a few millimeters to several centimeters and is most commonly observed on the lower labial mucosa.[188] Individuals typically report a history of a painless swelling, which appears and disappears periodically. The histologic examination reveals an area of spilled mucin surrounded by a granulation response without an epithelial lining. The diagnosis is made by the history, clinical presentation, and histology. In children, where compliance is an issue, small mucoceles of ≤5 mm may be monitored, as some will resolve spontaneously without treatment within a few months. Children should be advised not to use their teeth to bite or chew on the mucocele. Larger or chronic mucoceles displaying signs of fibrosis or keratinization will likely require surgical excision. Recurrences may occur, especially if the surrounding minor salivary glands are not removed during the removal of the original mucocele.

Common Malignant Conditions with Oral Mucosal Findings in Children

In the 5–14-year-old age group, cancer is the second most common cause of death. The most frequent malignancies in children are leukemias. Table 25-14 summarizes the common malignancies with oral mucosal findings in children.

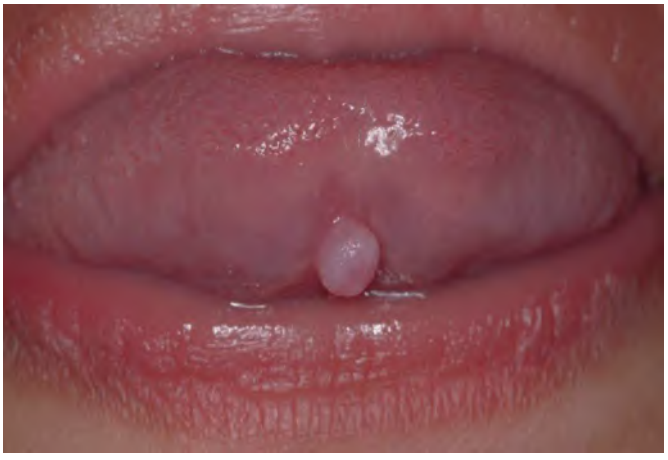

Figure 25-18 Mucocele.

Systemic Diseases and Related Medical Therapy with Significant Oral Mucosal Findings

Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis Syndrome

Periodic **f**ever, **a**phthous stomatitis, **p**haryngitis, and **a**denitis (PFAPA) syndrome is characterized by recurrent episodes of fever, malaise, chills, aphthous-like oral ulcerations, pharyngitis, headache, and tender cervical adenopathy of unknown origin. The condition occurs at 4- to 6-week intervals over periods of years.[193] PFAPA syndrome is typically diagnosed between the ages of 1 and 4 years and usually resolves spontaneously by 10 years of age. Oral ulcerations are present in about 40%–80% of PFAPA episodes. The oral ulcers resemble recurrent aphthous ulcerations and are usually observed on the labial or buccal mucosa.[194] The diagnosis is made clinically based on the exclusion of other causes of fever and a thorough history of the temporal relationship of the periodic fevers with clinical findings. The treatment is largely supportive, as the condition is self-limiting. Observation is an acceptable option if parents prefer no treatment. Antipyretics and nonsteroidal anti-inflammatory analgesics are not effective in relieving any of the signs and symptoms except for fever. As such, the preferred treatment is early administration of a single dose of prednisone (1–2 mg/kg), which will rapidly relieve the fever in a few hours; other symptoms will take longer to resolve. However, glucocorticoid therapy has been shown to result in an increase in episode frequency. In such individuals, prophylactic therapy with cimetidine (20–40 mg/kg/day in divided doses every 12 hours) or colchicine (children 4–6 years: 0.6–1.2 mg/day, children >6 years: 1.2–1.8 mg/day) may be considered.[195] Tonsillectomy is an effective treatment for PFAPA, especially in those who do not respond to drug therapy.[196]

Kawasaki Disease

Kawasaki disease is an acute vasculitis of primarily the medium-sized arteries of unknown etiology. The condition typically affects infants and children, with 80% occurring under 5 years of age. The highest prevalence is in Japan, at approximately 250 cases per 100,000 children, compared to 20 cases per 100,000 in the United States.[197,198] The prodrome consists of nonspecific findings such as cough, rhinorrhea, vomiting, diarrhea, abdominal pain, and irritability. The inflammation of the dorsum tongue with enlargement of the fungiform papillae imparts a "strawberry tongue" appearance.[199] The diagnosis is made clinically based on a history of fever above 101.3 °F for ≥5 days and ≥4 of the following physical findings:

- Bilateral bulbar conjunctivitis.
- Cervical lymphadenopathy (single lymph node >1.5 cm).

Table 25-14 Common malignancies with oral mucosal findings in children.

Malignancy	Key Features	Oral Presentations
Acute leukemia[189]	• Most common childhood malignancy • Acute lymphocytic leukemia (ALL) 80% of cases • Acute myeloid leukemia (AML) 15% of cases • 5-year survival rates: – ALL: 90% – AML: 40%	• Easy bruising and gingival bleeding secondary to thrombocytopenia • Neutropenic ulcers • Opportunistic infections, e.g., oral candida infections, herpetic infections • Leukemic infiltrates mostly observed with AML, which manifests as diffuse gingival enlargements or discrete mass secondary to leukemic infiltrates into the soft tissue
Langerhans's cell histiocytosis (LCH)[190,191] (Figure 25-19)	• About 10–20% occurs in jaws • Mean age of occurrence 1–4 years of age • Bone most commonly involved • Single-system LCH involves only one organ system, but may be unifocal or multifocal • Multisystem LCH has ≥2 organ systems involved • Prognosis is worse for children <2 years of age • 5-year survival rate 80%; however, 30%–50% of patients will experience recurrence	• Pain and/or tenderness • Mobile teeth • Rarely, LCH lesions may involve only oral soft tissues • Nonspecific oral findings including mucosal ulcerations, gingival hyperplasia, gingival bleeding • Jaw lesions may extend beyond bone and manifest as a gingival mass Radiographic features: • Jaw radiolucency with floating teeth appearance
Rhabdomyosarcoma[192]	• Accounts for 50% of sarcomas in childhood • About 35% occur in the head and neck region • Mean age of diagnosis 7–8 years of age • 5-year survival rate 44%–95% (varies based on histopathologic type)	• Painless, locally aggressive mass with rapid growth • Palate most common intraoral site

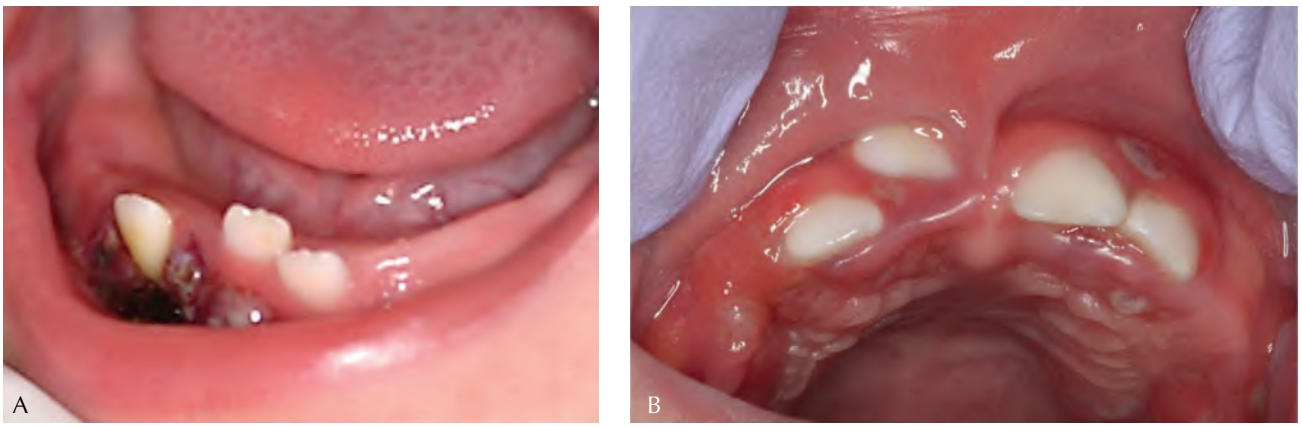

Figure 25-19 Langerhan's cell histiocytosis. (A) Bone to soft tissue. (B) Soft tissue.

- Oral mucosal changes including strawberry tongue, fissured or cracked lips, and oropharyngeal erythema.
- Extremities changes including erythema of the palms and soles, edema of the hands or feet, and periungual desquamation.
- Polymorphous diffuse maculopapular rash in the extremities and trunk.

All cases of Kawasaki disease should be treated with IV immune globulin infusion and aspirin at the time of diagnosis.[200] Some may also require glucocorticoid therapy. Delayed treatment is associated with a fivefold increase in the prevalence of coronary artery aneurysms.

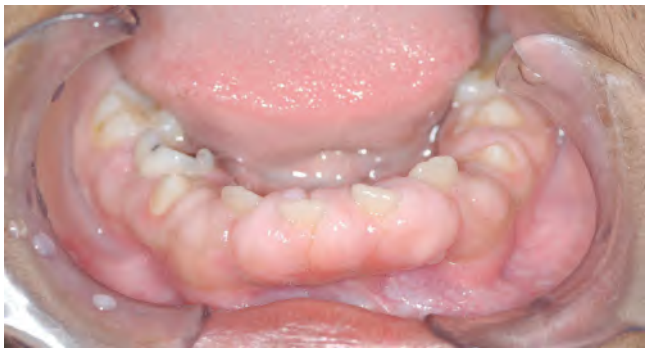

Figure 25-20 Phenytoin-induced gingiva hypertrophy.

Drug-Related Gingival Enlargement

Many systemic medications (e.g., nifedipine, cyclosporine, and phenytoin) are associated with abnormal gingival overgrowth (Figure 25-20). In children, most cases are secondary to phenytoin (50%) or cyclosporine therapy (>70%).[201] The gingival enlargement is typically seen within 1–3 months of drug use and originates at the interdental papilla. The anterior facial gingiva is the most commonly affected area. Severe cases may extend to the incisal or occlusal surfaces and interfere with speech, mastication, and maintenance of adequate oral hygiene. The enlarged gingiva is fibrotic, firm, and usually pink in color. In individuals with poor oral hygiene, the gingival tissues may be edematous, erythematous, and bleed easily. The diagnosis is made clinically based on the presentation and its temporal association with a medication known to cause gingival enlargement. As the severity of the enlargement is influenced by plaque control, the main treatment is implementation of a good oral hygiene program (e.g., frequent professional cleanings, meticulous home care to minimize plaque accumulation). Systemic antimicrobial therapy with azithromycin, metronidazole, and clarithromycin has been found to be beneficial for some cases.[202] The proposed mechanisms of action include antibacterial and anti-inflammatory properties as well as suppression of fibroblast activity. In severe cases, surgical intervention is needed for functional or esthetic reasons. However, recurrence is likely if the individual is still on the causative medication. The substitution of cyclosporine with tacrolimus to reduce the risk for gingival overgrowth may be considered, but this is not always feasible due to the constraints of the underlying systemic condition.

Impact of Cancer Therapy on Growth and Development

A unique complication in childhood cancer survivors is the impact of cancer therapy on their growth and development. The dental defects range from enamel defects, microdontia, or hypodontia to root abnormalities (e.g., shortened or V-shaped roots). The craniofacial abnormalities are retardation of the mandibular growth and vertical facial growth.[203,204] Multimodality cancer therapy, high-dose head and neck radiation, high-dose chemotherapy, especially regimens involving the use of alkylating agents and anthracyclines, as well as children younger than 5 years of age at the time of treatment are at increased risk for higher incidence and more severe dental and craniofacial abnormalities.[205,206]

Use of Bisphosphonate Therapy in Children

Bisphosphonates (BPs) are increasingly being prescribed in children for diseases associated with primary (e.g., osteogenesis imperfecta) or secondary osteoporosis (e.g., chronic corticosteroid therapy). BP-induced osteonecrosis of the jaws and the associated risk factors (e.g., age, diabetes) are well described in adults, but information in children is lacking. In a recent systematic review of the risk of BP-induced osteonecrosis of the jaw, the authors found no reported case of osteonecrosis in children.[207] The authors proposed that the risk of BP-induced osteonecrosis of the jaws was minimal in children for the following reasons: (1) BPs are typically used for genetic bone conditions in children and thus cannot effectively alter the biologic characteristics of the defective bone; (2) BPs do not reduce bone growth and trabecular bone formation in children; and (3) the higher bone turnover in children results in the increased likelihood of BPs being released into the circulation and excreted out of the system. The findings of this review should be interpreted with caution, as the majority of the studies included were on children with genetic bone diseases.[207] As such, their conclusions may not apply to those are on long-term BP treatment for secondary osteoporosis. In addition, the studies in the review either had small sample sizes or did not include individuals with risk factors (e.g., dental pathology) for the development of BP-induced osteonecrosis of the jaws.

Orofacial Pain in Children

Temporomandibular dysfunction and headaches are relatively common in school-age children and adolescents. However, it is difficult to estimate the prevalence due to the wide ranges reported in studies. A discussion of the etiology, diagnosis, and treatment is outside the scope of this chapter; readers are advised to refer to the guideline by the American Academy of Pediatric Dentistry on "Acquired Temporomandibular Disorders in Infants, Children and Adolescents" for an in-depth review.[208]

Neuropathic orofacial pain conditions without an identifiable organic cause (e.g., trauma, tumor) are rare in the pediatric population and the literature is limited to case reports.[209] As such, the diagnosis and treatment principles are largely extrapolated from the adult literature and are similar to those in adults.

DISTURBANCES IN TOOTH EXFOLIATION AND ERUPTION PATTERNS

Early Exfoliation of Teeth

The early exfoliation of deciduous or permanent teeth in the absence of trauma may be associated with an underlying systemic disease.[210,211] At times, this may be the first presentation of the underlying systemic condition. Table 25-15 summarizes the key systemic and oral findings.

Delayed Eruption of Teeth

Delayed tooth eruption is more often a localized problem rather than a symptom of an underlying systemic disease. Table 25-16 lists the systemic and local causes of delayed tooth eruption.[224]

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Table 25-15 Systemic causes for early tooth exfoliation.

Condition	Cause	Key Systemic Findings	Oral Findings
Congenital			
Immunologic Dysfunction			
Chediak–Higashi syndrome[211]	Mutation of the *CHS1/LYST* gene is postulated to result in a dysfunction in lysosome transport	• Partial oculocutaneous albinism and other ocular manifestations, e.g., nystagmus, strabismus • Immunologic and hematologic abnormalities, e.g., anemia, neutropenia, thrombocytopenia • Recurrent skin and respiratory infections • Hepatomegaly • Splenomegaly • Paresthesia • High risk of hemophagocytic lymphohistiocytosis	• Severe gingival inflammation and early-onset rapidly progressive periodontitis • Oral ulcerations
Cyclic neutropenia[212]	Mutation (majority of cases) of the *ELANE* gene results in defective neutrophil function	• Cyclic decrease in neutrophil counts (21-day cycle, but may range from 14 to 35 days) • Each episode is accompanied by malaise, fatigue, fever, pharyngitis, and stomatitis • Recurrent skin and respiratory infections • Diagnosis is confirmed by an acute neutrophil count of <200 cells/μl in three regularly spaced cycles	• Severe periodontitis • In cyclic neutropenia, each episode often manifests with recurrent aphthous-like ulcerations and gingivitis
Severe congenital neutropenia (infantile genetic agranulocytosis, Kostmann's disease)[211]		• Severe neutropenia (neutrophil count <500 cells/μl) present at birth or within 1 year of life • Recurrent bacterial infections • Global developmental delay • Seizures	
Leukocyte adhesion deficiency syndrome[211]	Mutation of the *ITGB2* gene (primarily) results in defective CD18 and impaired T-cell function	• Absent or minimal pus formation • Leukocytosis • Impaired wound healing • Recurrent bacterial infections, usually of the skin and mucosal surfaces • Delayed separation of umbilical cord	• Severe gingival inflammation and early-onset periodontitis • Opportunistic oral infections • Oral ulcerations
Papillon–Lefevre syndrome[211]	Mutation of the *CTSC* gene affects the production of serine proteinases in immune cells, resulting in defective function	• Hyperkeratosis of palms and soles • Increased risk of recurrent skin, respiratory, and systemic infections • Nail dystrophy	• Severe early-onset periodontitis (at 1–2 years of age), resulting in the loss of all deciduous teeth by 4–5 years of age and all permanent teeth by 14 years of age • Atrophy of alveolar ridges • Hypodontia

Condition	Cause	Key Systemic Findings	Oral Findings
Congenital			
Haim–Munk syndrome[211]		• Acro-osteolysis • Arachnodactyly • Hyperkeratosis of palms and soles • Onychogryphosis • Osteolytic defects of the phalanges of the hand • Recurrent pyogenic infections	• Severe early-onset progressive periodontitis affecting both deciduous and permanent dentitions
Periodontal Ehlers–Danlos syndrome (formerly type VIII)[211,213]	Mutations of the *C1S* and *C1R* genes result in C1s or C1r deficiencies and altered immune function	• Elastic skin • Hyperpigmented atrophic scars • Joint hypermobility • Short stature	• Severe early-onset generalized periodontitis leading to loss of teeth before 30 years of age • Gingival enlargement with varying degrees of hyperkeratosis • Lack of attached gingiva • Dental abnormalities, e.g., hypodontia, microdontia
Trisomy 21 (Down syndrome)[211]	–	• Characteristic dysmorphic facies • Intellectual disability • Atlanto-axial instability • Cardiovascular defects; most commonly complete atrioventricular septal defect • Growth abnormalities (e.g., short stature) • Eye and hearing problems • Hypothyroidism • Obstructive sleep apnea • Immunologic dysfunction • Increased risk of acute leukemia • Increased risk for gastrointestinal tract abnormalities (e.g., duodenal atresia or stenosis)	• Moderate to severe periodontitis due to altered immune function • Dental abnormalities, e.g., hypodontia, microdontia, taurodontism • Benign migratory glossitis (geographic tongue) • Tongue anomalies: fissured tongue, macroglossia • High-arched palate • May be associated with delayed tooth eruption
Unstable periodontitis stage 4 grade C with molar incisor pattern (formerly known as localized aggressive periodontitis)[214,215]	Multifactorial in origin; likely polygenic and influenced by environmental factors resulting in deficient immune response	• No associated systemic findings	• Increased susceptibility to aggressive periodontitis – Localized disease: affects incisors and first molars – Generalized disease: affects ≥3 teeth other than the first molars and incisors

(*Continued*)

Table 25-15 (Continued)

Condition	Cause	Key Systemic Findings	Oral Findings
Congenital			
Periodontium Defects			
Acatalasia (acatalasemia)[216]	Mutation of the *CAT* gene results in a lack of catalase enzyme, which is important for hydrogen peroxide metabolism	• Most are asymptomatic	• Early tooth loss due to the inability to degrade hydrogen peroxide produced by oral bacteria, resulting in periodontal tissue hypoxemia and necrosis • Oral ulcerations
Coffin–Lowry syndrome[217]	Mutation of the *RPS6KA3* gene results in a dysfunctional growth factor–regulated protein kinase	• Dysmorphic facial features, e.g., hypertelorism, thick lips, frontal bossing, anteverted nares • Broad tapering fingers • Brachydactyly • Hearing deficit • Global developmental disability • Paroxysmal movement disorder • Joint hyperflexibility • Skeletal abnormalities, e.g., scoliosis, kyphosis, delayed skeletal maturation • Short stature	• Early tooth loss is postulated to be due to hypoplastic root cementum • Dental abnormalities, e.g., hypodontia, microdontia • High-arched and narrow palate • May be associated with delayed tooth eruption
Hajdu–Cheney syndrome[218]	Mutation of the *NOTCH2* gene results in abnormal bone development and remodeling	• Acro-osteolysis of the distal phalanges • Characteristic dysmorphic facies • Bowing of the long bones • Renal cysts • Severe osteoporosis • Short stature • Vertebral abnormalities	• Early tooth loss is thought to be due to defective cementum, hypoplastic roots, and severe periodontitis (cause unclear) • May be associated with delayed tooth eruption • Cleft palate or high-arched palate
Hypophosphatasia[211]	Mutation of the *ALPL* gene results in an abnormal production of tissue-nonspecific alkaline phosphatase and poor skeletal and dental mineralization	• Clinical presentations range from mild to severe depending on type • Types: perinatal, prenatal benign, infantile, childhood, adult, and odontohypophosphatasia • Lethal perinatal and infantile types are the most severe and are associated with high mortality • Perinatal type: skeleton fails to form in utero, high mortality (i.e., stillborn or within first few days of life) due to respiratory failure resulting from chest deformities and undeveloped lungs	• Early tooth loss before 5 years of age is attributed to reduced amount or total lack of cementum on tooth root surface (one of the first signs) • Enamel hypoplasia • Enlarged pulp chambers

Condition	Cause	Key Systemic Findings	Oral Findings
Congenital			
		• Prenatal benign type: limb shortening and bowing, but often shows spontaneous improvement during the third trimester of pregnancy • Infantile type: symptoms become apparent at 6 months, respiratory complications, premature craniosynostosis, widespread demineralization • Childhood type: highly variable features, skeletal deformities (e.g., bowed legs), short stature, and waddling gait • Odontohypophosphatasia: only has dental findings characterized by premature loss of deciduous and permanent teeth	
X-linked hypophosphatemic rickets[219]	Mutation of the *PHEX* gene results in decreased serum potassium levels due to abnormal excretion of phosphate from the kidneys, leading to soft, weak bones	• Bowed legs • Craniosynostosis • Joint/bone pain • Muscle pain and weakness • Osteoarthritis • Osteomalacia • Rickets • Short stature	• Tooth extraction often necessitated due to the development of spontaneous dental abscess in the absence of trauma or decay. The cause of abscess is proposed to be due to bacteria infiltrating and infecting the pulp via the enamel and dentine microclefts in the tooth • Other enamel defects, e.g., hypoplasia • Large pulp chambers with pulp horns extending to the dentine-enamel junction
Dentin dysplasia type 1[220]	Mutation of the *SMOC2* gene	• None	• Early tooth loss attributed to short or absent roots, resulting in tooth mobility and early exfoliation • Periapical radiolucencies in sound teeth • Pulp obliteration

(*Continued*)

Table 25-15 (Continued)

Condition	Cause	Key Systemic Findings	Oral Findings
Congenital			
Acquired Causes			
Acrodynia (Pink disease)[221]	Infantile mercury poisoning	Early signs • Change in temperament, e.g., irritability, restlessness, melancholy • Tips of fingers, toes, and nose appear pinkish, eventually turning darker with patchy areas of ischemia Later signs • Alopecia • Desquamation of palms and soles • Nail abnormalities • Neurological abnormalities, e.g., neuritis, abnormal reflexes • Photophobia • Profuse perspiration • Swelling of fingers and toes • Pruritis and pain in hands and feet	• Tooth loss and jaw necrosis in severe cases • Gingivitis • Inflammation and ulceration of oral mucosa
Langerhans cell histiocytosis (LCH)[222]	Malignant proliferation of the Langerhans cells	• Clinical presentation depends on number of sites and extent of involvement • Bone followed by skin are the most commonly involved systems • Single-system LCH involves only one organ system and may be unifocal or multifocal – Typically does not have systemic signs and symptoms • Multisystem LCH has ≥2 organ systems involved – Involvement of hematopoietic system, liver, and/or spleen is associated with poorer prognosis	• Bone destruction leading to tooth mobility and eventual tooth loss • Jaw radiolucencies • Oral ulcers • Gingival lesions secondary to bony extension to soft tissue (more common) or primary soft tissue disease (less common)
Scurvy[223]	Vitamin C deficiency results in impaired collagen synthesis	• Arthralgia • Easy bruising • Hemarthrosis • Impaired wound healing • Nonspecific signs and symptoms, e.g., myalgia, malaise	• Increased tooth mobility and early tooth loss due to periodontium defects from impaired collagen synthesis

Table 25-16 Systemic and localized causes of delayed tooth eruption.

Systemic Causes	Localized Causes
Endocrine diseases • Congenital hypothyroidism (cretinism) • Hypoparathyroidism • Hypopituitarism • Pseudohypoparathyroidism type 1A (Albright hereditary osteodystrophy)	Causes related to the permanent tooth successor • Congenitally absent • Dilaceration • Ectopic eruption
Chronic drug therapy • Bisphosphonate therapy • Medications that inhibit prostaglandins pathway, e.g., antineoplastic chemotherapy	Obstruction due to • Fibrous gingival tissue and/or gingival enlargement • Odontogenic and nonodontogenic tumors and cysts • Odontome • Supernumerary tooth
Malnutrition	Chronic local infection
Premature birth	Malocclusion
Primary failure of eruption	Oral facial cleft
Genetic conditions (not an exhaustive list) • Amelogenesis imperfecta • Apert syndrome • Cherubism • Chondroectodermal dysplasia (Ellis van Creveld syndrome) • Cleidocranial dysplasia • Familiar adenomatous polyposis • Infantile osteopetrosis (Albers–Schonberg disease) • McCune–Albright syndrome • Mucopolysaccharidosis • Trisomy 21 (Down syndrome)	

Source: Based on Suri L, Gagari E, Vastardis H. Delayed tooth eruption: pathogenesis, diagnosis, and treatment. A literature review. *Am J Orthod Dentofacial Orthop*. 2004;126(4):432–445.

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26

Geriatric Oral Medicine

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Population aging—the shift in distribution of a nation's population to older ages—is occurring globally, with nearly all countries worldwide demonstrating population growth in older persons.[1] In 2019, there were 703 million persons aged 65 years or over globally, with this number projected to more than double to 1.5 billion by 2050.[2] People are living longer, and for the first time in recorded history most individuals can expect to live at least into their 60s, with current global life expectancy at birth being 72.3 years.[2] Population aging was first evident in higher-income countries, such as Japan, where 30% of the population is already older than 60 years.[2] However, low- and middle-income countries (such as China and Iran) are currently experiencing the greatest rate of population aging.[2] Even more pronounced is the increase in the world's population over 80 years, which nearly tripled in the past 30 years to nearly 143 million and is projected to triple again to 426 million by 2050.[2] In countries such as the United States, the number of people in the "oldest old" age group (>85 years) is projected to reach 18 million and account for 4.5% of the US population by 2050, up from 2.5% in 2030.[3,4] Finally, living to 100 is becoming increasingly common. Worldwide there are approximately 533,000 centenarians, with the United States having the highest absolute number at 72,000.[5] Japan has the highest rate of centenarians, who account for 48 in every 1000 Japanese.[5,6]

The growth in the number of older adults worldwide can be attributed to a variety of factors. First, advances in medicine and public health have led to a notable increase in life expectancy. A significant reason for the "graying" of the population is the aging of the baby boomer generation. For example, in the United States, the first baby boomer turned 65 in 2011. The last baby boomer will turn 65 in 2030,

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

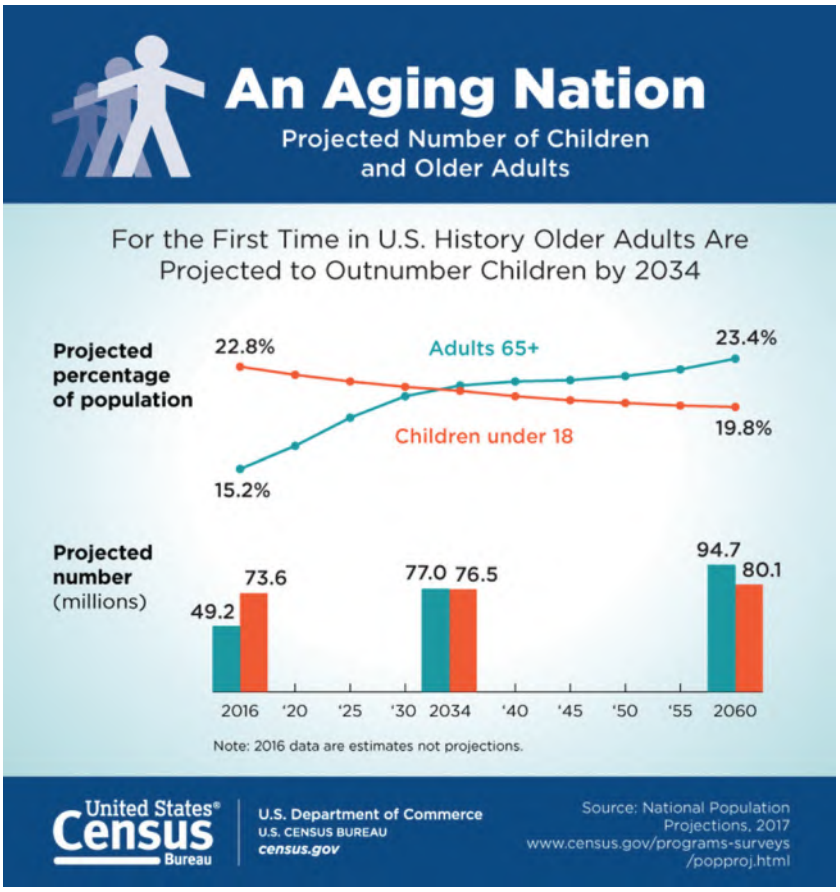

Figure 26-1 Population growth projections (2016–2034). Reproduced with permission from https://www.census.gov/content/dam/Census/library/visualizations/2018/comm/pop-projections-1.jpg.

creating a demographic where one in every five Americans will be over the age of 65 (see Figure 26-1).[7] With this dramatic change in the global landscape and the improved medical management of disease, oral healthcare professionals must possess the tools and knowledge to treat older adults comprehensively, keeping in mind their oral manifestations of systemic disease and their age-related specific oral changes.

CONCEPTS OF AGING

The age of 65 years was selected as the dividing line between middle-aged and elderly individuals in the late 1880s in Germany as a criterion for Social Security, and was adopted worldwide, mainly for the determination of pension and retirement systems.[8] It is now the accepted chronologic age for the elderly; this number is arbitrary, as aging is both chronologic and functional. The chronologic definition of age is simply a number. The functional definition, however, is based on the ability of the individual to travel to seek services. This assessment of how a person functions in daily life makes the functional definition of age much more appropriate than a chronologic one.[9] There are three functional age classifications:

- Functionally independent older adults or those who are physically well despite advanced age.
- Frail older adults or those at high risk for major adverse outcomes.
- Functionally dependent older adults or those who have experienced deterioration of physical capacities and must rely on assistance from others.[9]

The majority of older adults (78%) live in the community, approximately 5% of these people are homebound, and another 17% have a major limitation in mobility due to a chronic condition.[10,11] This leaves about 70% of the entire elderly population living in the community and capable of traveling to seek services independently, including to the dental office for oral healthcare.

Aging, systemic illness, and its' management directly influence oral health, function, and the provision of dental care.[12,13]

Because older adults are more likely to utilize dental healthcare services compared with previous older generations,[14,15] oral health professionals must be able to recognize, diagnose, and manage oral conditions in the aging patient. This chapter will provide background on the etiology, clinical manifestations, and treatment of common oral conditions that affect older individuals. In addition, a comprehensive review of age-related oral changes and the impact they have on oral health and the provision of dental care will be performed.

GERIATRIC PATIENT ASSESSMENT

The health assessment of an older adult can be quite different and significantly more complicated than the work-up of a younger patient. A geriatric assessment differs from a standard evaluation, because it includes nonmedical areas that emphasize functional capacity and quality of life, yielding a more complete and relevant list of medical problems, functional problems, and psychosocial issues. A variety of validated tools can make geriatric assessment more specific for older patients, as these instruments evaluate domains such as activities of daily living (ADLs), hearing, fecal and urinary continence, balance, and cognition; none of which is typically evaluated in a younger patient.[16] This assessment should also include a thorough review of prescription and over-the-counter medications and supplements, and also review of immunization status. An interprofessional team, which can include a primary care provider, nutritionist, social worker, pharmacist, psychologist, physical and occupational therapists, and oral healthcare professional, yields a more complete and relevant list of medical problems, functional problems, and psychosocial issues and therefore provides more comprehensive, whole-person, person-centered care.[17]

Dental treatment planning can also be complicated, as a multitude of factors affect decision-making and provision of care. Limitations due to social, economic, financial, family, medical, physical, and transportation constraints must all be considered when formulating a comprehensive oral healthcare plan for an older patient.[18] Treatment plan sequencing and communication of the plan can be challenging due to the variety of issues that complicate the progression of care. The final outcome can be difficult to predict, and therefore the treatment plan must be dynamic. Patient health may change as treatment proceeds, thus resulting in new treatment modifications that necessitate reassessment as well as communication based on these needs. Patients, their family, and their caregivers must continually be informed about their oral condition and the fact that treatment needs may change as treatment progresses. Optimal dental care for the geriatric patient requires an individualized approach that includes modifying factors and circumstances, such as disability that affects self-care or length of appointment.[19]

Utilizing a systematic approach when assessing older patients can aid in the development and delivery of comprehensive treatment. This approach starts with an assessment that answers several basic questions specific to older adults:

- How does the patient function in their environment?
- What role does pharmacotherapy play in the patient's medical and oral health?
- What social support systems for the patient exist?
- What diverse sociologic variables exist?
- How does oral healthcare fit into the patient's environment?

Dental management of the geriatric patient is consistent with any medically complex patient and involves the evaluation of four risks and subsequent modifications to the provision of dental care. Risk of infection, risk of bleeding, risk of drug actions and interactions, and risk of medical emergency during dental care need to be evaluated before routine dental treatment begins.[20] The elderly can be immunosuppressed or nonadherent with medications and instructions, therefore placing them at increased risk of infection. In addition, they may be taking anticoagulation medications or have a systemic disease that alters hemostasis. Depending on the invasiveness of the procedure, patients can be at increased risk of bleeding. The elderly are often taking more medications, are more sensitive to medications, may need renal dose adjustment, and have difficulty with drug compliance and accuracy.[21] Finally, it is imperative to evaluate the ability to withstand treatment based on systemic disease and compliance in control of the disease, and also to ensure that the dental team is prepared for a potential emergency.

A multidimensional assessment tool for planning oral healthcare for the older patient has been developed by the American Academy of Oral Medicine.[22] This tool is called OSCAR, a five-item mnemonic for Oral, Systemic, Capability, Autonomy, and Reality. OSCAR serves to guide dentists in identifying the dental, medical, pharmacologic, functional, ethical, and fiscal factors that need to be considered before dental treatment of older patients. This approach enables the clinician to evaluate each older patient in a comprehensive manner, incorporating all factors that may affect care.

The OSCAR approach starts with patients' oral needs and can include issues such as oral mucosal disease and periodontal and dental problems. Assessment of systemic factors is next and incorporates medical problems, medications, and collaboration with other healthcare providers to develop the treatment plan. Evaluating patients' capability is very important and involves the assessment of functional capacity, ability to move and be moved, and even their skill in performing oral hygiene. Next is evaluation of patients' autonomy, which

assesses decision-making ability, ability to communicate and understand, and even the ability to consent to care. Lastly, reality refers to financial issues, life expectancy, prognosis, and ability to perform oral hygiene and maintain oral health, which would affect the dental treatment plan. Taking each of these facets into consideration enables the clinician to provide patient-centered care that is specific for each older patient (see Table 26-1).[22]

PHARMACOTHERAPEUTICS IN OLDER ADULTS

Older adults make up approximately 15% of the US population, but are responsible for one-third of all prescribed medications.[23] Furthermore, it is projected that by 2040 older adults will be consumers of 40% of prescribed medications.[24] Due to increased medication exposure, older adults are at greater risk for drug-related complications. Problems such as drug–drug interactions, adverse drug reactions (ADRs), undermedication, polypharmacy (use of multiple medications or use of more medications than appropriate), and nonadherence are common among this population.[25] In addition, numerous changes occur as a result of physiologic aging that alter the way medications are absorbed, distributed, metabolized, and eliminated.[26] Medications therefore may need to be prescribed differently in this population by carefully choosing medications to avoid adverse effects or drug interactions, and adjusting doses to allow for functional changes of organs, such as the liver and the kidneys. Finally, certain medications may not be safe to use at all in older adults, and these are delineated in the Beers List of Medications to Avoid in Older Adults.[27] (A more in-depth understanding of the Beers List is addressed in what follows.)

Table 26-1 OSCAR approach to evaluation and treatment of the older dental patient.

Areas of Concern	
Oral	Dentition, restorations, fixed and/or removable prostheses, periodontium, oral mucosa, salivary glands
Systemic	Medical problem list, medications, age-related changes, interprofessional communication
Capability	Ability to perform instrumental activities of daily living, activities of daily living, caregivers, oral hygiene, transportation, mobility
Autonomy	Decision-making ability, consent to care, dependence on others for decisions
Reality	Financial limitation, life expectancy, prognosis, ability to maintain dental treatment, medical stability

Source: Adapted from Laudenbach J, Jacobsen PL, Mohammad AR, et al. *Clinician's Guide: Oral Health in Geriatric Patients*, 3rd edn. Seattle, WA: American Academy of Oral Medicine; 2011.

Pharmacokinetics

The pharmacokinetics of medications—absorption, distribution, metabolism, and elimination—can be altered due to the aging process. The *absorption* of medications is least affected. Most drugs are absorbed passively, simply by being in the stomach or intestine. If absorption is affected in older adults, it is usually decreased due to an increased amount of acid in the stomach, decreased movement of the muscles of the digestive system, or decreased surface area for absorption.[28,29] Many medications are not significantly affected by these changes, but the coadministration of certain medications, such as antacids, can further decrease absorption. As a consequence of the age-related changes in body composition, drug *distribution* can be affected. Drugs that are mainly water-soluble tend to have smaller volumes of distribution, resulting in higher serum levels in older people. Lipid-soluble medications have higher volumes of distribution, resulting in a prolongation of half-life.[29] Aging is associated with a reduction in first-pass *metabolism*, likely due to a reduction of liver mass and blood flow. The result is a decrease in the bioavailability of medications that undergo an extensive first-pass effect.[28,29] Medications that are prodrugs, however, need to be activated in the liver and hence their activation might be reduced.

Drug *elimination* is affected by aging due to a decline in renal function. As the body ages, there may be:

- Decreased kidney size.
- Decreased blood flow to the kidneys.
- Long-standing disease, such as diabetes or hypertension.[29]

The medication dose or dosing frequency may need to be altered; usually less frequent administration is needed, as it will take the body longer to eliminate the medication.

Pharmacodynamics

The pharmacodynamics of medications—the drug's action on the body—can also be affected by the aging process. As we age, multiple changes occur, such as changes in body composition (increased body fat, decreased lean muscle mass, and decreased body water), which can affect frequency of administration and dosage of medication. Medications that are lipophilic may have prolonged effects due to the increased amount of body fat. Drugs that are hydrophilic

may have a more rapid increase in concentrations in the blood because there is less water. These changes often necessitate lower dosing of medication.[28, 29] Drugs that are highly protein bound, however, have less protein upon which to bind, therefore more of that medication may be required for it to be effective. Finally, as adults age they may experience decreased or enhanced effects of drugs compared to younger populations. Changes occur at the medication's receptor site of action and can ultimately affect the way the body responds to the medication. For example, some older patients are susceptible to medications that cause sedation as a side effect. Sedation can have multiple comorbidities: risk of falls, confusion, and the inability to perform daily tasks.[28,29]

Polypharmacy

Polypharmacy is the use of multiple medications and/or the administration of more medications than are clinically indicated.[30,31] Polypharmacy may also be described as the use of one medication to treat the side effects of another medication, rather than changing to medication that may be better tolerated.[32] Polypharmacy is common among geriatric patients: 87% report taking one prescription medication, 36% report taking five or more prescription medications, and 38% use over-the-counter medications.[32] The likelihood of receiving a prescription increases with age, and polypharmacy may increase the incidence of ADRs as well as drug–drug interactions. Adverse drug events are responsible for one in six older adults being hospitalized.[33]

Medication Adherence

Medication adherence is the extent to which a patient's use of medications coincides with medical or health advice. Medication adherence is a significant problem among the geriatric population. Over 70% of Medicare beneficiaries take prescription medications, but as many as 30% are nonadherent.[34] Complex medication regimens, misunderstanding medication importance, forgetting to take medication, not getting medication refilled, worry about side effects, lack of understanding of indication, and cost all may contribute to decreased adherence.[34] Underprescribing appropriate medication can also occur in the medical management of older patients. Some medications may be underutilized for conditions such as pain, because of concerns about adverse effects or polypharmacy in the geriatric population.[35] Overall, concerns related to comorbidities, adverse drug events, limited life expectancy, and poor risk-to-benefit ratio can all be reasons why prescribers are more hesitant to write for indicated medications.[36]

The Beers Criteria

The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults was originally developed in 1991 by the late geriatrician Mark Beers as a catalogue of medications that cause adverse drug events in older adults due to their pharmacologic properties and the physiologic changes of aging.[28] Beers developed a list of medications, doses, and durations that should be avoided in patients older than 65 years in nursing homes. The list was created from expert consensus through extensive literature review. Since 2012, Beers Criteria have been revised every three years in order to be applicable to all adults 65 and older regardless of where they reside, and include criteria specific to diagnosis and condition. In 2019, the American Geriatrics Society (AGS), utilizing an enhanced, evidence-based methodology, published updated AGS Beers Criteria® to improve medication safety in older adults.[27] Each criterion on the list was rated by quality and strength of evidence, using the American College of Physicians' Guideline Grading System.[28] For the 2019 update, an interdisciplinary expert panel reviewed the evidence published since the last update (2015) to determine whether new criteria should be added or existing criteria should be removed or undergo changes to their recommendation, rationale, level of evidence, or strength of recommendation. Five criteria were used to eliminate 25 medications from the list published in 2015:

- Medications that are potentially inappropriate in most older adults.
- Those that should typically be avoided in older adults with certain conditions.
- Drugs to use with caution.
- Drug–drug interactions.
- Drug dose adjustment based on kidney function.[27]

Printable Beers Pocket Cards are available for download.[36]

Tools for Medication Assessment

Medication use in older adults can be complicated. Each person is different and all geriatric patients may not have the same degree of impairment, so an individualized approach is of the utmost importance. Evaluation of medications in the geriatric population is vital to ensure that medications are used appropriately and safely. Studies have shown that as many as 40% of nursing home residents in the United States were prescribed inappropriate medications.[37]

There are both implicit and explicit tools used to assess medication appropriateness. Implicit tools utilize patient-specific information and prescriber clinical judgment and experience

to address questions, statements, and algorithms in order to optimize medication regimens.[38] Implicit tools enable healthcare providers to identify both the medications that should be avoided as well as the incorrect doses, drug interactions, and patient preference. Examples of implicit tools—the Medication Appropriateness Index (MAI) and the ARMOR tool—are discussed in this section.[38,39] Explicit tools, on the other hand, do not consider patient-specific factors in determining medication appropriateness and comprise lists of medications developed by consensus panels after extensive literature and database review. An example of an explicit tool is the AGS Beers Criteria previously discussed.[27] Explicit tools can be used by anyone regardless of discipline to determine the appropriateness of prescribing, but are limited to medications recognized by the tools' developers. In contrast, implicit tools can be applied to any medication, but require clinical judgment and an understanding of physiology and pharmacology.

The MAI is a tool that uses implicit criteria to rate medications in order to reduce polypharmacy and inappropriate prescribing.[38] Its is very reliable and is structured in a way to evaluate medication use in geriatrics. Even when different clinicians evaluate the regimen, the results are generally similar. The MAI covers 10 elements of appropriate prescribing.[38] It is useful in a variety of situations, including patients in the community and hospital settings.[38]

The ARMOR tool is used to Assess, Review, Minimize, Optimize, and Reassess medication regimens (see Table 26-2).[39] The goal of ARMOR is to improve a patient's functional status and mobility. The tool was designed for nursing home residents receiving more than nine medications, seen for initial assessment, with falls or behavioral disturbance, or who are admitted for rehabilitation.[39] This tool was tested in a long-term care facility and was evaluated by a multidisciplinary team from medicine, nursing, physical/occupational therapy, recreational therapy, and social work. The ARMOR tool can also be utilized for all geriatric individuals and has led to a reduction in polypharmacy, cost of care, and hospitalization.[39]

Table 26-2 ARMOR tool of medication assessment.

ARMOR
Assess the patient for the total number of medications with a potential for adverse effects (beta blockers, antidepressants, antipsychotics, pain medications, medications on the Beers criteria)
Review medications for possible drug–drug interactions, drug–disease interactions, pharmacodynamic (how drugs act in the body) interactions, impact on function, and adverse effects
Minimize the number of nonessential medications, particularly medications with a clear lack of evidence, or if the risk outweighs the benefits of using the medication
Optimize therapy. Evaluate duplicate treatments, adjust doses for kidney or liver function, and adjust doses to achieve treatment goals
Reassess the patient and medications using information such as heart rate, blood pressure, oxygen saturation, functional status, cognitive status, and medication compliance

Source: Adapted from Haque R. ARMOR: a tool to evaluate polypharmacy in elderly persons. *Ann Longterm Care.* 2009;17:26–30.

Geriatric patients are more likely to be on multiple medications, many of which can complicate the provision of oral care. It is therefore imperative for oral healthcare professionals to evaluate patient medications in the context of pharmacokinetics and pharmacodynamics, potential adverse reactions, and complications as a part of the comprehensive oral/medical evaluation. A 2018 study showed that over 75% of patients surveyed are aware of the importance medications have in interacting with dental health and treatment, and consequently disclose all medications prior to dental care.[40] The dental team can therefore provide evaluation of medication adherence and reconciliation as part of whole-person care.

HEALTH LITERACY

Health literacy is defined as "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decision.s"[41] Health literacy is not only the ability to read, as it also involves listening, analyzing, and decision-making together in healthcare situations. Patients may be well educated and knowledgeable in any number of areas, but may have limited knowledge about health and healthcare. Findings of the 2003 National Assessment of Adult Literacy revealed that although the majority of adults in the United States had intermediate or proficient literacy, 36% had only basic or below basic health literacy.[42]

Results of this survey also revealed that compared to adults in younger age groups, adults aged 65 years and older had lower average health literacy. Among adults aged 60 years and older, 71% have difficulty using print materials, 80% have difficulty using documents such as forms or charts, and 68% have difficulty interpreting numbers and performing calculations.[42] In addition, estimates suggest that 66% of older adults are not able to understand information received about their prescription medications.[43] Activities requiring health literacy include communicating with clinicians about health and illness, reading and understanding health information, taking medications, making appointments, and filling out medical forms.[42,43]

Health literacy is especially important among the geriatric population because it affects a patient's ability to navigate

Table 26-3 Teach-Back method: confirmation of understanding.

Do not ask a patient "Do you understand?"
Ask patients to explain or demonstrate
Ask questions that begin with "how" and "what," rather than closed-ended, yes/no questions
Organize information so that the most important points stand out and repeat this information
Ensure agreement and understanding about the care plan. This is essential to achieving adherence

Source: Adapted from Stein PS, Aalboe JA, Savage MW, Scott AM. Strategies for communicating with older dental patients. *J Am Dent Assoc*. 2014;145(2):159–164.

the healthcare system, share personal and health information with providers, engage in self-care in chronic disease management, and even adopt health-promoting behaviors. Low health literacy is associated with increased use of inpatient and emergency care, decreased use of preventive and primary care, and deficits in self-care. Limited health literacy also leads to underutilization of services, poor understanding of health, poor health outcomes, and increased healthcare costs.[44]

The entire oral healthcare team must be aware and sensitive to the effect health literacy has on the provision of care.[44,45] Some simple strategies are as follows:

- Explain things clearly to the patient using nonscientific, plain language, starting with the most important information first.
- Emphasize one to three points and encourage questions.
- Provide written instructions for important information and provide useful educational materials.
- Use the teach-back method to confirm the patient's understanding. This approach has the provider ask the patient to describe and/or demonstrate the information that has been explained. This is accomplished by asking open-ended questions (e.g., do not ask the patient, "Do you understand?").[46,47]
- Ensure agreement and understanding about the care plan; this is essential to achieving adherence (see Table 26-3).[47]

COMMON CHRONIC CONDITIONS AND LEADING CAUSES OF DEATH

Advances in medical treatment and effective public health strategies have contributed to a striking increase in average life expectancy. Since 1900, global average life expectancy has more than doubled and is now above 70 years.[48] In the United States, diseases that were fatal 100 years ago are no longer leading causes of death. Since 1910, heart disease has been the leading cause of death every year except 1918–1920, when there was an influenza epidemic. Since 1938, cancer has been the second leading cause of death every year. Other chronic diseases such as stroke, chronic respiratory diseases, Alzheimer disease, and diabetes continue to be the most common chronic diseases for those aged ≥65 years in the United States (Figure 26-2).[49]

Approximately one in three adults globally suffers from multiple chronic diseases. The societal burden of chronic diseases impacts healthcare expenditures, primary care and specialist provider access, and both emergency department and hospital admissions. The burden of chronic disease on the afflicted individual is substantial, causing disability, unemployment, financial burden, and worsening quality of life.[50]

At first there may be difficulty with instrumental activities of daily living (IADLs), such as money management, grocery shopping, preparing meals, and taking medications properly.[51] As physical and/or mental ability declines, the capability to perform the most basic activities (ADLs) is affected, which can include tasks such as personal hygiene, self-feeding, getting dressed, and toileting. The inability to perform ADLs can alter social engagement with family and friends. Restriction of mobility in the home and of engagement in the community can greatly narrow an older person's world and ability to do the things that bring pleasure and satisfaction. The inability to care for oneself in a safe and appropriate manner leads to further dependence on others and very often to the need for care in an institutional setting (see Table 26-4).[51]

AGE-RELATED SYSTEMIC CHANGES

Changing demographics and improved medical management of disease are placing increased demand on oral healthcare professionals for improved knowledge of both oral manifestations of disease and the provision of dental care for patients with systemic disease. Aging is influenced by genetic factors, lifestyle choices, and environmental exposures, but the predominant physiology of aging is characterized by a breakdown in maintenance of certain molecular structures and pathways, with resultant loss of physiologic reserves needed to handle challenges to homeostasis.[52] As people live longer and as organ systems gradually decline, there is an increase in chronic conditions and illnesses that influence the provision of oral care. The diseases themselves, as well as their treatment, can affect the oral cavity. In addition, chronic impairments, such as hearing or visual or orthopedic disability, can directly affect oral health and impair dental treatment.[52] Simple steps can be taken by dental professionals to help improve communication, oral care, and maintenance.

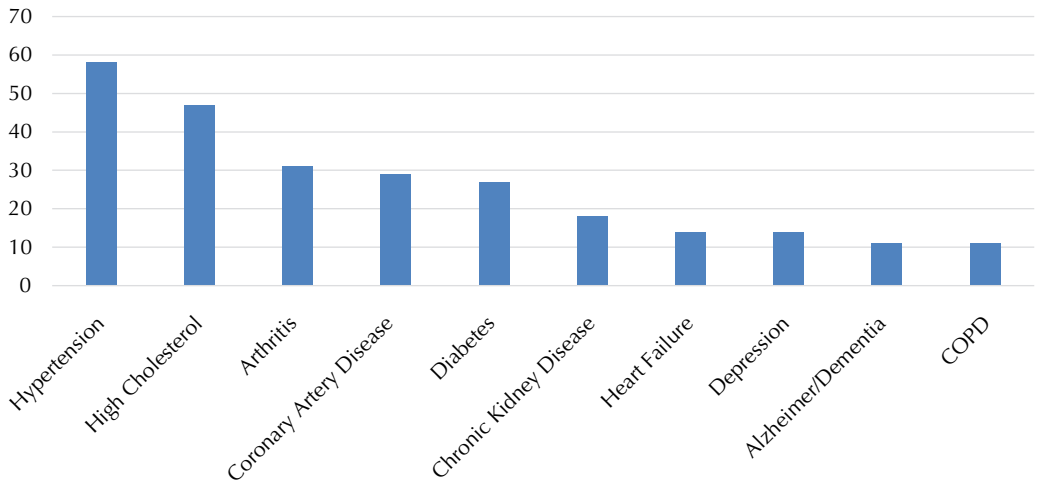

Figure 26-2 Percent distribution of the 10 most common chronic diseases, age ≥65 years in the United States in 2015. *Source:* Data from https://www.ncoa.org.

Table 26-4 Instrumental activities of daily living (IADLs) vs. activities of daily living (ADLs).

IADLs	ADLs
Handling transportation (driving or navigating public transit)	Toileting
Shopping	Selecting proper attire
Preparing meals	Grooming
Using the telephone (and other communication devices)	Maintaining continence
Managing medications	Putting on clothes
Housework and basic home maintenance	Bathing
Managing finances	Feeding
	Walking and transferring (such as moving from bed to wheelchair)

Source: Adapted from Pol MC, Poerbodipoero S, Robben S, et al. Sensor monitoring to measure and support daily functioning for independently living older people: a systematic review and roadmap for further development. *J Am Geriatr Soc.* 2013;61(12):2219–2227.

MOST COMMON SYSTEMIC DISEASES IN OLDER ADULTS

The most common systemic diseases among older adults include hypertension and cardiovascular diseases, arthritis, chronic obstructive pulmonary disease, diabetes mellitus, depression, chronic kidney disease, and Alzheimer disease and dementia.[53] These medical conditions are discussed in detail in various chapters throughout this book. However, two of the most common chronic diseases deserve particular mention within the geriatric context, dementia and arthritis, as they most often affect the elderly.

Dementia

Dementias are a considerable problem among the elderly population. Worldwide, an estimated 50 million people are currently living with dementia. This number is projected to reach 82 million by 2030 and 152 million by 2050.[54] Dementias comprise many illnesses, with the most common being Alzheimer disease and vascular dementia, both of which are characterized by mental and physical decline.[55] With increased severity of dementia, there is progressive cognitive and memory loss, development of social and behavioral problems, and inability to perform daily activities. Progression of dementia is accompanied by a gradual inability to perform self-care (including adequate oral hygiene), self-neglect, and loss of cognitive and motor skills.[56] Persons with dementia often have impaired oral health as a result of poor oral hygiene, reduced salivary flow, more gingival plaque, bleeding, and calculus compared to age- and gender-matched adults.[56] Further, poor gingival health and oral hygiene have been found to increase with the severity of dementia.[57]

Oral care, treatment planning, and behavioral management for persons with dementia must be designed with consideration of the severity of disease and must involve family members or caregivers.[58] Aggrssive preventive and interceptive steps need to be formulated to preserve existing oral health early in the disease process. As dementia progresses, treatment becomes problem based, recall and preventive measures are more frequently needed, and the role of the

caregiver becomes more critical in providing daily oral hygiene and assessing symptoms that arise.[58,59] In severe dementia, complex and time-consuming dental treatment should be avoided and the emphasis should be on keeping the patient pain free, nourished and hydrated.

A comprehensive preventive dental plan is crucial in patients with dementia, as is involving the caregiver as a co-therapist. Patients with dementia may forget oral hygiene, dental appointments, and instructions, unless the caregiver is involved. Dental treatment is best if provided in the morning, when cooperation tends to be greatest, with the usual caretakers present. Treating the patient in an upright or semi-upright position may aid in the prevention of aspiration and postural hypotension.[58,59]

Arthritis

It is estimated that nearly half of all people older than 65 years have arthritis that causes limitation of activity.[60] Patients with arthritis often have diminished manual dexterity that affects maintenance of oral hygiene. Utilizing modified oral hygiene tools can enable improved oral hygiene.[61] Toothbrushes with specially adapted handles (e.g., a bicycle handle grip or the addition of a tennis ball) enable patients to hold and maneuver the brush more easily. In addition, these patients may benefit from electric or sonic toothbrushes to lower the burden of oral hygiene.[61,62]

Patients with arthritis are best treated in the late morning or early afternoon, as joint stiffness and pain tend to improve during the day. Supine positioning may be uncomfortable for them, and they may need neck and leg support. Finally, arthritis patients may need assistance ambulating as well as transporting into and out of the dental chair. Caution must be taken to minimize adverse outcomes, such as falls, as well as to maximize patient comfort.

AGE-RELATED ORAL CHANGES

Age alone does not play a major role in impaired oral health. However, there are age-related oral changes that can predispose older individuals to oral disease. Decay, gingivitis, periodontitis, mucosal diseases, salivary dysfunction, and resorptive bone disease can worsen or be exacerbated by systemic conditions and their treatment.[62,63] Oral diseases give rise to pathogens that can become aspirated into the lungs, causing serious, even life-threatening consequences. Systemic, mucocutaneous, dermatologic, and neurologic diseases can manifest initially in the oral cavity, predisposing older individuals to additional oral problems. Oral healthcare providers must therefore be able to recognize, diagnose, and treat oral conditions in elderly patients that are caused by age-related changes and systemic influences (see Table 26-5).[62]

Oral Motor and Sensory Function

Not only does the sense of smell diminish with age, but the ability to discriminate between smells decreases as well. More than 75% of people over the age of 80 years have evidence of major olfactory deterioration, with that decline being most significant after the age of 70.[64] Taste disorders are far less prevalent than olfactory losses with age. Gustatory dysfunction may be attributed to the normal aging process, but many times a perceived defect in taste is actually a primary defect in olfaction. Other frequent causes of taste dysfunction are upper respiratory infection, head injury, drug

Table 26-5 Common structural and functional oral effects in older adults.

Oral Structure or Function	Associated Oral Effects Related to Age
Oral mucosa	Cancers Vesiculobullous diseases Ulcerative diseases Inflammatory diseases
Dentition	Root caries Coronal caries Attrition Fracture/chipping
Periodontium	Gingivitis Periodontitis Abscesses Tooth loss
Salivary glands	Hypofunction Cancers
Sensory function	Olfactory dysfunction Dysgeusia
Motor dysfunction	Dysphagia Aspiration Masticatory muscle weakness
Pain sensation	Atypical facial pain Burning mouth syndrome Trigeminal neuralgia Postherpetic neuralgia Temporomandibular disorders
Removable prosthesis	Atrophic mandible Ill-fitting dentures Inflammatory lesions secondary to ill-fitting dentures Poor denture hygiene

Source: Adapted from De Rossi SS, Slaughter YA. Oral changes in older patients: a clinician's guide. *Quintessence.* 2007;38(9):773–780.

use, and idiopathic causes.[64,65] Mastication problems associated with tooth loss, ill-fitting dentures, or reduction in saliva production can also inhibit proper taste sensation. Patients who have diminished food recognition and enjoyment as well as altered smell and taste function can therefore have quality-of-life issues and malnutrition.[65] Oral healthcare professionals can serve an important role in nutritional counseling to prevent malnutrition, dehydration, and diminished quality of life.

Alterations in mastication, swallowing, and oral muscular posture occur with aging. The most commonly reported oral motor dysfunction is altered mastication.[64] Even fully dentate elderly patients are less able to prepare food for swallowing due to decreased muscular strength.[62] This muscle weakness can be exacerbated by various systemic diseases such as Parkinson's disease, a history of head and neck cancer and its treatment, multiple sclerosis, and cerebrovascular accidents. Subsequent effects on swallowing and deglutition may lead to choking and aspiration.[66] Motor issues may cause challenges to restorative dental treatment, therefore extra time should be allowed and extra patience should be exercised. In addition, the dentist should eliminate dental-related factors that might further inhibit the ability to eat properly. Finally, referral to appropriate healthcare providers is important in cases where interventions beyond the scope of dental care are needed. Speech and swallow experts, otolaryngologists, and nutritionists can provide beneficial information and treatment to elderly patients suffering from oral and maxillofacial motor and sensory dysfunction.

Orofacial Pain

An accurate diagnosis of a painful condition is often more difficult in the elderly due to a greater frequency of chronic diseases and altered pain response.[67] Understanding the nature and prevalence of pain in this group is paramount to a correct diagnosis, being cautious to avoid the oversimplification that "pain decreases with age."[68] The most prevalent types of pain in the orofacial complex are associated with the dentition, periodontium, oral mucosa, and bone. In addition, peripheral neuropathies such as burning mouth syndrome and atypical odontalgia are particularly common among the elderly population.[68] Extraoral pain disorders are similarly common with aging and may include trigeminal neuralgia, postherpetic neuralgia, various degenerative joint diseases of the temporomandibular joint, and persistent dentoalveolar pain from a neuropathic process (such as atypical facial pain or persistent idiopathic facial pain).[69] See Chapters 11 and 13 for more detailed explanation and management of various orofacial pain disorders.

Many elderly patients have diminished pulpal sensitivity.[70] A prompt and correct diagnosis is key, as it is important to minimize treatment and avoid unnecessary therapy in patients with dentoalveolar pain that is neuropathic in origin.[69] Pain assessment can be made by means of pain scales and specific open- and closed-ended questions. In patients who suffer from temporomandibular pain, appointments should be short and have frequent jaw rest. In patients with neuralgia, avoidance of trigger areas is imperative. Some practitioners may underestimate the severity of pain in older adults, and subsequently not prescribe appropriate analgesics when indicated.[71] In general, management of acute or chronic orofacial pain in geriatric patients is not significantly different than younger counterparts; however, it requires thorough examination and management, often involving multiple healthcare providers.

Dentition

Geriatric dental care is no longer simply denture care. For example, in the United States, only 13% of adults in the age 65–74 group were edentulous in 2009–2012, whereas this same age group had 55.4% edentulism in 1957–1958.[72] As people live longer and retain more natural teeth, the complexity of treatment increases and can include complex restorative procedures, aesthetic dentistry, and implants. Age-related changes to the dentition, such as occlusal attrition, pulpal recession, fibrosis, and decreased cellularity, may lead to diminished tooth sensitivity and reduced perception of painful stimuli.[70] Cementum thickness and pulp dimensions are also reduced with age.[70] Over time, dentin undergoes a reduction in thermal, osmotic, and electrical sensitivity and pain perception to caries decreases.[70] In addition, staining, chipping, and increased susceptibility to tooth fracture are common in older patients.

Caries is the most common tooth-related pathology.[70,73] For example, in the United States, nearly all adults (96%) aged 65 years or older have had a cavity; 1 in 5 has untreated tooth decay.[74] Root caries occurs as a result of increased gingival recession, salivary gland dysfunction, less effective oral hygiene, and diminished oral motor function. The risk factors for root caries include root exposure, dry mouth, oral hygiene status, bacterial virulence, and fluoride exposure.[73] Mandibular molars, premolars, and maxillary canines are most commonly affected, with the surfaces involved most often being facial and proximal.

Strategies to prevent root caries include gingival recession prevention, plaque control, use of multiple fluoride sources (including rinses, sprays, mouthwashes, and varnishes), dietary and nutritional counseling, and improvement of salivary flow.[75,76] Fluoride provides important antimicrobial and remineralization actions and also alters tooth surface energy.[75] Fluoride has the ability to concentrate in carious lesions as well as increase salivary pH. Several systematic

reviews have demonstrated the use of silver diamine fluoride (SDF) as a successful treatment strategy in preventing and arresting root caries in older adults.[76–78]

Restorative management of root caries involves multiple factors: isolation, gingival morphology, lesion location, preparation design, and choice of restorative material. Rubber dam is an ideal form of isolation; however, due to the often subgingival extension of root caries, cotton roll isolation or a VAC ejector system may be indicated. Removing gingival obstructions with a gingivectomy, retraction cord, or even a full-thickness flap may also be indicated. Restorative materials must be evaluated for advantages and disadvantages for each patient and lesion:

- Amalgam is effective when isolation is poor, but requires gross mechanical retention and has minimal plaque resistance.
- Glass ionomer cures quickly, needs moderate isolation, has sufficient chemical bonding, and has good plaque resistance.
- Composite resin has strict isolation requirements for bonding, has poor plaque resistance, and requires a rubber dam.[74]

Restorative maintenance includes a low-carbohydrate diet, patient education with intense hygiene instruction, and frequent recall. Addressing the cause of decay through a caries risk assessment as well as utilizing remineralization therapies both in the dental office and at home can aid in maintenance. Fluoride-releasing restorative materials should also be considered when evaluating treatment options.[75] Finally, conservative treatment plans such as the use of SDF in high caries-risk patients, especially among those who are unable to maintain their restorations, is vital.

Periodontal Tissues

Aging can be associated with healthy periodontium over the life course, resulting in a high level of tooth retention and function. Older adults who receive consistent dental care retain more teeth than those who do not, but this consistent care is not always sufficient to prevent the progression of periodontal disease with comparable success to younger counterparts.[79] The interplay of compositional change of plaque and the reaction of the periodontium to the plaque together with systemic diseases, their complications, and pharmaceutical management counter the degree of success seen in younger individuals.[80] Gingival recession with loss of periodontal attachment and poor oral hygiene predisposes the aging patient to tooth loss and masticatory insufficiency. Problems with deglutition soon follow, which can then lead to serious consequences such as dehydration and malnutrition.[79] Periodontal disease requires more frequent recall and more conservative restorative treatment plans.[80] Home care can be difficult due to psychomotor deficiencies, but can be aided by adaptation to hygiene products specific for this population. Toothbrushes with modified handles, electric toothbrushes, three-sided brushes, finger toothbrushes, and suction brushes provide creative approaches to consistent oral hygiene. Education is at the core of prevention, both for the patient and for the caregiver.

Oral Mucosa

The clinical appearance of oral mucosa in healthy older adults is indistinguishable from that in younger patients. Changes over time, including mucosal trauma, mucosal diseases, oral habits, and salivary gland hypofunction, can alter the clinical appearance and character of oral tissues. Declining immunologic responsiveness with age further increases susceptibility to oral mucosal infection and trauma.[52,81] Systemic disease and a variety of medications can also result in oral mucosal disorders. Finally, the oral epithelium becomes thinner, loses elasticity, and atrophies with age, making it more susceptible to pathology.[81] A brief discussion of the more common oral mucosal disorders seen in the elderly demographic follows. More in-depth discussions of each topic are found in Chapters 3, 4, and 6.

Traumatic Ulcers

Traumatic ulcerations of the oral mucosa most frequently affect the labial and buccal mucosa and are associated with lip and cheek biting, factitial habits, motor dysfunction, pressure necrosis, improper hygiene, broken teeth, irritation by faulty restorations, and ill-fitting removable prostheses.[63] Traumatic ulcerations appear as shallow ulcerations with a necrotic center and varying degrees of erythema at the periphery. Treatment of these lesions involves identifying the etiology and removing it. If no resolution occurs within a two-week period, an incisional biopsy for histologic diagnosis is prudent, as chronic traumatic lesions can be indistinguishable from oral cancer. Palliation with topical emollients and anesthetics may be helpful.

Lichen Planus

One of the more common ulcerative disorders of the oral mucosa is lichen planus, which also includes lichenoid reactions from medications. Although the etiology may be idiopathic, virally induced, or drug related, most lichenoid lesions are likely due to some precipitating event that leads to a T cell–mediated chronic inflammatory response in the oral tissues, resulting in a reticular striated, plaque-like or ulcerative mucosal condition.[82] The possibility of lichenoid

reactions to dental materials also exists. Lichen planus should be diagnosed with biopsy, as there is an associated malignant transformation in patients with chronic oral lichen planus.[82] Patients diagnosed with lichen planus should be counseled as to the increased risk of malignant transformation and the need for biannual reevaluation even if asymptomatic. More frequent recall is also needed in patients with desquamative gingivitis, because painful, sore, and tender gingiva often affect oral hygiene. See Chapter 4 for an in-depth, detailed discussion of lichen planus and lichenoid reactions.

Inflammatory Lesions

Inflammatory lesions in older adults occur often as a result of poorly fitting dentures.[83] Papillary hyperplasia is a common finding in patients with loose maxillary dentures. Clinically, these lesions represent multiple, polypoid, and papillary nodules, found typically on the hard palate, giving a cobblestone appearance. There also may be comorbid candidiasis.[83] Treatment includes decreased or discontinued use of the denture. Tissue conditioners may reduce papillary hyperplasia, along with concomitant treatment with an antifungal agent. Occasionally, surgical removal of the hyperplastic tissue and/or construction of new prostheses may be indicated. Another denture-related inflammatory lesion is epulis fissurata, which appears as hyperplastic, redundant tissue in the vestibule due to overextended denture flanges. Dentures become overextended because of resorption of the alveolar bone or significant weight loss.[83] Hyperplastic granulation tissue surrounds the denture flange and can be associated with pain, bleeding, and ulceration. Small lesions may resolve if denture flanges are reduced. However, surgical excision is necessary for larger fissurata prior to rebasing or relining a denture.

Candidiasis

Older patients are at increased risk of developing intraoral candida infections due to systemic disease, poor immune function, medication- or disease-induced dry mouth, and removable prostheses.[80] Pseudomembranous candidiasis is the most common clinical presentation and appears as a white plaque on any intraoral mucosal surface that can be wiped away, leaving an erythematous base. Less commonly, candida infections appear as generalized, diffuse erythema throughout the oral tissues. Patients may complain of pain or burning in the oral cavity as well as a change in taste sensation, but many cases are asymptomatic. The diagnosis of intraoral candidiasis includes a thorough review of systems along with disease history and can be made clinically in many instances.[80] Direct cytologic smear for periodic–acid Schiff staining is helpful to confirm a diagnosis. In severely debilitated patients, extension of the yeast to the esophagus and trachea may lead to significant morbidity and mortality. Use of both topical and systemic antifungals is indicated, as well as direct topical treatment of any prostheses.

Angular Cheilitis

Angular cheilitis is a common variant of a candida infection that is seen very commonly in the older patient. Angular cheilitis can occur not only due to candidiasis, but also due to diminished occlusal vertical dimension or nutritional deficiencies, such as vitamin B or iron deficiencies.[80,83] Commonly, patients have wrinkled and sagging skin at the lip commissures, with desiccation and mucosal cracking along the corner of the vermillion border. The most effective treatment includes a combination antifungal and steroid cream applied to the affected areas several times daily. To prevent chronic symptoms, vitamin deficiencies should be excluded and vertical dimension of occlusion issues should be eliminated. For further information on oral candidiasis, refer to Chapter 4.

Vesiculobullous Disease

Pemphigus vulgaris is a serious life-threatening autoimmune vesiculobullous disorder that usually affects individuals after their fifth and sixth decades of life (see Chapter 3). *Cicatricial or mucous membrane pemphigoid* is another immunologically mediated vesiculobullous disorder that primarily affects older women (see Chapter 3). Early and accurate diagnosis with biopsy for both routine and direct immunofluorescence study is vital. Dental management considerations include more frequent hygiene recall and careful use of removable prostheses to avoid exacerbation of mucosal lesions. Older patients afflicted with pemphigus or pemphigoid require the same topical and/or systemic treatments as their younger counterparts; however, drug–drug interactions and comorbid systemic disease must be considered when choosing treatment.[84]

Recurrent herpes labialis, recurrent intraoral herpes, and *herpes zoster* reactivation along any of the three distributions of the trigeminal nerve can cause vesiculobullous ulcerations and significant oral pain in the older patient.[85] It is important for the dentist to avoid elective dental care during these acute flares and to consider prophylactic antiviral medications in patients with a history of reactivation of the virus and oral lesions secondary to dental treatment. Treatment of recurrent herpetic lesions is more effective when started in the prodromal stage before lesions ulcerate and crust. Topical ointments and creams as well as systemic antiviral therapies are often indicated. Occasionally, prophylactic systemic antiviral therapy may be appropriate. Herpes zoster, or shingles, most commonly occurs in people who are

over 50 and those who are immunosuppressed.[86] The shingles vaccine is recommended by the Advisory Committee on Immunization Practices to reduce the risk of shingles and its associated pain in people 60 years old or older.[86]

See Chapter 3 for detailed explanations of these and other vesiculobullous diseases.

Oropharyngeal Cancer

Incidence rates of oral cancer increase with age. Over 50,000 new oral cavity and pharyngeal cancers were diagnosed in 2020, comprising 2.9% of all cancer diagnoses.[87] Nearly 11,000 Americans will die from this disease in that same year.[87] Oral cancer has an overall five-year survival rate of approximately 66.2%—a rate that increases significantly with advanced stageing.[87] Typical sites of oral malignancy in the elderly include the tongue, lips, buccal mucosa, floor of mouth, and posterior oropharynx. The most common risk factor other than increased age is the use of tobacco and alcohol. Oral malignant lesions are typically squamous cell carcinomas and can appear as diffuse, poorly defined exophytic masses that can metastasize to regional lymph nodes before involving distant organs.

An oral cancer screening examination should be performed at every dental visit, as well as reinforcement of prevention by means of limiting risk factors such as sun exposure, alcohol intake, and tobacco use.[88] Patients diagnosed with and treated for oropharyngeal cancer will have extensive acute and long-term complications related to cancer treatment. For explanation of these side effects and their management, see Chapter 8.

Salivary Glands

Salivary glands are known to undergo histologic changes with age. Secretory components of the glands are replaced by fibrous and adipose tissue, making them less effective at producing saliva.[89] Clinically significant decreases in major salivary gland flow do not occur in healthy older people, although age-related changes in salivary quality and electrolytes have been demonstrated. [89] Changes in salivary quantity and quality cannot be attributed only to aging, as it is more likely that changes in saliva occur due to the effects of medications, polypharmacy, and systemic disease.[90] Diminished salivary output can cause dental decay, oral mucosal infections, sensory disturbances, speech dysfunction, decreased nutritional intake, and difficulty in chewing, swallowing, and denture retention.[90]

An appropriate diagnosis for oral dryness is vital, as there is a plethora of both salivary and nonsalivary causes.[91] In addition, the management of salivary gland hypofunction and xerostomia is multidisciplinary and multimodal, requiring communication and collaboration among multiple clinicians, the patient, and the patient's caregiver.[92] A comprehensive discussion of salivary gland diseases, decreased salivary flow, and management is found in Chapter 9.

INSTITUTIONALIZED OLDER ADULTS

Although most of the world's population lives independently, a significant number of older adults are completely dependent for all aspects of life. Approximately 1.3 million elderly reside in 15,600 nursing homes in the United States.[11] These individuals are likely to have diminished physical capabilities as well as cognitive impairment, which together can compromise general and oral health status. Multiple studies have reported that large proportions of nursing home residents have a host of dental diseases and rarely seek dental care services.[11] Currently, on admission to a nursing home, residents are to receive a comprehensive health assessment that includes an oral evaluation. This evaluation is federally mandated for all facilities that receive either Medicaid or Medicare reimbursement, which is about 98% of all US long-term care facilities.[11] Admission oral evaluations are typically performed by dietitians, clinical nurse assistants, or other healthcare professionals, who are not necessarily able to accurately identify oral problems and cannot always recommend appropriate follow-up care. In addition, oral healthcare is not adequately considered in most protocols on personal hygiene for the elderly in hospitals or long-term care units.[11]

Oral disease is rarely life-threatening. However, it plays an essential role in the management of medical problems, nutrition, social interaction, and the quality of life of older adults. For example, in 2000, the link between oral health and general health was brought to the forefront when the US Surgeon General released a report on *Oral Health in America*.[93,94] This report highlighted the "silent epidemic" of oral disease that affects the most vulnerable citizens in the United States, among whom are the elderly. Multiple studies support the notion that institutionalized subjects are at greater risk not only of developing pneumonia, but also of having dental plaque colonization by respiratory pathogens.[95] Although federal legislation that funds payments to nursing homes for the care and housing of their residents requires that there should be no oral neglect, in the absence of a consensus definition of oral neglect there can be no systematic enforcement of this legislative mandate.[96] A consensus definition of oral neglect would provide minimum standards for the oral health status of nursing home residents, operational oral health standards for nursing home

administrators, enforceable guidelines for agencies responsible for quality, and provide the general public with a clear statement of dentistry's ethical and professional stance on this topic.[96]

SPECIAL CONSIDERATIONS FOR COMMUNICATION AND ORAL HYGIENE INSTRUCTION

Older adults have various functional and behavioral changes that require special consideration during dental treatment and oral hygiene education. Communication between oral healthcare provider and patient very often needs to be adjusted so the patient gleans the most out of both the treatment and the instruction.[47] There can be slowing of speed of thought or associations in older adults, hence making suggestions gradually, even over a series of appointments, and adapting the patient's current approach to make it more effective are valuable.[47] Many times older adults have difficulty in timing sequential events, therefore their skills become separate movements. In this situation, it is best to guide the patient's demonstration of their oral hygiene to avoid embarrassment.[47] The rate of learning changes with age, even though the ability to learn does not.

There are useful strategies in teaching oral hygiene for the aging patient. See Table 26-6 for a summary of different approaches.[61]

Table 26-6 Strategies for teaching oral hygiene practices in the aging patient.

Bridging	Involves engaging the individual's senses, especially sight and touch, to help understand the task you are trying to do for them
Chaining	The caregiver begins the oral hygiene task and the individual then helps to finish it
Hand over hand	Technique that helps to improve sensory awareness of takes and gives individuals the sensation that they are performing the task with you
Rescuing	Used to help with completing hygiene tasks for individuals with dementia
Distraction	Involves placing a familiar item in the individual's hands during oral hygiene care

Source: Adapted from Weening-Verbree L, Huisman-de Waal G, van Dusseldorp L, van Achterberg T, Schoonhoven L. Oral health care in older people in long term care facilities: a systematic review of implementation strategies. *Int J Nurs Stud*. 2013;50(4):569–582.

CONCLUSION

As the global population ages and as medical management of disease continually improves, the landscape of oral healthcare will also change. Oral healthcare professionals must possess the tools and knowledge to manage oral manifestations of systemic disease and age-related oral changes. Older adults are more susceptible to medical conditions that directly and/or indirectly lead to malnutrition, altered communication, increased susceptibility to infection, and diminished quality of life. Increased medication usage alone puts this population at greater risk for complications due to drug interactions, polypharmacy, and medication compliance. In addition, this age group has social determinants of health that have an impact on comprehensive dental care. Oral healthcare professionals play an important role in whole-person care by performing a systematic, comprehensive oral and medical evaluation of the geriatric patient, enabling the dental team to be an essential component in screening for disease, disease control, medical risk assessment, and medication adherence and reconciliation.

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27

The Role of Genetics in Oral Medicine

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BASIC HUMAN GENETIC PRINCIPLES

History of Genetics and the Human Genome Project

Since the dawn of civilization, humans have been aware of heredity and applied its principles to improve crops and domestic animals. Pedigrees of horses and possibly inherited characteristics were found on a Babylonian tablet more than 6000 years old.[1] However, the mechanism by which a genotype resulted in a phenotype was first described only about 150 years ago, when Gregor Mendel discovered independent assortment of traits through his cross-pollination experiments between variants of the garden pea. Most of the mechanisms of heredity remained a mystery until the nineteenth century, when genetics as a science began. It was the identification of genes, the fundamental units of heredity, which brought genetics into being. In the twentieth century, tremendous strides were undertaken to understand the nature of genes and their function. In 1905, English biologist William Bateson introduced the word "genetics" to describe the study of heredity and the science of variation.[2] In 1908, British physician Archibald Garrod applied genetic knowledge to human diseases and disorders. Garrod proposed that the human disease alkaptonuria was caused by "inborn errors of metabolism," suggesting for the first time that genes had molecular action at the cell level.[1] In 1909, Danish botanist, plant physiologist, and geneticist Wilhelm Johannsen introduced the term gene to denote the basic unit of heredity. In 1944, molecular biologist Oswald Avery showed that genes and chromosomes were composed on deoxyribonucleic acid (DNA). Ironically, for most of the twentieth century, clinicians viewed genetics as a somewhat esoteric academic specialty.

A major breakthrough occurred in 1953, when American genetics and biophysicist James D. Watson and British biophysicist Francis Crick and Maurice Wilkins discovered a double helix model for DNA structure.[3,4] Watson, Crick, and Wilkins shared the 1962 Nobel Prize in Physiology or Medicine for their discovery. Watson and Crick's discovery has helped researchers to understand human life more closely. In 1958, American molecular biologist Mathew Meselson and American geneticist Franklin W. Stahl for the first time demonstrated experimentally the strand separation method for DNA replication (semiconservative method).[5] In the 1970s, American biologists Allan M. Maxam and Walter Gilbert and English biochemist Frederick

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

Sanger pioneered DNA sequencing techniques, for which Gilbert and Sanger shared the 1980 Nobel Prize in Chemistry. In 1983, American biochemist Kary B. Mullis invented polymerase chain reaction (PCR), a simple technique that allows a specific piece of DNA to be copied billions of times in a few hours.[6] In recognition of their invention, Mullis and Michael Smith shared the 1993 Nobel Prize in Chemistry.

On October 1, 1990, an international team of researchers began the Human Genome Project (HGP), which aimed at sequencing and mapping all of the human genes, known as the genome. Completion of the HGP in April 2003 for the first time provided the ability to read nature's complete genetic blueprint for building a human being.[7–10] Meanwhile, rapid advances in high-throughput sequencing and bioinformatics analyses made the "$1000 genome" (the cost to read the sequence of nearly a person's entire DNA sequence of ca. 3 billion DNA bases) a reality. This, in turn, greatly expanded the potential use of DNA sequencing as a tool for diagnostics and prognosis that emphasizes individualized or *personalized* health care.[11–13] In 2008, the 1000 Genomes Project was initiated through an international collaboration in which researchers aimed to sequence the genomes of a large number of people from different ethnic groups worldwide. Completion of the 1000 Genomes Project in 2015 enabled the creation of a catalog of genetic variations.[14,15]

Even though the completion of the HGP and the 1000 Genomes Project as well as the enormous public interest in genomics did not abruptly change or transform the fields of medicine and dentistry, the growing and evolving body of knowledge and information has significantly expanded how we think about and use human genetics in medicine and dentistry. Completion of the HGP has had a profound impact on genetic prediction of individual risks of disease and responsiveness to drugs.[16,17] Knowledge of the human genome sequence has enabled the development of designer drugs, based on a genomic approach to targeting molecular pathways disrupted in disease.[17–19] Genomic medicine holds the ultimate promise of revolutionizing the diagnosis and treatment of many illnesses.[20]

DNA Makes RNA Makes Protein

Genetics is the study of genes at all levels, including their function in the cell and the ways in which they are transmitted from parents to offspring. Modern genetics focuses on deoxyribonucleic acid (DNA), the chemical substance that genes are made of, and the ways in which it affects the chemical reactions.

All genetic diseases involve errors occurring at the level of the cell, for example DNA replication errors or errors in translation of genes into proteins. These errors often produce single-gene disorders. Errors occurring during cell division may results in disorders involving entire chromosomes.

Human somatic cells are diploid: they contain two copies of each chromosome, one from the mother and one from the father, for a total of 23 pairs (46 chromosomes). Of the 23 pairs of chromosomes, 22 pairs (numbered 1–22 from largest to smallest) are autosomal chromosomes and 1 pair is sex chromosomes. In a normal male, the sex chromosomes are a Y chromosome from the father and an X chromosome from the mother. Normal females have two X chromosomes. Gametes (egg and sperm cells) are haploid and contain a single copy of chromosomes (23 chromosomes).

Deoxyribonucleic Acid (DNA)

DNA is the genetic blueprint for making all proteins in the body. The discovery of the molecular structure of DNA revealed that it was made of a long chain of nucleotides arranged in two strands, forming a spiral called a double helix. Nucleotides are the building blocks of DNA that are made up of three components: a phosphate group, a 5-carbon sugar, and a nitrogenous base. The four nitrogenous bases in DNA are adenine (A), guanine (G), cytosine (C), and thymine (T), which is replaced by uracil (U) in ribonucleic acid (RNA). Adenine and guanine are purine bases and cytosine, thymine and uracil, and pyrimidine bases. The information in DNA is stored as a code of these four chemical bases that pair up with each other via hydrogen bonds, such that A pairs with T via a double hydrogen bond and C pairs with G via a triple hydrogen bond. The complementary base pairing is important during DNA replication, in which DNA polymerase enzyme uses a single strand of the double-stranded DNA molecule as a template for the synthesis of a new, complementary strand, making an identical copy of DNA. Different sequences of nucleotide bases specify different proteins. Therefore, the order of the bases determines the information for building and maintaining an organism.

The majority of human DNA (approximately 3 billion nucleotide pairs per haploid genome) is packaged in the cell nucleus by coiling around a histone protein core to form a nucleosome, which then forms a solenoid that makes up the chromatin loops. Some DNA is also stored in the mitochondria (16,569 nucleotide pairs that encode 9 genes). A small portion of human DNA (1%–2%) encodes functional genes. Humans are estimated to have 20,000–25,000 functional genes, which are sequences of DNA that code for RNA or proteins. The vast majority of the human genome is not as yet informative, which includes pseudogenes (19,000 identified human pseudogenes), or repetitive DNA sequences.[9,12,13]

From Genes to Proteins

DNA contains instructions for making proteins. It resides and is replicated in the cell nucleus; however, protein synthesis takes place in the cytoplasm. Therefore, information/instructions contained in DNA have to be "transported" into

cytoplasm, where they can direct the process of protein synthesis. A series of steps must occur before proteins are made from DNA. First, information contained in a piece of DNA sequence (gene) is transcribed to messenger RNA (mRNA) by RNA polymerase II enzyme. Transcription occurs in the cell nucleus and involves making an mRNA copy of a gene encoded within the DNA template through complementary base pairing. The DNA sequence of a gene has several elements: (1) a start sequence, which begins mRNA transcription; (2) a promoter sequence, which is located upstream (before) the start sequence and contains transcription factor binding sites that act as switches that can turn transcription "on" or "off"; and (3) enhancers or repressors, which are typically 2000 nucleotides long and are located further upstream from a start site. These additional control elements regulate the rate, amplitude, or quantity of transcription by responding to DNA-binding proteins, hormones, certain types of vitamins, for example retinoic acid, or growth hormones. The body of a gene contains (1) exons, which are coding DNA sequences that produce protein products; (2) introns, which are noncoding sequences separating exons; and (3) a stop sequence that terminates transcription.

The transcription process begins with RNA polymerase II enzyme binding to a promoter site on the DNA and pulling a portion of a DNA strand apart. Exposed unmatched DNA bases become a template for the sequence of the primary mRNA transcript. Before the primary mRNA transcript leaves the nucleus it undergoes splicing, in which nuclear enzymes remove sections of the RNA (introns) and the remaining sections (exons) are spliced together to form the functional mRNA. After the gene splicing is complete, mature mRNA transcript leaves the nucleus and migrates into the cytoplasm, where it is translated into a protein. Genes that encode ribosomal RNA (rRNA) and transfer RNA (tRNA) are also transcribed and migrate to the cytoplasm, where they facilitate protein synthesis. Some genes contain alternative splice sites, allowing the primary transcript to be spliced in different ways. Alternative splicing produces different protein products from the same primary transcript. The process of alternative splicing is common, therefore the proteome reflecting the human genome (20,000–25,000 genes) well exceeds the number of genes in the human genome. For example, the *AMELX* or *AMELY* gene encodes amelogenin, which is the major protein forming enamel extracellular matrix. In human and other mammals, there are six to eight different isoforms of amelogenin, differing in molecular weights and cross-reactive with anti-amelogenin rabbit antibodies. These different amelogenin proteins were shown to be produced by alternative splicing of the *AMEL* gene and not, as previously believed, by post-translational modifications.[21,22] Another example of the effects of alternative splicing on phenotype is dentinogenesis. The dentin sialophosphoprotein gene (*DSPP*) encodes two different noncollagenous proteins: (1) dentin sialoprotein and (2) dentin phosphoprotein.[23,24] Mutations in type I collagen and/or *DSPP* genes produce five different patterns of dentinogenesis imperfects (inherited dentin defects).[23,24]

Translation is the process in which mRNA provides a template for the synthesis of a precise sequence of amino acids known as polypeptide or protein. Translation and protein synthesis occur at a ribosome. A tRNA bound to a particular amino acid contains an anticodon that pairs with a codon in mRNA. During translation, tRNAs and their attached amino acids arrive at the ribosomes. The linear sequence of codons of mRNA determines the order in which amino acids are added into a protein. There are 20 different types of amino acids that are encoded by units of 3 mRNA bases known as codons. Of the 64 possible codons, 3 (UAA, UGA, and UAG) signal the end of a gene and are known as stop codons. The remaining 61 codons are functional codons and specify amino acids. There are 64 possible codons ($4\ \text{mRNA bases}^{3\ \text{triplets}} = 64$) and only 20 amino acids, which means that most amino acids can be encoded by more than one codon. Therefore, genetic code is degenerate. Replication of one strand of DNA to a copy strand of DNA, transcription of DNA into mRNA, and translation of mRNA into proteins are cellular processes critical for biologic activity (Figure 27-1).

Regulation of Gene Expression

All somatic cells have exactly the same DNA sequence; however, there is a large variety of different cell types making different proteins. This is because cells differ at which genes are actively expressed. For example, muscle cells have a different set of genes that are turned on in the nucleus and a different set of proteins that function in the cytoplasm than do for example nerve cells. In most cells only a small fraction of genes is actively transcribed and most genes are transcribed only in specific tissues at specific points in time. For example, the globin genes are transcribed in the progenitors of red blood cells where they help to form hemoglobin, and the low-density lipoprotein receptor genes are transcribed in liver cells. Some genes, called housekeeping genes, are transcribed in all cells of the body, as they encode key products necessary for a cell's maintenance and metabolism. A variety of mechanisms regulate gene expression, which can be broadly divided into transcriptional regulation, post-transcriptional regulation, and epigenetic mechanisms.

Inherited Variation

Transcriptional Regulation of Gene Expression

Gene expression is initiated by transcription factors binding to a promoter region of a gene. General transcription factors are used by all genes, and specific transcription factors

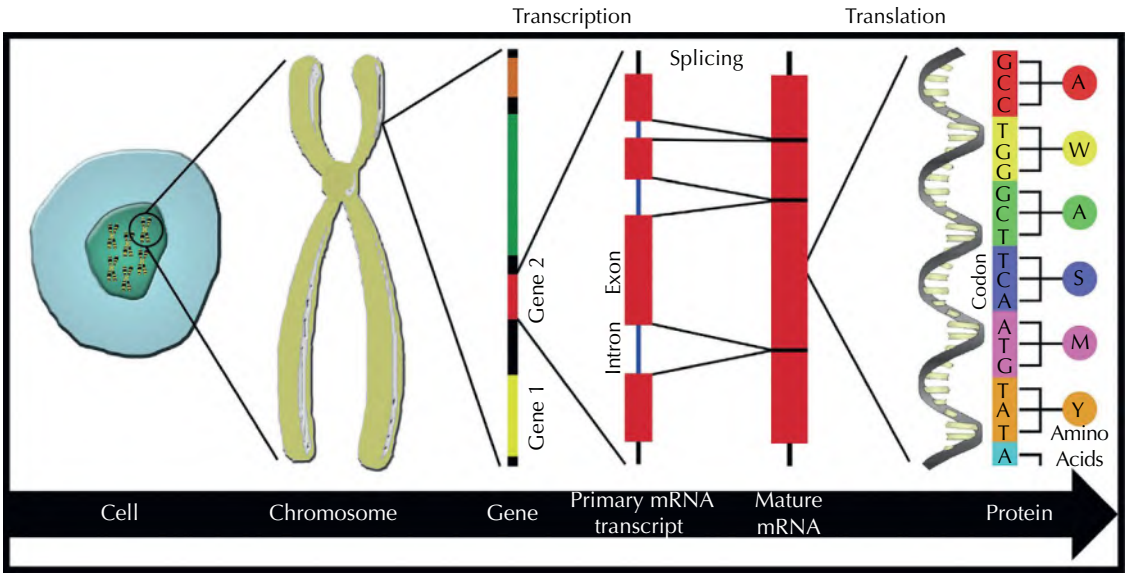

Figure 27-1 Central dogma of molecular biology: from DNA through mRNA to protein. Majority of human DNA resides in the cell nucleus and is organized in chromosomes. Chromosomes contain thousands of genes that are sequences of nucleotides along the chromosome (colored blocks). Genes on a chromosome are separated by noncoding DNA (black blocks). Each genes contains exons, which are coding DNA sequences that produce proteins (red blocs in the primary mRNA transcript), and introns, which are noncoding sequences separating exons (blue lines in the primary mRNA transcript). The primary mRNA transcript is transcribed from the DNA blue print in the nucleus. The primary mRNA contains both exons and introns and undergoes splicing to create mature mRNA transcript. Splicing occurs in the nucleus and involves removal of introns by nuclear splicing enzymes and splicing exons together. Mature mRNA leaves the nucleus and translocate into the cytoplasm to serve as a template for making proteins. In the cytoplasm, the mature mRNA is read in triplicates of nucleotides (codons) that are translated into amino acids (building blocks of proteins) (colored circles).

initiate transcription of only certain genes at specific points in time. Transcription factors contain DNA-binding motifs that allow them to interact with specific DNA sequences. Basal transcription levels can be modulated by binding of transcription factors to other regulatory regions such as enhancers and silencers, located thousands of bases away from the transcribed gene. Enhancers do not directly interact with a transcribed gene, but are bound by specific transcription factors (activators) that bind to a second class of specific transcription factors (co-activators) that in turn bind to general transcription factor complex, enhancing the expression of specific genes at specific points in time. Silencers repress the transcription of genes. Mutations in genes encoding transcription factors as well as mutations in enhancer, silencer, or promoter sequences can result in faulty expression of vital genes, leading to genetic disease. For example, tooth agenesis (oligodontia or hypodontia) is caused by mutations in one or more transcription factors (e.g., MSX1, MSX2, DLX5, PAX9) that may result in inhibition, arrest, or retarded tooth development.[25–28]

A number of morphoregulatory master genes encoding highly conserved transcription factors such as *HOX* (homeotic) genes, *PAX* genes, and *T-Box* genes have been identified. These transcription factors are highly conserved from fish to humans and bind with specific nucleic acid sequence motifs with high affinity. They are major regulators of animal development.[29] Mutations in either the *FOXC1* or the *PITX2* homeobox genes have been found in 40% of Axenfeld–Rieger syndrome (ARS), an autosomal dominant developmental disorder with anomalies of the anterior segment of the eyes, iris hypoplasia, tooth anomalies, craniofacial dysmorphogenesis, cardiac defects, limb anomalies, pituitary anomalies, intellectual disabilities, and neurosensory defects (Figure 27-2).[30]

Post-transcriptional Regulation of Gene Expression This form of gene regulation includes mechanisms of RNA processing (splicing), mRNA transport, mRNA stability, and translation. For example, alterations in RNA splicing may result in different isoforms of a gene. MicroRNA regulation is another mechanism of post-transcriptional regulation. MicroRNAs (miRNA) are 17–27 nucleotide-long RNA molecules that are not translated into proteins. MiRNAs can downregulate the expression of genes they are complementary to by binding to their mRNA transcript. MiRNAs play a crucial role in the control of gene expression. Dysregulation of miRNA expression results in grossly aberrant gene expression, leading to disease,[31–36] and altered miRNA expression has been associated with the progression of cancer.[37,38]

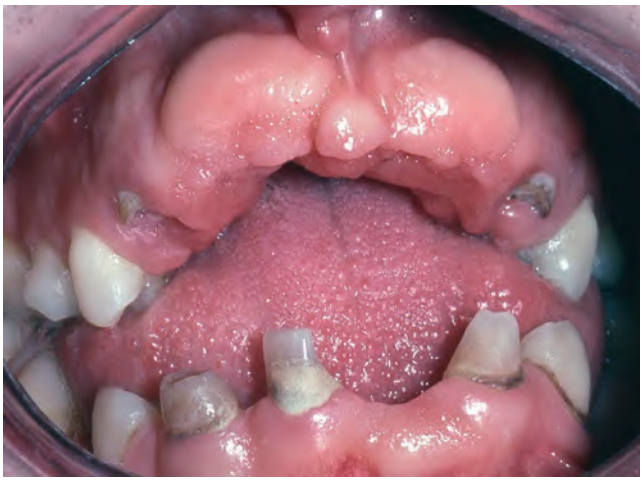

Figure 27-2 Clinical presentation of Axenfeld–Rieger syndrome (ARS). Mutations in PITX2 (pituitary homeobox transcription factor 2) and/or FOXC1 (forkhead box transcription factor C1) result in ARS, which represents a spectrum of diseases and disorders, including those of the dentition (i.e., extreme dental hypoplasia, as shown in this figure). *Source:* Courtesy of Dr. Carl Allen.

Epigenetic Control

Epigenetic mechanisms play an essential functional role in the regulation of transcription. Genetic control of gene expression depends on changes in DNA sequence. Epigenetic changes are heritable (from cell to daughter cell, or from parent to child) changes that do not depend on changes in genome sequence. Epigenetic controls are post-translational modifications of chromosomal proteins, such as methylation and acetylation, which regulate human conditions via gene–gene and gene–environment influences.

Pretranscriptional Regulation of Gene Expression DNA is wrapped around histone proteins forming chromatin (a highly organized and densely packaged structure). Chromatin remodeling enzymes alter the folding and basic structure of chromatin, making it more open. Euchromatin is an open structure accessible to transcription factors and therefore transcriptionally active. Histone acetylation is a dynamic epigenetic modification that regulates gene expression. This lysine modification is reversibly controlled by histone acetyltransferases, which add acetyl groups to lysine residues of histones, and deacetylases, which remove the acetyl groups from lysine residues. Addition of acetyl groups reduces histone binding to DNA, helping decondense the chromatin and promoting transcription.

DNA methylation is another epigenetic mechanism that plays an important role in gene regulation.[39] It is controlled by DNA methyl transferase enzymes (DNMTs) that add methyl groups to the DNA molecule. Methylation can change the activity of a gene and, when located in a gene promoter, it typically suppresses transcription of that gene.

Additionally, gene actions depend on interaction with the environment. Monozygotic (MZ) twins are genetically identical. However, as MZ twins develop and age they become phenotypically discordant, for example they differ in susceptibilities to diseases and even in anthropometric measurements. Epigenetic regulation can explain phenotypic discordance in MZ twins. Studies of a large cohort of MZ twins found that while they are epigenetically (DNA methylation and histone acetylation profiles) indistinguishable early in life, older MZ twins differ drastically in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, and therefore in their gene expression profiles.[40,41] Epigenetic control of gene expression provides an explanation for how different phenotypes (e.g., arthritis, osteoporosis, periodontal disease, fibromyalgia, Alzheimer's disease and other forms of dementia) can originate from the identical genotype.

TYPES OF DNA VARIATION

All genetic variation results from a process known as mutation, which is defined as a permanent change in the DNA sequence that can range in size from a single DNA base pair affecting a single gene to a large segment of a chromosome affecting many genes. The effects of gene mutations on health vary depending on where they occur and whether they alter the function of essential proteins. Mutations can be classified into hereditary and acquired (somatic) mutations.[42] Hereditary mutations are inherited from a parent and are present in every cell of the body throughout a person's life. Hereditary mutations are also called germline mutations because they are present in a parent's gametes (either egg or sperm) and therefore in each cell of an offspring that grows out of the fertilized egg.[42] Acquired (somatic) mutations occur at some point during a person's life and are present only in some cells. They can occur as a result of environmental exposures such as ultraviolet radiation from the sun, or as a result of an error made in DNA replication during cell division. Acquired mutations cannot be passed to the next generation.[42]

De novo (new) mutations can be either hereditary or somatic. De novo hereditary mutations arise when a mutation occurs in a person's egg or sperm cell but is not present in any of the other cells, or when a mutation occurs in the fertilized egg shortly after fertilization. The de novo hereditary mutations are present in every cell of a growing embryo. De novo hereditary mutations may explain genetic disorders in which an affected child has a mutation in every cell in the body but the parents do not, and there is no family history of the disorder.[42]

Mosaicism occurs when a somatic mutation occurs in a single cell early in embryonic development when the embryo includes several cells, but is not present in a parent's egg or sperm cells, or in the fertilized egg. As cells divide, the cell containing the mutation will give rise to altered cells, while other cells will not. Mosaicism may or may not cause health problems, depending on the type of mutation and the number of cells affected.[42]

Mutations are also classified based on their size, ranging from changes of a single base (point mutations or single nucleotide polymorphisms, abbreviated SNPs; Figure 27-3), to insertions and deletions of two or more bases up to a dozen or more bases, or copy number variations (CNVs) up to chromosomal rearrangements involving millions of DNA bases.

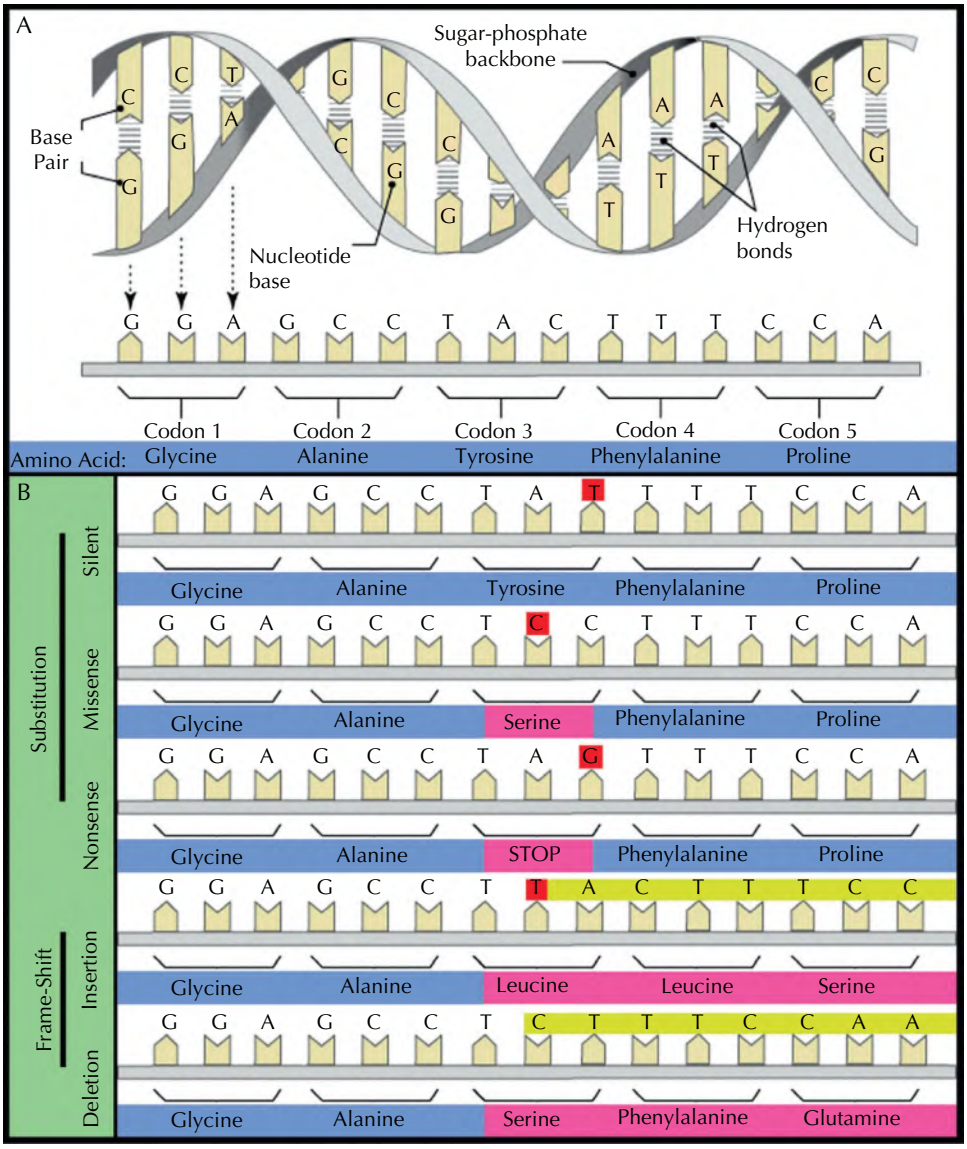

Figure 27-3 A. Molecular composition of DNA. DNA is composed of a phosphate–sugar backbone and four nitrogenous bases: adenine (A), cytosine (C), guanine (G), and thymine (T). Adenine always pairs with thymine and guanine always pairs with cytosine. The order of bases determines information encoded in a gene. Nucleotides are read in triplicates called codons and each codon codes for one amino acid (building blocks of proteins). B. Five major types of mutations. Silent mutations result in no change in the encoded amino acid sequence, as multiple codons can code for the same amino acid. In missense mutations, a single nucleotide change results in a change of encoded amino acid. Nonsense mutations occur when a single nucleotide change results in the formation of a stop codon (TAA, TAG, and TGA), leading to premature termination of translation and therefore a shortened protein product. Frame-shift mutations (insertions or deletions) shift a reading frame by shifting nucleotide positions in each triplet codon. They result in a change of the encoded amino acid sequences from the point of mutation. Mutated nucleotides are highlighted in yellow and affected amino acids are highlighted in pink.

Single Nucleotide Polymorphisms

SNPs are the most common type of genetic variation among humans. As the name implies, a SNP is a single base pair change in the DNA sequence at a particular location, for example a SNP may replace a cytosine (C) nucleotide for a thymine (T) nucleotide in a certain stretch of DNA. The frequency of SNPs is on average one in every 1000 nucleotides, resulting in approximately 4–5 million SNPs in a person's genome.[42] SNPs within a gene or its regulatory region may affect the function of the gene and thus have a more direct role in disease. Some SNPs may affect an individual's response to certain drugs, susceptibility to environmental factors, and risk of developing a particular disease. Most SNPs have no effect on health or development.[42] Depending on the effects of an SNP on the encoded amino acid, SNPs can be classified as synonymous (silent) or nonsynonymous. A synonymous SNP occurs when a single base pair change does not result in a change in the amino acid in the protein encoded by a gene. Nonsynonymous SNPs can be further classified as missense or nonsense. A missense SNP occurs when a change in one DNA base pair results in the substitution of one amino acid for another in the protein made by a gene. Examples of human conditions caused by missense mutations are hemoglobinopathies such as sickle cell anemia (typically caused by a single missense mutation resulting in a substitution of valine for glutamic acid at position 6 of the β-globin) and osteogenesis imperfecta. A nonsense SNP occurs when a change in one DNA base pair results in a stop codon prematurely signaling the cell to stop building a protein. This may result in a shortened protein that may function improperly or not at all.[43] SNPs can act as biologic markers, helping scientists locate genes associated with a disease. Genome-wide association studies (GWAS) have been used to scan markers (SNPs) across genomes of many people to find genetic variations associated with a particular disease (Figure 27-4). GWAS are particularly useful in finding genetic variations contributing to common, complex diseases, such as asthma,[44,45] cancer,[46] diabetes,[47] and heart disease.[48]

Insertions and Deletions

Insertion and deletion mutations result in a change of the number of DNA bases in a gene by either adding or removing a piece of DNA, respectively. These mutations can range in size from small (insertion or deletion of a single or a few base pairs) to large (entire gene insertion or deletion). Insertions and deletions are also known as frame-shift mutations, as they can affect the codon reading frame depending on the number of nucleotides inserted or deleted. Depending on the size and location, insertions and deletions can affect protein function.

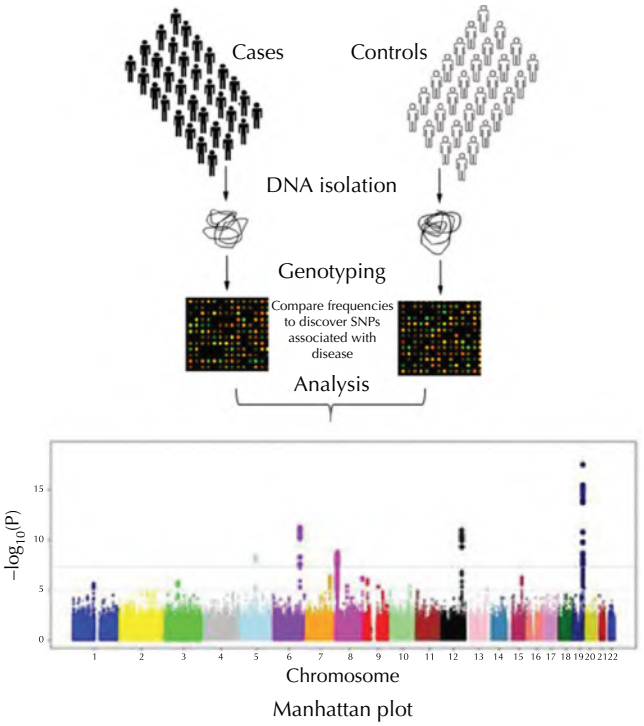

Figure 27-4 Genome-wide association study (GWAS). GWAS aim at comparing frequencies of a large number of SNPs between cohorts of age- and sex-matched cases and controls. For this reason, DNA is isolated from each individual and genotypes of SNPs are determined on microarrays and subjected to statistical analysis to determine if some alleles are significantly more frequent in either cases or controls. The results of GWAS are usually represented as a "Manhattan" plot (shown at the foot of the figure), where each dot represents an SNP, the horizontal axis indicating chromosomes and the vertical axis indicating the statistical significance of disease association. A P-value $<5 \times 10^{-8}$ (horizontal line) is generally considered as being statistically significant at the genome-wide level.

Copy Number Variations

CNVs are a type of genetic variation characterized by a variable number of copies of gene(s). The human genome has two copies of most genes (one copy from each parent). In some cases the number of copies vary, and one, three, or more copies of a gene are present. CNVs account for a significant amount of genetic differences between individuals. Much of the variation due to CNV does not affect health and development, but some variations may affect a person's risk of developing a disease or response to certain drugs. Examples of disorders caused by CNVs include Williams–Beuren syndrome (an autosomal dominant condition caused by deletion of the 7q11.23 locus), Gaucher disease (an autosomal recessive condition caused by deletion of the *NPHP1* gene), and intellectual disability (an X-linked condition

caused by duplication of the *HUWE1* gene). CNVs in the *CYP2D6* gene can affect the response to about 30 drugs, including opioids, tamoxifen, and antipsychotics.[49]

Chromosomal Rearrangements

Chromosomal mutations can range from changes in chromosomal structure when fragments of chromosomes get rearranged, missing, or duplicated to changes in chromosome numbers (aneuploidy). Chromosomal rearrangements include translocations, duplications, deletions, and inversions. Translocations occur when a fragment of one chromosome breaks off and attaches to another chromosome. Translocations can be balanced (no genetic material is gained or lost in a cell) or unbalanced (there is a gain or loss of genetic material in a cell). Duplications occur when a part of a chromosome is copied too many times, resulting in extra copies of genetic material from the duplicated segment. Chromosomal deletions result in loss of genetic material anywhere along the chromosome. Aneuploidy refers to a gain or loss of chromosomes from the normal 46.

Changes in chromosome structure or the number of chromosomes lead to problems with the growth, development, and function of the body's system. Examples of conditions caused by changes in chromosome number include Down syndrome (trisomy 21), which results from the presence of an extra copy of chromosome 21, and Turner syndrome (monosomy of the X chromosome), which is caused by a deletion of one of the X chromosomes in a female. Conditions caused by chromosomal rearrangement include William syndrome, which is caused by a deletion of a region on chromosome 7 (7q11.23, the Williams–Beuren syndrome critical region) containing the elastin gene, and Potocki–Lupski syndrome, caused by duplication of a region on chromosome 17 (17p11.2).

GENETIC DISEASES AND DISORDERS

Most diseases have a genetic component and it is believed that genes play a role in over 10,000 human diseases.[50,51] It is estimated that approximately 1 in 10 people in the United States—almost 30 million people—has a rare disease, equivalent to the number of people who have diabetes. Although individually rare on a population level, over 5000 single-gene disorders (called Mendelian disorders because they follow predictable inheritance patterns) have been identified.[51] Thousands of these disorders have some phenotypic effect on the oral cavity/craniofacial complex and are therefore seen by dentists. For many of these conditions, (e.g., most forms of amelogenesis imperfecta and isolated cleft palate), the major clinical findings are seen in the oral cavity. For others (e.g., syndromic forms of dentinogenesis imperfecta and syndromic forms of orofacial clefting), the condition may manifest dental as well as significant extraoral findings (e.g., vascular, bone, kidney), meaning these conditions are best managed by an interdisciplinary healthcare team. For some of these conditions the dental findings are the most apparent, and the dentist may be the first to recognize that a genetic condition exists in an individual and/or family.[52] Dentists may be the first healthcare provider to detect certain genetic disorders due to their seeing patients across critical times of growth and development.[53] Thus, it is important for dental health professionals to have an understanding of basic genetic concepts.[54]

As our understanding of the genetic basis of diseases improves, the amount of clinically relevant genetic information increases. Web-based databases that continually catalog and update this information are important resources that allow clinicians to rapidly scan the available information and identify resources to help manage patients (Table 27-1). Online Mendelian Inheritance in Man (OMIM) is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and can help develop differential diagnoses.[51] This database offers overviews of information on all known Mendelian disorders and over 15,000 genes. It focuses on the relationship between phenotype and genotype and is updated daily. Clinicians can use the database to enter clinical findings and help check and develop a differential diagnosis for genetic conditions of interest. Table 27-2 lists information from the OMIM database for many of the conditions discussed in this section.

Like all healthcare providers, dentists are facing an increase in the application of genetic knowledge in clinical practice. The ability to take a family history to construct a three-generation pedigree can be important to make a correct diagnosis for both dental and nondental conditions. Disorders of the teeth and periodontium can be inherited. Seemingly isolated dental defects may have extraoral health consequences. Making a correct diagnosis is crucial for a discussion of phenotypic consequences, management, and genetic counseling for recurrence risks. Recurrence is the risk of having a second child in a later pregnancy affected by the same disease or health condition. Sometimes clinical evaluation is enough to establish a diagnosis, but at other times genetic testing is needed.

The decrease in cost to sequence DNA has resulted in increased sequencing of the exome (focusing on the 2% of the genome that codes for proteins) and genome (the entire 3 billion base pairs of DNA). Such sequencing has revealed pathogenic variants underlying conditions such as amelogenesis imperfecta,[55] tooth agenesis,[56] latent transforming growth factor–beta-binding protein 3 (*LTBP3*)-related disorders,[57]

Table 27-1 Genetic resources.

Resource	URL	Use
Online Mendelian Inheritance in Man (OMIM)	www.omim.org	Type in phenotypic features for a list of disorders that include those features
GeneReviews	http://www.ncbi.nlm.nih.gov/books/NBK1116	Provides overviews of many genetic disorders, including diagnosis, management, and recurrence risks
Genetic Alliance	www.geneticalliance.org	Network of disease-specific advocacy organizations, universities, private companies, government agencies, and public policy organizations
Genetic and Rare Disease Information Center (GARD)	https://rarediseases.info.nih.gov	Provides information on specific genetic disorders to the public, including healthcare professionals, patients, and families
National Organization of Rare Diseases	https://rarediseases.org	Patient advocacy organization focused on individuals with rare diseases and the organizations and clinicians that serve them
American College of Medical Genetics and Genomics	www.acmg.net	Locate a geneticist
Orphanet	http://www.orpha.net/consor/cgi-bin/index.php	
National Society of Genetic Counselors	www.nsgc.org	Locate a genetic counselor
Genetic Counsellor Registration Board	www.gcrb.org.uk	
Australasian Society of Genetic Counsellors	http://www.hgsa.org.au/asgc	
Genetic Testing Registry	http://www.ncbi.nlm.nih.gov/gtr	Locate a testing facility
EuroGentest	http://www.eurogentest.org/index.php?id=160	
Orphanet	www.orpha.net	
Clinical Trials	https://clinicaltrials.gov/	Locate a clinical trial worldwide

and genes not previously known to be involved in tooth development. *LTBP3* pathogenic variants are associated with amelogenesis imperfecta, short stature, and predisposition to thoracic aortic aneurysms and dissections.[58] Thus, the association of amelogenesis imperfecta and short stature should prompt consideration of referral for cardiac evaluation. Other dental phenotypes may also prompt referral for evaluation. For example, oligodontia can be associated with colon cancer.[59] The finding of amelogenesis imperfecta and gingival hyperplasia in an individual may suggest referral for renal imaging.[60] Knowledge of the underlying genetic defect can be important in developing treatment plans, such as dental treatment for amelogenesis imperfecta (https://www.dentistry.unc.edu/dentalprofessionals/resources/defects/ai).

As shown in Figure 27-3, a variety of DNA nucleotide sequence changes can occur. With the availability of inexpensive DNA sequencing, many thousands of human genomes have been sequenced, revealing hundreds of thousands of DNA sequence variants. The challenge is to determine which of these are important and have a biologic or phenotypic consequence when present. When a sequence change is identified, it must be evaluated to determine whether the change, or variant, produces a phenotype and is therefore pathogenic. Guidelines have been published to aid

Table 27-2 Examples of dental-craniofacial genetic conditions from the Online Mendelian Inheritance in Man (OMIM) database. Information includes syndrome name, associated OMIM syndrome number, mode of inheritance, and tooth/oral findings. The name of each specific gene(s) involved in the etiology, gene symbol, chromosomal location, and OMIM gene number are included.

Type	Syndrome	OMIM Number for Syndrome	Inheritance	Overview of Craniofacial-Oral-Dental Features	Gene Name	Gene Symbol	Chromosomal Location	OMIM Number for Gene
Mendelian								
Tooth-Dentin								
Dentinogenesis Imperfecta Col1A1 Related								
	Osteogenesis Imperfecta, type 1	166200	AD	Variable tooth findings, teeth may be normal or dentinogenesis imperfecta. Hearing loss, blue sclera (eyes), cardiovascular: mitral valve prolapse. Mild osteopenia, varying degree bone fractures. Thin skin, easily bruise.	Collagen, Type 1, Alpha-1 Chain	*COL1A1*	17q21-.33	120150
	Osteogenesis Imperfecta, type II	166210	AD	Beaked nose, blue sclera, wormian bones, soft calvaria, absent calvarial mineralization, large fontenelles. Short limb dwarfism.	Collagen, Type 1, Alpha-1 Chain	*COL1A1*	17q21-.33	120150
	Osteogenesis Imperfecta, type III	259420	AD	Dentinogenesis imperfecta (both primary and secondary dentition). Triangular face, frontal bossing, micrognathia. Multiple bone fractures. Short limb dwarfism.	Collagen, Type 1, Alpha-1 Chain	*COL1A1*	17q21-.33	120150
	Osteogenesis Imperfecta, type IV	166220	AD	Dentinogenesis imperfecta. Wormian bones (skull). Ears: hearing loss, otosclerosis.	Collagen, Type 1, Alpha-1 Chain	*COL1A1*	17q21-.33	120150
Dentinogenesis Imperfecta *DSPP* Related	Dentinogenesis Imperfecta, type II	125490	AD	Dentinogenesis imperfecta, brown-blue opalescent teeth, bulbous-shaped crown, absent pulp chambers, narrow roots, root canals small or obliterated. Primary and secondary teeth affected.	Dentin Sialop hosphoprotein	*DSPP*	4q22.1	125485
	Dentinogenesis Imperfecta, type III	125500	AD	Dentinogenesis imperfecta, brown- opalescent teeth, severe attrition both dentitions, enamel pitting secondary teeth, normal to enlarged pulp chamber primary teeth, obliterated pulp chamber secondary teeth, periapical radiolucencies, shell teeth, bulbous-shaped crowns.	Dentin Sialop hosphoprotein	*DSPP*	4q22.1	125485
Dentin Dysplasia *DSPP* Related	Dentin Dysplasia, type II	125420	AD	Dentin dysplasia, amber, translucent primary teeth, pulp chamber obliteration primary teeth, normal root shape primary teeth, normal tooth color secondary teeth, thistle-shaped pulp chamber secondary teeth, multiple pulp stones secondary teeth, normal root shape secondary teeth.	Dentin Sialop hosphoprotein	*DSPP*	4q22.1	125485
Dentin Dysplasia Not *DSPP* Related								
	Dentin Dysplasia Type 1	125400	AR	Absent to short roots, radicular abscesses, absent pulp chambers primary teeth, crescent/chevron-shaped pulp chambers secondary teeth, absent root canals.	Sparc-Related Modular Calcium-Binding Protein-2	*SMOC2*	6q27	607223

	Dentin Dysplasia Type 1	125400	AD	Absent to short roots, radicular abscesses, absent pulp chambers primary teeth, crescent/chevron-shaped pulp chambers secondary teeth, absent root canals.	C. Elegans Homolog F	*SSUH2*	3p25.3	617479
	Dentin Dysplasia Type 1	125400	AD	Absent to short roots, radicular abscesses, absent pulp chambers primary teeth, crescent/chevron-shaped pulp chambers secondary teeth, absent root canals.	Vacuolar Protein Sorting 4 Homolog B	*VPS4B*	18q21.33	609983
Tooth Enamel								
Amelogenesis Imperfecta Related	Amelogenesis Imperfecta 1E, AI1E	300391	XLD	Amelogenesis imperfecta, hypomineralized enamel, soft enamel, thin enamel, pitted enamel, vertical ridges on enamel, anterior open bite, "snow-capped" appearance of teeth.	Amelogenin	*AMELX*		301200
	Amelogenesis Imperfecta, Type 1A	104530	AD	Amelogenesis imperfecta, hypoplastic. Thin enamel. Pitted enamel. Grooved enamel. Tooth sensitivity. Taurodontism reported 1 case.	Laminin, Beta-3	*LAMB3*	1q32.2	150310
	Amelogenesis Imperfecta, Type 1H	616221	AR	Amelogenesis imperfecta. Thin enamel. Hypomineralized enamel. Rough tooth surface. Pitted enamel. Discolored teeth, yellow-brown. Normal enamel-dentin contrast reported on radiograph. Tooth sensitivity. Anterior open-bite and class III malocclusion reported.	Integrin, Beta-6	*ITGB6*	2q24.2	147558
	Amelogenesis Imperfecta, Type IIIB	617607	AD	Amelogenesis imperfecta. Reduced enamel mineral density (radiograph).	Amelotin	*AMTN*	4q13.3	610912
	Amelogenesis Imperfecta, Type 1F	616270	AR	Amelogenesis imperfecta hypoplastic. Pitted enamel, discolored teeth.	Ameloblastin Enamel Matrix Protein	*AMBN*	4q13.3	601259
	Amelogenesis Imperfecta, Type 1C	204650	AR	Amelogenesis imperfecta. Decreased enamel mineralization. Yellow-brown discoloration of teeth. Anterior open-bite malocclusion. Retrognathic mandible.	Enamelin	*ENAM*	4q13.3	606585
	Amelogenesis Imperfecta, Type 1B	104500	AD	Amelogenesis imperfecta, hypoplastic. Enamel has horizontal rows of pits or linear depressions. Incisal edge or occlusal surface usually not involved.	Enamelin	*ENAM*	4q13.3	606585
	Amelogenesis Imperfecta, Type IIA4	614832	AR	Amelogenesis imperfecta. Yellow-brown enamel. Enamel hypoplasia. Decreased enamel volume. Hypomineralized enamel with reduced contrast between enamel and dentin radiographically.	Odontogenesis-Associated Phosphoprotein	*ODAPH*	4q21.1	614829
	Amelogenesis Imperfecta, Type IIIA	130900	AD	Amelogenesis imperfecta hypocalcified. Enamel thickness is normal. Enamel is soft and lost from tooth surface soon after eruption. Anterior open bite (60% of cases). Class III malocclusion.	Family with Sequence Similarity 83, Member H	*FAM83H*	8q24.3	611927

(*Continued*)

Table 27-2 (Continued)

Type	Syndrome	OMIM Number for Syndrome	Inheritance	Overview of Craniofacial-Oral-Dental Features	Gene Name	Gene Symbol	Chromosomal Location	OMIM Number for Gene
	Amelogenesis Imperfecta, Type IIIC	618386	AR	Amelogenesis imperfecta. Rough enamel surface. Yellow-brown enamel. Hypocalcified enamel. Loss of enamel on occlusal surface. Anterior open bite reported.	Receptor Expressed in Lymphoid Tissues	*RELT*	11q13.4	611211
	Amelogenesis Imperfecta, Type IIA	612529	AR	Amelogenesis imperfecta. Yellow-brown enamel, thin enamel with rough surface. Increased sensitivity to thermal stimuli. Decreased radiopacity of enamel. Anterior open bite.	Matrix Metallo proteinase 20	*MMP20*	11q22.2	604629
	Amelogenesis Imperfecta, Type IIA6	617217	AR	Amelogenesis imperfecta. Opaque enamel (both primary and secondary dentition). Yellow-brown enamel discoloration. Hypomineralized enamel with localized surface roughness. Enamel fractures, decreased contrast between enamel and dentin on radiograph.	G Protein-Coupled Receptor 68	*GPR68*	14q32.11	601404
	Amelogenesis Imperfecta, Type IIA5	615887	AR	Amelogenesis imperfecta, soft enamel, discolored (yellow-brown) enamel, normal enamel volume, premature loss of enamel, decreased enamel radiodensity. Little contrast between enamel and dentin on radiograph.	Solute Carrier Family 24 (Sodium/ Potassium/Calcium Exchanger) Member 4	*SLC24A4*	14q32.12	609840
	Amelogenesis Imperfecta, Type IIA3	613211	AR	Amelogenesis imperfecta, opaque enamel color, chipping of enamel post eruption, rough enamel, discolored enamel, decreased enamel radiodensity. Sensitive teeth (thermal and physical stimuli).	WD Repeat-Containing Protein 72	*WDR72*	15q21.3	613214
	Amelogenesis Imperfecta, Type IG	204690	AR	Amelogenesis imperfecta, hypoplastic. Yellow-brown teeth, delayed permanent dentition, coronal and radicular pulpal calcifications. Gingival overgrowth, Nephrocalcinosis.	Family with Sequence Similarity 20, Member A Sequence Similarity	*FAM20A*	17q24.2	611062
	Amelogenesis Imperfecta, Type IJ	617297	AR	Amelogenesis imperfecta. Thin enamel, enamel discoloration, tooth sensitivity to thermal stimuli, overbite. Interdental spacing. Dental caries.	Acid Phosphatase 4	*ACP4*	19q13.33	606362
	Amelogenesis Imperfecta, Type IIAI	204700	AR	Amelogenesis imperfecta. Yellow-brown discolored teeth, normal size and shape teeth, enamel thickness normal, teeth sensitive to hot and cold, enamel prone to chipping, caries. Enamel slightly more opaque than dentin on radiograph. Anterior open bite.	Kallikrein-Related Peptidase 4	*KLK4*	19q13.41	603767
	Amelogenesis Imperfecta, Type 1E	301200	XLD	Amelogenesis imperfecta, hypomineralized enamel, thin enamel, pitted enamel, wide-spaced teeth, discolored teeth, rough tooth surface, vertical ridges on enamel, normal dentin, anterior open bite, "snow-capped" teeth.	Amelogenin	*AMELX*	Xp22.2	300391

Other Enamel/Dentin Disorders								
	Trichodento Osseous Syndrome (TDO)	190320	AD	Thin enamel, small widely spaced teeth, taurodontism (reduced dentin). Dolicephaly, frontal bossing. Increased bone density (skull, spine, long bones). Skull decreased mastoid pneumatization, obliteration of calvarial diploe. Kinky hair (50%) straightens after childhood.	Distal-less Homeobox 3	*DLX3*	17q21.33	600525
X-Linked Conditions								
	Incontinentia Pigmenti	308300	XLD	Hypodontia, delayed eruption, conical teeth, accessory cusps. Head: microcephaly; Eyes: microphthalmos, cataracts, strabismus. Hair: thin, sparse, coarse (childhood).	Inhibitor of Kappa Light Polypeptide Gene Enhancer In B Cells, Kinase of Gamma	*IKBKG*	Xq28	300248
	Hypop hosphatemic Rickets	307800	XLD	Hypomineralized enamel, enlarged pulp chambers, recurrent dental abscesses, premature tooth loss. Frontal bossing.	Phosphate-Regulating Endopeptidase Homolog, X Linked	*PHEX*	Xp22.11	300550
	Duchenne Muscular Dystrophy	310200	XLR	Red-green color defect in many patients with deletion downstream of exon 30.	Dystrophin	*DMD*	Xp21.2-p21.1	300337
	Amelogenesis Imperfecta, Type 1E	301200	XLD	Amelogenesis imperfecta, hypomineralized enamel, thin enamel, pitted enamel, wide-spaced teeth, discolored teeth, rough tooth surface, vertical ridges on enamel, normal dentin, anterior open bite, "snow-capped" teeth.	Amelogenin	*AMELX*	Xp22.2	300391
Gingiva								
	Gingival Fibromatosis	135300	AD	Gingival fibromatosis (slowly progressive enlargement of gingiva).	SOS Ras/Rac Guanine Nucleotide Exchange Factor 1; Son of Sevenless-1	*SOS1*	2p22.1	182530
	Noonan Syndrome Type 4	610733	AD	Macrocephaly, low-set posteriorly rotated ears, downslanting palpebral fissures, hypertelorism, flat nasal bridge, short neck, webbed neck. Cardiovascular: congenital heart defect, ventricular septal defects, cardiomyopathy. Short stature.	SOS Ras/Rac Guanine Nucleotide Exchange Factor 1; Son of Sevenless-1	*SOS1*	2p22.1	182530
Periodontitis	Papillon–Lefèvre Syndrome	245000	AR	Severe, early-onset periodontitis, premature tooth loss (both primary and secondary dentition), atrophy alveolar ridge. Extraoral: palmar planter hyperkeratosis.	Cathepsin C	*CTSC*	11q14.2	602365
Chromosomal Disorder								
Contiguous Gene Deletion (3 Genes Deleted)	Wolf–Hirschhorn Syndrome	194190	IC	Hypodontia, retained primary molars, cleft lip, cleft palate, downturned corners mouth. Head: microcephaly, cranial asymmetry, micrognathia, short philtrum, high forehead, prominent glabella. Beaked nose, wide nasal bridge. Hypertelorism.	Contiguous gene deletion: syndrome due to deletion of 3 genes: *NSD2*; *LETM1*; *MSX1*		4p16.2-4p16.3	

(*Continued*)

Table 27-2 (Continued)

Type	Syndrome	OMIM Number for Syndrome	Inheritance	Overview of Craniofacial-Oral-Dental Features	Gene Name	Gene Symbol	Chromosomal Location	OMIM Number for Gene
					Nuclear Receptor-Binding Set Domain Protein 2	*NSD2*	4p16.3	602952
					Leucine Zipper/EF-Hand-Containing Transmembrane Protein 1	*LETM1*	4p16.3	604407
					MSH Homeobox 1	*MSX1*	4p16.2	142983
Imprinting Disorders								
Multiple Genes Involved (2 Genes)	Prader–Willi Syndrome	176270	AD	Thick, viscous saliva. Thin upper lip, small mouth. Eyes: almond-shaped eyes. Hypotonia with poor sucking in in fancy, global developmental delay, hyperphagia.	Necdin	*NDN*	15q11.2	602117
					Small Nuclear Ribonucleoprotein Polypeptide N	*SNRPN*	15q11.2	182279
	Angelman Syndrome	105830	AD	Widely spaced teeth. Protruding tongue, macrostomia, excessive drooling. Face: prognathia, microcephaly, brachycephaly, flat occiput, occipital groove. Strabismus. Excessive chewing. Happy demeanor.	Ubiquitin-Protein Ligase E3A	*UBE3A*	15q11.2	601623
Multiple Genes Involved (4 Genes)	Beckwith–Wiedemann Syndrome	130650	AD	Macroglossia. Coarse facial features, midface hypoplasia. Metopic ridge, large fontanel, prominent occiput. Prominent eyes. Linear ear lobe creases, posterior helical indentations.	Multiple genes (listed below) in imprinted area: *H19*; *ICR1*; *KCNQ10T1*; *CDKN1C*		11p15.5-11p15.4	
					H19, Imprinted Maternally Expressed Noncoding Transcript 19	*H19*	11p15.5	103280
					H19/IGF2-Imprinting Control Region	*ICR1*	11p15.5	616186
					KCNQ1-Overlapping Transcript 1	*KCNQ1OT1*	11p15.5	604115
					Cyclin-Dependent Kinase Inhibitor 1C	*CDKN1C*	11p15.4	600856

AD, autosomal dominant; AR, autosomal recessive; ; IC, isolated cases; XLD, X-linked dominant; XLR, X-linked recessive.
Source: HUGO Gene Nomenclature Committee Approved Gene Nomenclature. HGNC Database, February 2020. https://www.genenames.org.

in the interpretation of sequence variants.[61] A five-scale classification system is used: pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign. The term mutation and polymorphism are no longer used in order to be clearer regarding the functional consequence of identified variants. In general, the term pathogenic variant is now used instead of the term mutation. As more individuals have their genomes sequenced, variants may be reclassified. A recent study found that approximately 25% of variants of uncertain significance have been reclassified over time, including upgrades and downgrades.[62]

Mendelian Diseases and Disorders

Human disorders can be inherited in a variety of ways. Genetic disorders are broadly characterized into three categories: Mendelian, chromosomal, and multifactorial or complex. Mendelian disorders follow predictable inheritance patterns and are typically rare on a population basis. Chromosomal disorders may be sporadic or inherited and involve numeric (addition or deletion of whole chromosomes) or structural aberrations (addition, deletion, or rearrangement of less than a whole chromosome). Finally, multiple genes and/or environmental factors play a role in phenotypes such as many common forms of oral clefting, periodontitis, diabetes, hypertension, and so on. These are known as multifactorial or complex traits. Many genes may be involved in the etiology of complex traits, with the contributions of most genes being relatively small, and individually not sufficient to cause disease.

Modes of Inheritance

Mendelian disorders are those that follow predictable inheritance patterns and are due to pathogenic variants in single genes. Disorders can be inherited as autosomal (gene is located on a non-sex chromosome) or sex-linked (gene is on the X or Y chromosome) traits. Dominant or recessive refers to the number of pathogenic variants needed to express the phenotype: one for dominant and two for recessive.

In autosomal dominant disorders, both males and females are affected. Male-to-male transmission can occur. Often there are affected individuals in each generation (known as vertical transmission). Examples of autosomal dominant disorders include achondroplasia, the most common form of short-limbed dwarfism, and amelogenesis imperfecta, a disorder that affects the quality and/or quantity of tooth enamel. An individual with an autosomal dominant disorder has a 50% risk of passing on the pathogenic variant to their offspring. While many individuals with a dominant disorder will have inherited a pathogenic variant from an affected parent, others will have the disorder due to a new mutation, also called a de novo mutation. In this case, the affected person has a 50% chance of passing on the pathogenic variant to their children, but their parents are not likely to have another affected child. Approximately 80% of individuals with achondroplasia have a de novo mutation.[63] Some autosomal disorders exhibit reduced penetrance and/or variable expressivity. Reduced penetrance means that some individuals with a pathogenic variant will not express the phenotype. In a condition with 80% penetrance, it means that 20% of individuals who have a pathogenic variant will not express the phenotype. Variable expressivity means that individuals who have a pathogenic variant may be mildly or severely affected, even within the same family. Van der Woude syndrome (VWS) involves congenital, usually bilateral, lip pits and cleft lip with or without cleft palate and is caused by pathogenic variants in *IRF6*. Penetrance has been estimated at 92% and variable expressivity is observed.[64] Mixed clefting—an unusual occurrence in which one family member has isolated cleft palate and another family member has cleft lip with or without cleft palate—occurs in VWS. Tricho dento osseous syndrome (TDO) is an autosomal dominant condition that derives its name from the three primarily affected tissues: hair, teeth, and bone. Due to the pleiotropic effects of *DLX3* mutation, development of enamel, dentin, and bone is affected. Detailed clinical characterization of individuals with TDO (confirmed *DLX3* gene mutation) from multiple families shows marked variability in the hair, tooth, and bone phenotype (Figure 27-5). In some individuals the enamel is very thin, and teeth are smaller and appear widely spaced. Some affected individuals have significant taurodontism, with large, elongated pulp chambers. Bones of the skull and long bones show increased thickness and density with age, which is evident radiographically. Affected individuals have distinct curly hair that straightens in later childhood in almost 50% of cases. Dentin defects can also be inherited as autosomal dominant traits, either as isolated or syndromic forms. Pathogenic variants in *DSPP* underlie isolated forms of dentinogenesis imperfecta and dentin dysplasia type II (Figure 27-6). It is now thought that these disorders represent a continuum, with dentin dysplasia type II on the mild end and dentinogenesis type III on the severe end. Variable expressivity is also observed. Reduced penetrance and variable expressivity can make genetic counseling challenging.

In autosomal recessive inheritance, typically each parent is a carrier of a recessive allele and does not show any phenotype. When a child inherits the recessive allele from each parent, the child will express the phenotype. Both males and females are affected. Often only a single generation may be affected (known as horizontal transmission). Consanguinity (reproduction between close relatives descended from a common ancestor) increases the possibility of an individual inheriting the same recessive allele from each parent. The higher the degree of relationship between the parents, the

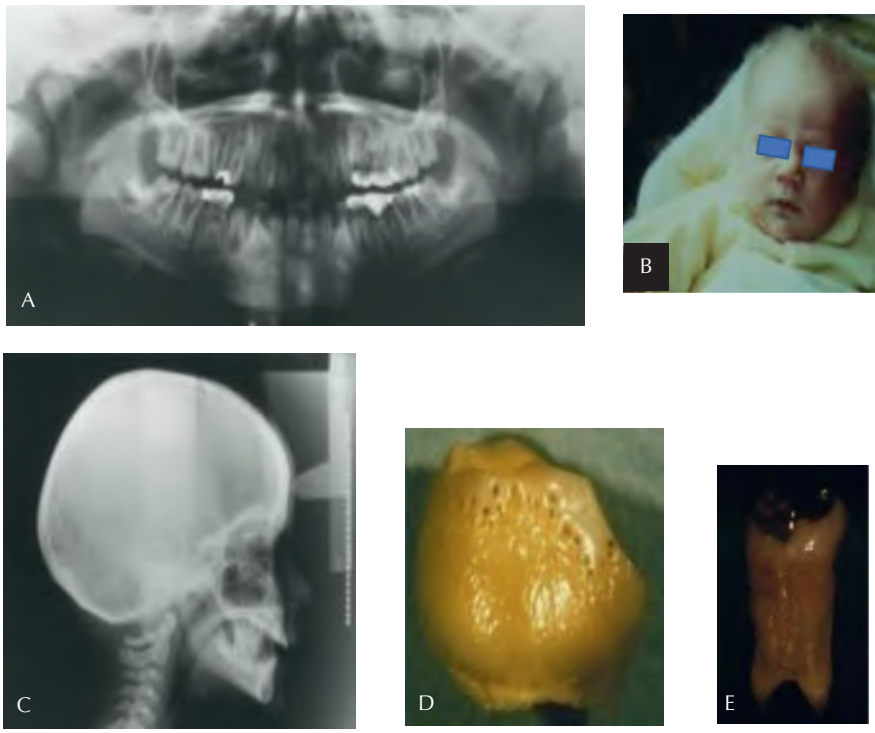

Figure 27-5 Tricho dento osseous syndrome. A. Panogramic radiograph illustrating taurodontism of posterior teeth and decreased enamel radiodensity. B. Distinctive curly hair. C. Increased density of skull and obliteration of calvaria diploe. D. Thin pitted enamel in primary molar. E. Taurodontism with elongated pulp chamber and short roots in secondary tooth.

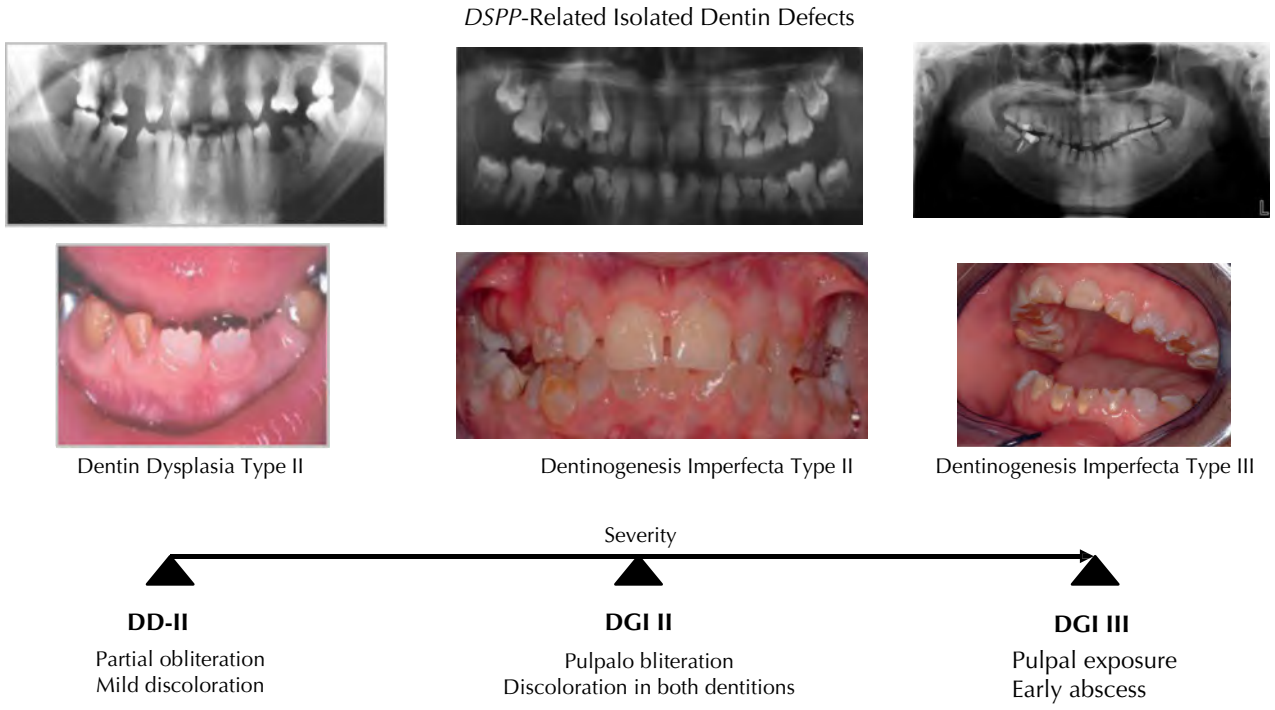

Figure 27-6 *DSPP*-related dentin disorders. Pathogenic variants in *DSPP* can result in dentin dysplasia type II, dentinogenesis imperfecta type II, and dentinogenesis imperfecta type III. All are inherited as autosomal dominant disorders. It is now felt that these conditions represent a continuum of severity, from dentin dysplasia type II on the mild end to dentinogenesis imperfecta type III on the severe end.

higher the risk for each parent to be a carrier. Examples of autosomal recessive traits include cystic fibrosis, sickle cell anemia, amelogenesis imperfecta, and Papillon–Lefèvre syndrome. Offspring of a couple where both are carriers for the same autosomal recessive disorder have a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of the wild type (not affected nor a carrier). If an affected individual has two copies of the same pathogenic variant, the individual is said to be homozygous. If an affected individual inherited a different pathogenic variant from each parent, the individual is said to be compound heterozygous. Only very rarely are children affected by a recessive disorder when only one parent is a carrier. In this case, both copies of the chromosome have been inherited from the carrier parent and none from the other parent, a condition known as uniparental disomy. In this situation, recurrence risk is very low. Papillon–Lefèvre syndrome is a recessive condition caused by pathogenic variants of the *CTSC* gene that encodes for the cathepsin C enzyme. These pathogenic variants cause loss of function of the cysteine protease, necessary to activate serine proteases, which function in the inflammatory response. Carriers with only one *CTSC* mutation generally have about half the normal activity of cathepsin C and experience no clinical problems. Individuals who inherit pathogenic variants in both copies of this gene have no cathepsin C enzyme activity (additive inheritance of enzyme activity, since one mutation reduces the activity by half). However, such homozygous genotypes develop early-onset aggressive periodontitis with significant oral bone loss and premature loss of primary teeth (recessive inheritance of the clinical condition or disease). After exfoliation of primary teeth, the periodontium heals and can appear healthy. Eruption of secondary teeth is typically associated with inflammation and progressive destruction of the periodontium with premature loss of the secondary dentition, although third molars are sometimes spared (Figure 27-7).

In X-linked conditions, the causative gene is on the X chromosome. Most X-linked disorders are inherited as X-linked recessive traits, but a few are inherited as X-linked dominant traits. Females have two X chromosomes and therefore can be homozygous, heterozygous, or compound heterozygous. Because males have a single X chromosome, they are hemizygous with respect to X-linked traits. The presence of male-to-male transmission excludes X-linked inheritance.

An example of an X-linked dominant condition is incontinentia pigmenti (IP), which is characterized by skin lesions, hypodontia and malformed teeth, alopecia, and dystrophic nails.[65] The phenotype is due to loss of function variants in *IKBKG*. Affected males are not observed due to male lethality. About 65% of affected females have IP as a result of a de novo pathogenic variant. Daughters of an affected heterozygous female have a 50% chance of inheriting the pathogenic variant and being affected. Among liveborn children of a woman with IP, the expected ratio is 1/3 unaffected females,

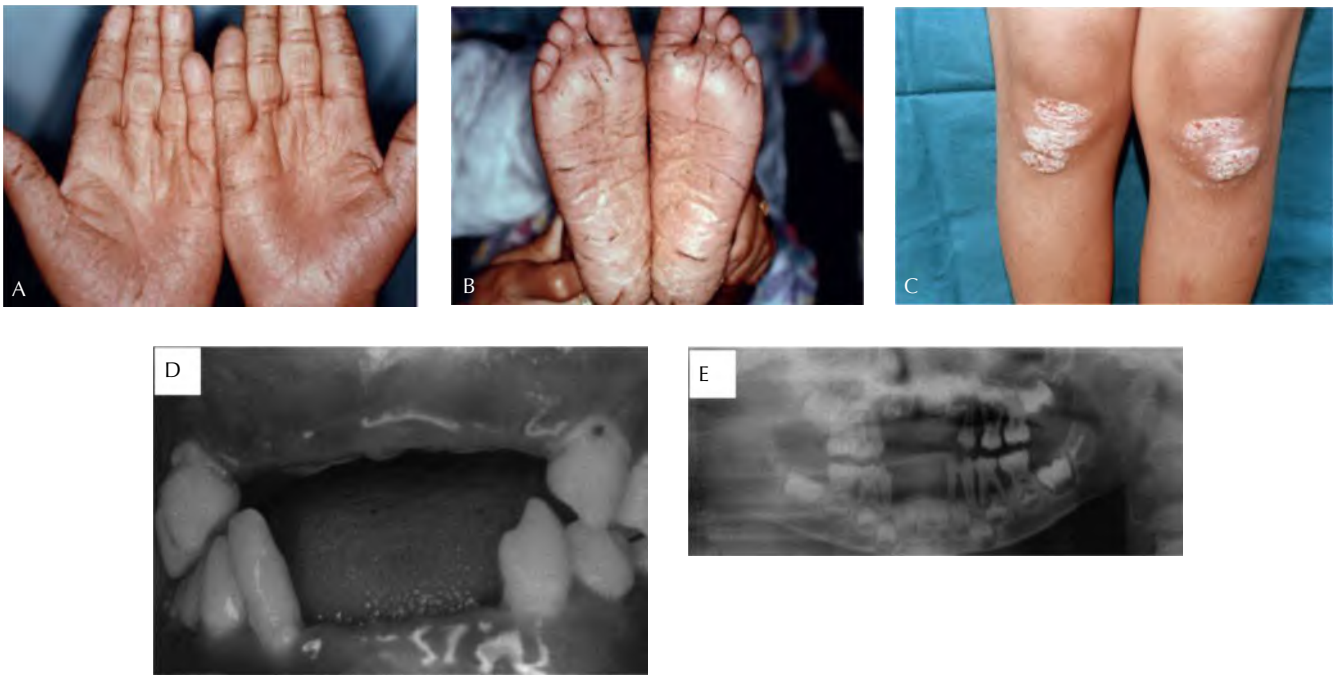

Figure 27-7 Clinical and radiographic findings of an individual with Papillon–Lefèvre syndrome. A. Hyperkeratosis of the palms (mild). B. Hyperkeratosis and fissures on the soles. C. Hyperkeratosis of transgressions on knees. D. Premature loss of teeth due to periodontitis. E. Severe bone loss around primary molars.

1/3 affected females, and 1/3 unaffected males. An X-linked dominant condition that dentists may be consulted on is hypophosphatemic rickets due to a mutation in the *PHEX* gene. Affected individuals have low blood levels of phosphate. Phosphate is necessary for proper mineralization of bones and teeth. In addition to short stature and growth retardation, affected individuals have defective enamel and dentin mineralization, resulting in recurrent abscesses, endodontic problems, and premature tooth loss.[66]

Examples of X-linked recessive conditions are hemophilia and Duchenne muscular dystrophy (DMD). For X-linked recessive traits, the incidence of the trait is much higher in males than in females. Heterozygous females are usually unaffected. For some conditions, a significant number of isolated cases are due to new mutations. A woman who is a carrier of an X-linked trait has a 50% chance of transmitting it to each of her offspring. Each of her sons will be affected if they inherit the pathogenic variant because males are hemizygous (they only have one X chromosome). The phenotype of daughters who inherit the pathogenic variant depends upon X inactivation, also called lyonization. Because females have two X chromosomes, they inactivate most genes on one X chromosome, so that gene dosage is fairly comparable between males and females. This process is typically random, occurs early in embryonic development, and, once established, all descendants of that cell have the same X chromosome inactivated. Sometimes there is skewing of X inactivation, with one X chromosome preferentially inactivated. Females can be affected with X-linked recessive traits through a variety of mechanisms, with skewed X inactivation typically the most common.[67] Other causes include uniparental disomy from an affected father or carrier mother, consanguinity, assortative mating between a carrier female and an affected male, and hemizygosity (the affected female also has Turner syndrome).

Lyonization can be apparent in females with pathogenic variants in *AMELX*, the gene that encodes amelogenin, the predominant protein in enamel. These females are carriers of a wild-type allele that produces healthy enamel crystals and an allele with a pathogenic variant that causes faulty enamel development, resulting in amelogenesis imperfecta. Affected females often exhibit vertical banding of their enamel: alternating columns of normal and defective enamel (Figure 27-8). In the column of normal enamel, the wild-type X is active and the X with the pathogenic variant is inactive. In the column of abnormal enamel, the opposite is true: the wild-type X is inactive and the X with the pathogenic variant is active. Some females in the family who inherit the pathogenic variant may not exhibit this banding if skewed X inactivation occurs. Their enamel may look

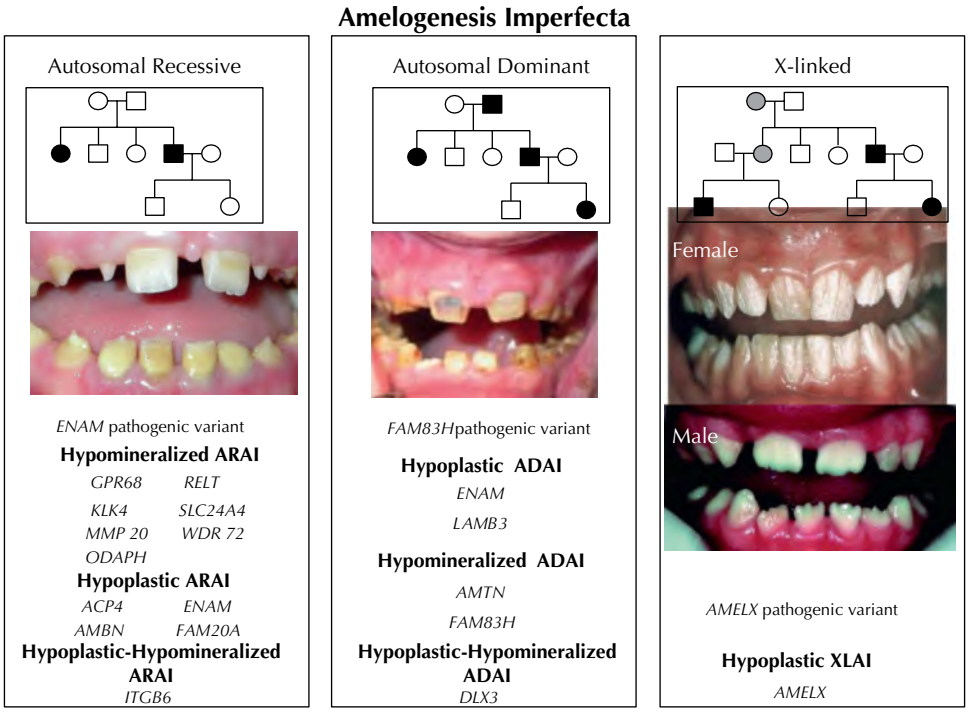

Figure 27-8 Amelogenesis imperfecta. Amelogenesis imperfecta (AI) is transmitted by three Mendelian modes of inheritance. Genes for the pathogenic variants that have been identified for each of the Mendelian modes of transmission are illustrated. Clinical photographs illustrating representative clinical cases for each mode of transmission are shown. ADAI, autosomal dominant AI; ARAI, autosomal recessive AI; XLAI, X-linked AI. *Source:* Modified from Hart PS, Hart TC. Disorders of human dentin. *Cells Tissues Organs*. 2007;186:70–77.

normal (wild-type X is preferentially active) or like that of affected males (X with pathogenic variant is preferentially active).

Gonadal mosaicism is common in some X-linked conditions, such as DMD. In this situation, the mother of an affected boy does not have the pathogenic variant in her blood and the recurrence risk would be presumed to be low. If she has a second affected son, it is clear that she has the pathogenic variant in her gonads, since the odds of having two de novo mutations would be extremely low. Gonadal mosaicism is estimated at 15% for DMD.[68]

Mechanisms of Disease

As shown in Table 27-3, there are various mechanisms of disease. Recessive conditions typically result from a loss of function. An example is amelogenesis imperfecta due to mutations in *MMP20*. MMP20 is a matrix metalloproteinase that degrades amelogenin, the major protein component of dental enamel matrix. Proper removal of the enamel matrix is necessary to allow enamel mineralization. The pathogenic variants of *MMP20* produce a protein that is unable to degrade amelogenin properly. Another example is Papillon–Lefèvre syndrome (PLS). In PLS, pathogenic variants in the *CTSC* gene produce inactive cathepsin C protein. Carriers have about 50% of normal cathepsin C activity, which is enough to enable normal biologic function. Affected individuals have little or no functional cathepsin C and cannot activate serine proteases. While genetic (DNA) testing of the *CTSC* gene can be used to test for PLS, it is also possible to test for cathepsin C enzyme activity to test for PLS.[69]

Dominant disorders can result from a variety of mechanisms. The first is a gain of function. In this case, the mutant protein has a new functional capability and performs a new function, or does its usual function to a greater extent. This is the mechanism for achondroplasia. The FGFR3 protein is a receptor that normally helps limit growth. Pathogenic variants in *FGFR3* cause constitutive (constant) activation of the receptor, resulting in overlimitation of growth.

Another mechanism is haploinsufficiency. In this situation, the normal (wild-type) protein is made, but in only half the normal amount. This quantity is "insufficient" for normal function, and results in phenotypic consequences, including diseases. An example is osteogenesis imperfecta (OI) without dentinogenesis imperfecta. This type of OI is associated with null alleles, meaning no protein is made from that allele. The type 1 collagen that is produced from the wild-type allele is not enough to prevent brittle bones.

Dominant negative means that a mutant protein is made and interferes with the wild-type protein's function. This is the mechanism underlying osteogenesis imperfecta types 2, 3, and 4 and some forms of type 1 OI. For example, if a missense substitution occurs in one of the chains for type I collagen, typically a glycine residue replaced by another amino acid, then both wild-type and mutant proteins are made. Because collagen is a triple helix, incorporation of the mutant protein into the helix prevents normal helical formation. The net result is that only 25% of the collagen helical molecules are normal. In this case, dentinogenesis imperfecta also occurs and often this dental manifestation is the most penetrant finding (Figure 27-9).[52]

Chromosomal Rearrangements

Humans have 23 pairs of chromosomes: 22 autosomes (chromosomes 1, 2, 3, . . . 22) and the sex chromosomes (X and Y). One member of each pair is inherited from the mother (maternal) and one from the father (paternal). Sometimes there can be differences in chromosome number and/or structure. Individuals with chromosomal disorders often resemble each other more than their own family members.

Numeric variants in whole chromosomes are further classified into gains (extra chromosomes like Down

Table 27-3 Mechanisms of disease.

Mechanism	Explanation	Example
Loss of function	Protein cannot do its job	Amelogenesis imperfecta due to mutations in *MMP20*. MMP20 is a matrix metalloproteinase that degrades amelogenin. Pathogenic variants produce a protein that is unable to degrade amelogenin appropriately.
Gain of function	Protein does new job or does usual job to greater extent	Achondroplasia. FGFR3 is a receptor involved in limiting growth. Pathogenic variants in *FGFR3* cause constitutive activation of the receptor, resulting in too much growth restriction.
Haploinsufficiency	Only normal protein is made, but the amount (~50%) is not enough to do the job completely	Type 1: osteogenesis imperfecta without dentinogenesis imperfecta.
Dominant negative	The mutant protein interferes with the normal protein doing its job	Type 1: osteogenesis imperfecta with dentinogenesis imperfecta.

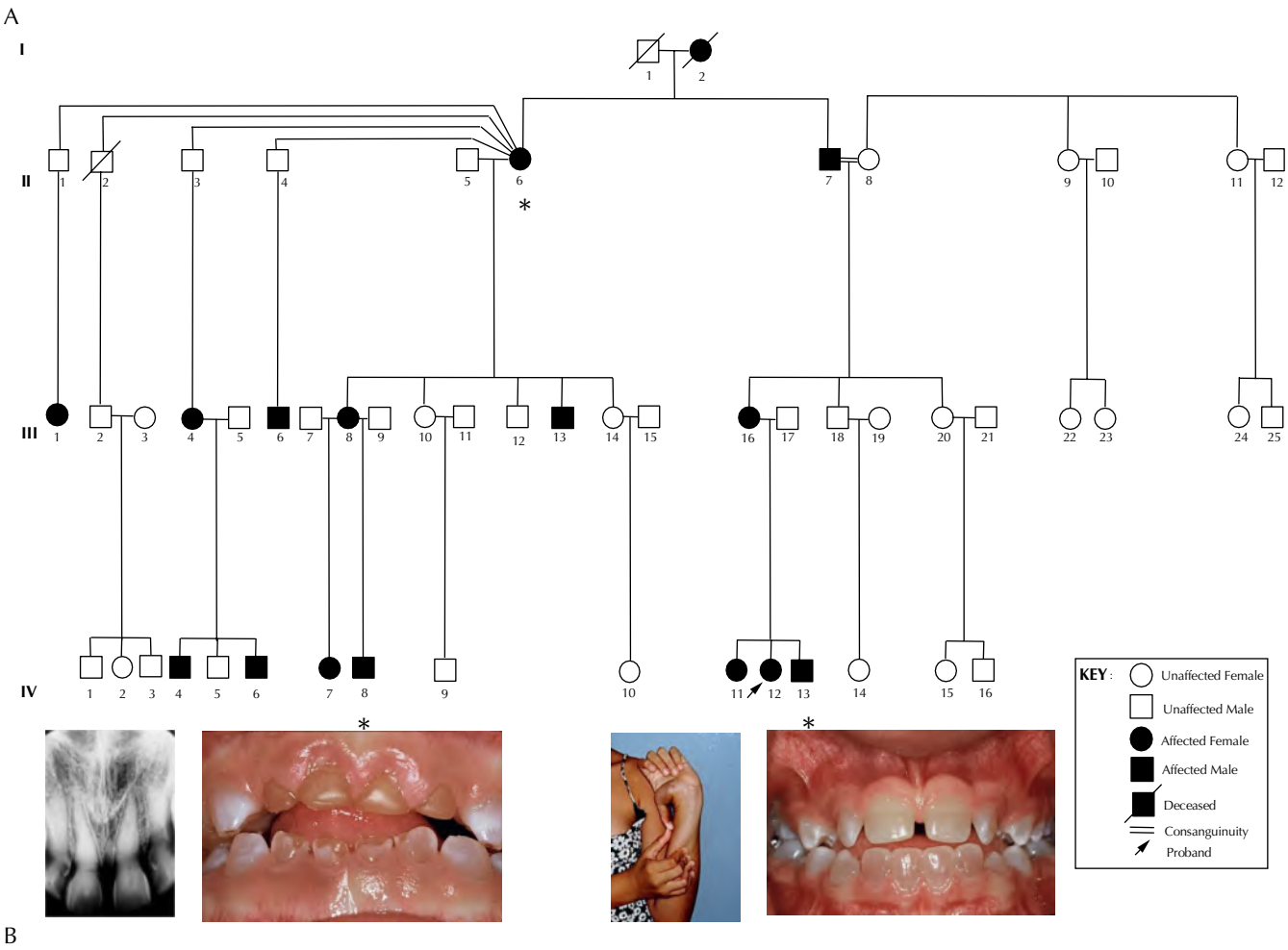

Figure 27-9 osteogenesis imperfecta with dentinogenesis imperfecta. (A) The pedigree of the family demonstrating autosomal dominant inheritance. All affected individuals had dentinogenesis imperfecta. Variable expressivity was observed regarding joint pain, hyperextensible joints, and increased bone fractures with moderate trauma. *Source:* Modified from Pallos D, Hart PS, Cortelli JR, et al. Novel COL1A1 mutation (G559C) [correction of G599C] associated with mild osteogenesis imperfecta and dentinogenesis imperfecta. *Arch Oral Biol*. 2001;46:459–470. (B) From left to right: radiograph showing bulbous crowns with prominent cervical constrictions and shortened roots, affected primary dentition, hyperextensible joints, affected permanent dentition.

syndrome due to trisomy 21) or losses (missing chromosomes like Turner syndrome due to monosomy X). These conditions are called aneuploidy, reflecting that the total number of chromosomes is different than 46 (the euploid number in humans). Aneuploidy of most chromosomes is not compatible with life. Aneuploidy is typically associated with phenotypic consequences, although they can mild as seen with 48,XYY and 48,XXX individuals. Many of these conditions, including Down syndrome, have craniofacial manifestations.

There are many types of structural variants of chromosomes that involve parts of chromosomes. Structural variants of chromosomes may involve one or more chromosomes and include translocations, inversions, deletions, insertions, and ring and supernumerary chromosomes.[70] The amount of genetic material involved in a chromosomal abnormality can be large, containing many genes, or small, involving only a few genes. When large they can be visualized under the microscope, but when smaller, involving fewer than 5–10 million nucleotide base pairs, they can only be detected using molecular cytogenetic techniques such as microarray. Often the carrier of a structural variant is phenotypically normal and only comes to medical attention because of infertility or recurrent pregnancy loss.[71]

Wolf–Hirschhorn syndrome (WHS) is an example of a chromosomal structural variant associated with craniofacial dysmorphism. The disorder is due to a deletion of the short arm of chromosome 4. Affected individuals have intellectual disability, hypotonia, seizures, developmental and growth delay, and a characteristic facial appearance, known as the

Greek warrior helmet appearance.[72] The size of the deletion can vary between individuals, but typically at least three genes are deleted: NSD2, LETM1, and MSX1.[73] It is believed that haploinsufficiency for MSX1 underlies the dental abnormalities often seen in individuals with WHS, including tooth agenesis and retained primary molars. Cleft lip with or without cleft palate is observed in 30% of cases.

As mentioned above in the Mendelian disorder section, sometimes one parent contributes both members of a pair of chromosomes and the other parent does not contribute a copy. This is called uniparental disomy (UPD) and has implications for dominant, recessive, and imprinting disorders (discussed below). UPD is a mechanism by which a child can have a recessive condition for which only one of their parents is a carrier. It can also lead to homozygosity for dominant traits.[74]

Imprinting Disorders

Some genes in the human genome are only expressed from either the maternal or paternal allele. The other parent's allele is silenced, such as by methylation of the genomic DNA.[75] The silenced allele is said to be imprinted. During gametogenesis, the imprints must be erased and reestablished based upon the sex of the individual. In essence, the chromosome inherited from the parent of the opposite sex must be reimprinted. For example, a female has to reimprint the chromosome she inherits from her father to a female pattern in her gonads; males have to reimprint maternal chromosomes in their gonads. When genes are only expressed from one parental allele, failure to inherit a chromosome from the parent whose allele is active, failure to reestablish imprints during gametogenesis, or abnormal silencing or removal of methylation will result in a phenotypic consequence.

Examples of imprinting disorders include Prader–Willi and Angelman syndromes, both involving genes on chromosome 15. In this region of 15q11, most genes are expressed from the father's (paternal) allele. In about 70% of cases of Prader–Willi syndrome (PWS), a de novo deletion occurs on the chromosome 15 transmitted by the father.[76] Because the genes in this region are only expressed from the father's allele, which has been deleted in the father's allele passed to the child, no gene expression occurs. Another 25% of PWS occurs because of maternal UPD. In this case, although there are two copies of chromosome 15 present and the chromosomes are structurally intact, the offspring's genes in the 15q11 region are silenced on both chromosomes, since they both were inherited from the mother. It is the inability to produce these gene products that results in the PWS phenotype: severe hypotonia and feeding difficulties in early infancy, followed by hyperphagia and gradual development of morbid obesity. The saliva is also very thick and sticky.[77] De novo deletions and UPD are associated with a very low risk of recurrence. The same is not true for individuals who cannot reset the imprinting pattern based upon their own sex. A man who is unable to reimprint the chromosome 15 he inherited from his mother to a male pattern will also have a child with PWS, because the genes that should be expressed from the paternal allele remain methylated and therefore silenced. Importantly, in this case the recurrence risk can be as high as 50%.

Another imprinting disorder is Beckwith–Wiedemann syndrome (BWS), an overgrowth disorder associated with macrosomia, omphalocele, macroglossia, and visceromegaly.[78] BWS is associated with abnormal gene expression of two imprinted domains on chromosome 11p15.5. Analogous to the 15q11 region, on chromosome 11p15.5 there are genes expressed solely from the maternal allele and other genes expressed solely from the paternal allele. Approximately 50% of BWS cases involve abnormal methylation of genes in this region, including either gain or loss of methylation. Another 20% involve paternal UPD. Most individuals with BWS are sporadic cases, but 15% have a family history consistent with a parent of origin autosomal dominant transmission.

Mitochondrial Disorders

The major function of mitochondria is to carry out oxidative phosphorylation. Mitochondria are the only animal cellular organelles that contain their own DNA. Mitochondrial DNA (mtDNA) is inherited almost exclusively from the mother. mtDNA is a small, circular molecule of 16,569 nucleotides that encodes 37 genes, including 13 polypeptides necessary for the oxidative phosphorylation (OXPHOS) complexes I and III–V. The remaining genes code for transfer RNA (tRNA) and ribosomal RNA (rRNA). mtDNA uses nonuniversal codons, meaning the codons are different than those used by nuclear DNA-encoded genes. Each mitochondrion contains multiple copies of mtDNA and there are hundreds to thousands of mitochondria per cell, depending upon the energy needs of the cell. mtDNA has a high mutation rate because of limited proofreading and repair, and the lack of protective histone proteins. Mitochondria segregate randomly during cell division, so cells can end up with varying levels of mtDNA containing pathogenic variants. Heteroplasmy refers to the presence of both wild-type and mutant mtDNA in a given mitochondrion. Many of the mitochondrial disorders need a certain level of mutant mtDNA before phenotypic consequences occur, known as the threshold effect. It is important to remember that because of random mitotic segregation, analysis of the mutant load in peripheral blood cells may not reflect the level in affected tissue like muscle.

The other 84 components of the OXPHOS complexes are encoded by nuclear genes, mutations of which can also lead to mitochondrial dysfunction. Recently mutations in the nuclear gene *MRPS28,* which encodes the small mitoribosomal subunit protein bS1m, were identified in a patient with intrauterine growth retardation, dysmorphic facies, and developmental delay.[79]

It is estimated that 1 in 5000 adults has a mitochondrial disorder.[80] Mitochondrial disorders can affect almost every tissue and may occur at any age. The symptoms can be nonspecific and depend on which tissues are affected. Often more than one organ is involved. Because of mitotic segregation, there can be extreme variability of phenotype within a family. A recent study found that patients consult multiple physicians, on average eight, before a diagnosis of mitochondrial disorder is made.[81] During this diagnostic odyssey, patients undergo multiple, often unnecessary, tests and are often given conflicting diagnoses.

Multifactorial Disorders

In contrast to Mendelian disorders, most chronic diseases are etiologically complex and are caused by interactions of genes and environment. These are known as multifactorial traits and represent conditions such as diabetes, heart disease, and hypertension. The risk of developing these conditions results from the interactions of major and minor genes, and epigenetic and environmental factors. In contrast to Mendelian disorders, where a single pathogenic variant in a gene can result in a disorder, complex disorders often involve contributions from many genes. Unlike Mendelian conditions, the contribution of individual genes is very small, and the contribution of any one gene is not sufficient to cause disease alone. It is the threshold effect of interactions of many genes and environmental factors that causes disease.

Oral clefts are an example of multifactorial traits. In contrast to the Mendelian disorders, recurrence risks for multifactorial traits are increased by the number of affected individuals, the severity of the defect, and potentially the sex of the affected parent and/or child. Most affected children have unaffected parents, but a more severely affected parent is more likely to have an affected child. If the two sexes have a different probability of being affected, the less likely sex, if affected, is the more likely sex to produce an affected offspring. For example, if a child with an isolated cleft has no other affected first- or second-degree relative, the recurrence risk is 2%–5%. If a first-degree relative of the child is also affected with an isolated cleft, then the risk for an offspring or sibling is 8%–10%. If both parents are affected with a cleft, the empiric risk for a cleft in the offspring ranges from 25% to 50%, similar to the risk for Mendelian disorders. Cleft lip and palate occurs in about 1 in 1000 births and represents 50% of all clefts. The frequency varies by racial groups, with higher rates in Asians and certain groups of Native Americans and lower rates in American Americans. Up to 13% of cases present with other birth defects. Isolated cleft palate occurs in about 1 in 2000 babies and represents about 30% of all clefts. All racial groups have a similar risk, but it occurs more often in female children. Isolated cleft lip, representing about 20% of all clefts, occurs more often in male children. Pathogenic variants in many genes have been determined to cause syndromic cleft lip with or without cleft palate and cleft palate. Some of these same genes have been implicated in nonsyndromic cleft lip with or without cleft palate and cleft palate. Synergistic heterozygosity (being heterozygous at two different genes), epigenetic factors, and environmental influences may combine with specific genetic variants to produce nonsyndromic clefting

Phenotypic and Genetic Heterogeneity

As shown in Table 27-4, there are a variety of types of heterogeneity seen with human genetic disorders. Genetic heterogeneity refers to the production of the same phenotype by different genetic mechanisms. An example is amelogenesis imperfecta, which can be caused by loss of function pathogenic variants in *MMP20* or gain of function variants in *FAM83H*.

Clinical heterogeneity refers to different phenotypes resulting from pathogenic variants in the same gene. Pathogenic variants in *SOS1* can result in hereditary gingival fibromatosis type 1, an autosomal dominant isolated form of gingival overgrowth. Other pathogenic variants in *SOS1* cause Noonan syndrome, an autosomal dominant disorder characterized by a typical facial appearance, short stature, developmental delay, and congenital heart defects.

Table 27-4 Type of heterogeneity seen in human disorders.

Type	Explanation	Example
Allelic	Multiple pathogenic variants in the same gene produce the phenotype	22 different pathogenic variants in *ENAM* cause amelogenesis imperfecta
Clinical	Different phenotypes result from pathogenic variants in the same gene	Hereditary gingival fibromatosis type 1 and Noonan syndrome due to pathogenic variants in *SOS1*
Genetic	Same phenotype is produced by different genetic mechanisms	Amelogenesis imperfecta can be caused by loss of function and gain of function pathogenic variants
Locus	Same phenotype is produced by pathogenic variants in different genes	Amelogenesis imperfecta is caused by pathogenic variants in at least 17 genes

Allelic heterogeneity refers to the same phenotype caused by different pathogenic variants in the same gene. This can be illustrated by amelogenesis imperfecta, where 27 different pathogenic variants in the *FAM83H* gene have been identified.[82] Another example of allelic heterogeneity is illustrated by the 22 pathogenic variants in the *ENAM* gene that also cause amelogenesis imperfecta.[83]

Locus heterogeneity refers to the same phenotype arising from pathogenic variants in different genes. While the above example of mutations in the *FAM83H* gene illustrate allelic heterogeneity, the fact that pathogenic variants in *FAM83H* and *ENAM* both cause amelogenesis imperfecta is an example of locus heterogeneity. In fact, amelogenesis imperfecta can result from pathogenic variants in at least 17 different genes (Table 27-5; Figure 27-8). Sometimes the clinical and radiographic appearance of enamel and mode of inheritance can be used to narrow down the list of potentially causative genes for amelogenesis imperfecta. Unless there is a clear X-linked inheritance, there are at least 5 genes associated with autosomal dominant inheritance and at least 13 genes associated with autosomal recessive inheritance of amelogenesis imperfecta.

Sometimes individuals with the same pathogenic variant can have different phenotypic features. In the most extreme form, some individuals who have inherited a pathogenic variant for an autosomal dominant trait do not show any features of the disorder, and it is only after the birth of an affected child that it is recognized that they have the pathogenic variant. This is an example on nonpenetrance: an individual has a pathogenic variant but does not express the phenotype. Another example is variable expressivity, where individuals with the same dominant pathogenic variant, sometimes even within the same family, have very different phenotypes. Sometimes even monozygotic twins can be discordant for a genetic disorder, where one twin is affected and one is not.[84]

Table 27-5 Genes that cause amelogenesis imperfecta.

Gene	Chromosome	Phenotype	Mode of Inheritance
LAMB3	1	Hypoplastic	Autosomal dominant
ITGB6	2	Hypoplastic/ hypomineralized	Autosomal recessive
AMTN	4	Hypomineralized	Autosomal dominant
AMBN	4	Hypoplastic	Autosomal recessive
ENAM	4	Hypoplastic	Autosomal dominant and autosomal recessive
ODAPH	4	Hypomaturation	Autosomal recessive
FAM83H	8	Hypomineralized	Autosomal dominant
RELT	11	Hypocalcified	Autosomal recessive
MMP20	11	Hypomaturation	Autosomal recessive
GPR68	14	Hypomaturation	Autosomal recessive
SLC24A4	14	Hypomaturation	Autosomal recessive
WDR72	15	Hypomaturation	Autosomal recessive
DLX3	15	Hypomaturation/ hypoplastic	Autosomal dominant
FAM20A	17	Hypoplastic	Autosomal recessive
ACP4	19	Hypoplastic	Autosomal recessive
KLK4	19	Hypomaturation	Autosomal recessive
AMELX	X	Hypoplastic/ hypomaturation	X-linked

Phenocopies

A phenocopy is an environmentally induced phenotype that looks like a genetic disorder. An example is gingival overgrowth. Gingival overgrowth can occur as an isolated autosomal dominant trait, as part of a syndrome, or as the result of certain medications, including cyclosporin, calcium-channel blockers, and phenytoin (Figure 27-10).[85] Not everyone who takes the drug will develop gingival overgrowth, which is an unwanted side effect. Cessation of medicine will result in resolution of the overgrowth over time without the need for surgical treatment. Genetic forms of gingival overgrowth typically require surgical intervention unless very mild. It is important to distinguish phenocopies, which can often be elucidated by a thorough clinical and family history, including duration of symptoms, whether anyone else in the family is similarly affected, and changes to medications.[86]

GENOMICS IN THE FUTURE

Knowledge of the effects of genetic variation continues to increase at an exponential pace in advancing our understanding of both basic biologic mechanisms and risk of most health conditions addressed by the field of oral medicine. Along with these advances come "growing pains" as scientist-clinicians press the limits (and occasionally step beyond solid ground) of what these powerful data can and cannot tell us about disease diagnosis, risk, prognosis, and optimizing treatments and prevention. For many simple (single-gene) conditions, genetic tests provide solid answers, as shown in examples presented in this chapter. However, for complex phenotypes such as dental caries and periodontitis, the associations with one or a few genetic variants reported thus far are neither sufficiently strong nor consistent enough across studies to provide any clinical utility for use in patients. It remains uncertain whether the much larger genetic studies currently underway, incorporating measures of subjects' microbiomes, diet, and other risk factors, may ultimately lead to genetic tests that will be useful in the clinic for these complex conditions.

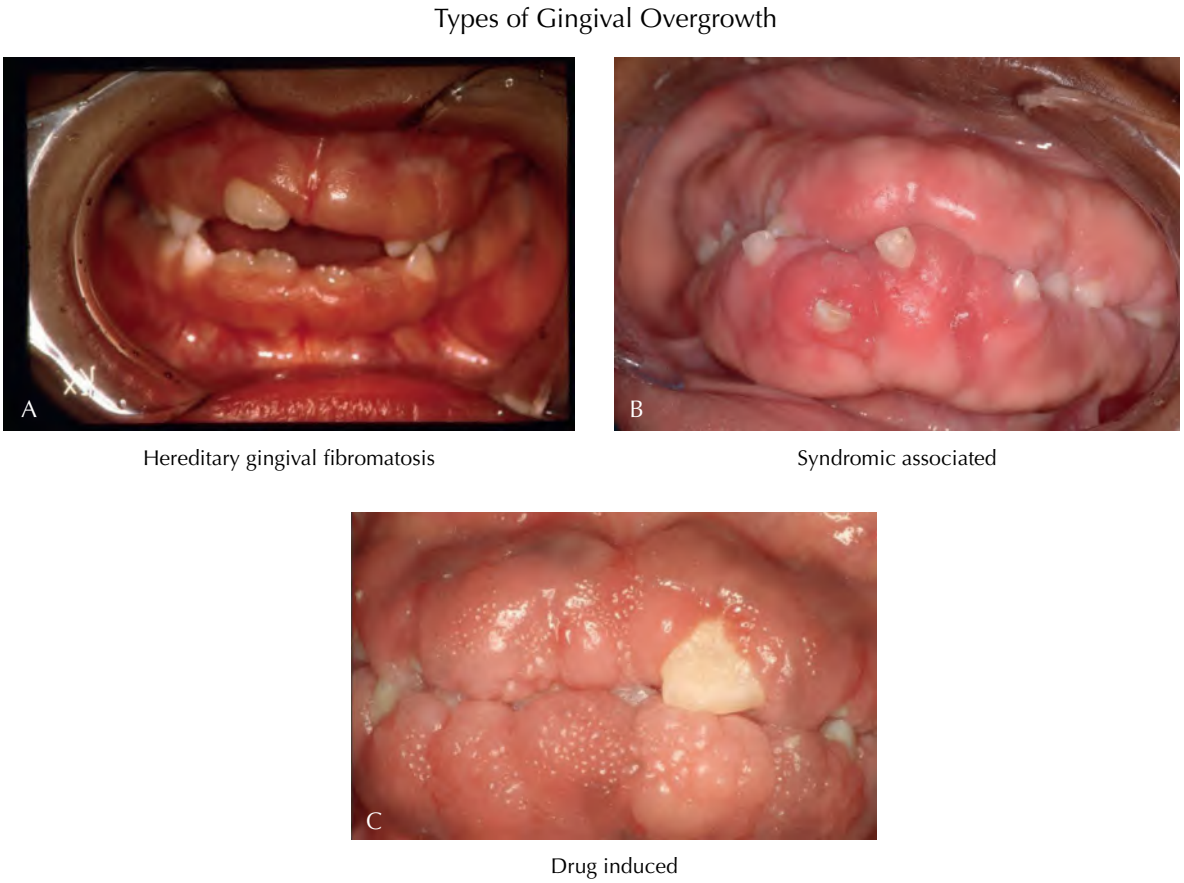

Figure 27-10 Examples of gingival overgrowth. (A) This individual has an autosomal dominant isolated form of gingival overgrowth, termed hereditary gingival overgrowth type I, due to pathogenic variants in *SOS1*. (B) This individual has a syndromic form of gingival overgrowth (Zimmermann–Laband syndrome), meaning they have other phenotypic features in addition to gingival overgrowth. (C) This individual has gingival overgrowth as a side effect of medication: calcium-channel blocker and cyclosporin. This is known as a phenocopy.

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Tabak L, Green E, Devaney S, Somerman M. Precision health: bringing oral health into the context of overall health. *Adv Dent Res.* 2019;30:31–33.

ONLINE RESOURCES

Genetics Home Reference (US National Library of Medicine): https://ghr.nlm.nih.gov

Genetics and Oral Health (American Dental Association): https://www.ada.org/en/member-center/oral-health-topics/genetics-and-oral-health

Genomics and Medicine (US National Human Genome Research Institute): https://www.genome.gov/health/Genomics-and-Medicine

Stanford Center for Genomics and Personalized Medicine: http://med.stanford.edu/scgpm.html

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28

Laboratory Medicine and Diagnostic Pathology

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Pathology has traditionally been divided into laboratory medicine and anatomic pathology. Laboratory medicine is the division of medical science dealing with the qualitative and quantitative assessment or analysis of blood (formed elements and fluid components) and other cells and body fluids, while anatomic pathology involves the determination of disease through gross and microscopic examination of tissue. Clinical chemistry, microbiology, hematology, immunology, molecular diagnostics, cytology, toxicology, therapeutic drug monitoring, genetics, and histology are various components of laboratory medicine.

Diagnostic testing is performed on samples of blood, tissue, and other cells and bodily fluids to provide the clinician with information about a person's health, such as establishing a diagnosis of a condition or disease; screening for disease in asymptomatic patients; and excluding the diagnosis of a disease or condition or monitoring therapy.

The need for this chapter on laboratory medicine in a textbook of oral medicine stems from the National Academy of Medicine report in 2015, which indicated that the medical history of almost every adult in the United States contains a minimum of one diagnostic error.[1] It is difficult to determine the impact of laboratory testing on medical decisions. Historically it has been accepted that 70% of medical decisions are a direct result of laboratory testing.[1] More recently, reports of the use of laboratory tests in patient care medical decisions ranged from 38% for general internists and 29% for family physicians.[2] The percentage of medical decisions made as a direct result of laboratory results is apparently less than the historically estimated 70%, but clearly laboratory testing plays a major role in the provision of healthcare. The Centers for Medicare and Medicaid Services (CMS) estimate that the overall spending on healthcare in the United States in 2017 was $3.5 trillion. National healthcare spending in the United States is projected to grow at an average rate of 5.5% per year for 2018–2027 and to reach nearly $6.0 trillion by 2027.[3] Laboratory testing accounts for approximately $97 billion, 28% of overall US healthcare spending per year. In

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

2027, the estimated economic impact of laboratory testing in the United States will approach $1.68 trillion.

A significant proportion of diagnostic errors in medical histories are due to problems with ordering, performing, reporting, and interpreting laboratory tests. Unfortunately, schools of medicine, dentistry, and allied health do not routinely provide formal courses in laboratory medicine. With the increasing complexity of laboratory testing and little clinically oriented support from practitioners of laboratory medicine, medical, dental, pharmacy, and nursing professionals are confused and uncertain about the proper use of laboratory results.

The aims of this chapter are to provide an introduction to the general principles of laboratory medicine, which should be a part of every oral healthcare professional's knowledge base, as well as help fulfill two of the goals of the Institute of Medicine report: to employ more effective teamwork in the diagnostic process and to enhance healthcare professionals' education and training in the diagnostic process (Table 28-1). Laboratory testing includes three steps: preanalytic—activities such as test ordering and sample collection that take place before actual testing; analytic—laboratory performance of the test; and postanalytic—the process of reporting and interpreting the result. As the analytic phase of laboratory testing is highly regulated and under tight quality control, most laboratory-associated errors occur in the preanalytic and postanalytic stages. For this reason and also for the reason that those two areas are most affected by the decisions of medical/dental professionals, this chapter will focus on the preanalytic and postanalytic stages of laboratory testing.

PREANALYTIC PHASE OF LABORATORY TESTING

Appropriate laboratory testing is defined as "ordering of the right test, using the right method, at the right time, to the right patient, with the right costs and producing the right outcome."[4] The increasing emphasis on the appropriateness of laboratory testing is shown by the development of

Table 28-1 Institute of medicine september 2015 diagnosis recommendations.

Goal 1: Facilitate more effective teamwork in the diagnostic process among health care professionals, patients, and their families	
Recommendation 1A In recognition that the diagnostic process is a dynamic team-based activity, health care organizations should ensure that health care professionals have the appropriate knowledge, skills, resources, and support to engage in teamwork in the diagnostic process. To accomplish this, they should facilitate and support: • Interprofessional and intraprofessional teamwork in the diagnostic process. • Collaboration among pathologists, radiologists, other diagnosticians, and treating health care professionals to improve diagnostic testing processes.	Recommendation 1B Health care professionals and organizations should partner with patients and their families as diagnostic team members and facilitate patient and family engagement in the diagnostic process, aligned with their needs, values, and preferences. To accomplish this, they should: • Provide patients with opportunities to learn about the diagnostic process. • Create environments in which patients and their families are comfortable engaging in the diagnostic process and sharing feedback and concerns about diagnostic errors and near misses. • Ensure patient access to electronic health records (EHRs), including clinical notes and diagnostic testing results, to facilitate patient engagement in the diagnostic process and patient review of health records for accuracy. • Identify opportunities to include patients and their families in efforts to improve the diagnostic process by learning from diagnostic errors and near misses.
Goal 2: Enhance health care professional education and training in the diagnostic process	
Recommendation 2A Educators should ensure that curricula and training programs across the career trajectory: • Address performance in the diagnostic process, including areas such as clinical reasoning; teamwork; communication with patients, their families, and other health care professionals; appropriate use of diagnostic tests and the application of these results on subsequent decision making; and use of health information technology (IT). • Employ educational approaches that are aligned with evidence from the learning sciences.	Recommendation 2B Health care professional certification and accreditation organizations should ensure that health care professionals have and maintain the competencies needed for effective performance in the diagnostic process, including the areas listed in Recommendation 2A.

Table 28-1 (Continued)

Goal 3: Ensure that health information technologies support patients and health care professionals in the diagnostic process			
Recommendation 3A Health IT vendors and the Office of the National Coordinator for Health Information Technology (ONC) should work together with users to ensure that health IT used in the diagnostic process demonstrates usability, incorporates human factors knowledge, integrates measurement capability, fits well within clinical workflow, provides clinical decision support, and facilitates the timely flow of information among patients and health care professionals involved in the diagnostic process.	Recommendation 3B ONC should require health IT vendors to meet standards for interoperability among different health IT systems to support effective, efficient, and structured flow of patient information across care settings to facilitate the diagnostic process by 2018.	Recommendation 3C The Secretary of the U.S. Department of Health and Human Services (HHS) should require health IT vendors to: • Routinely submit their products for independent evaluation and notify users about potential adverse effects on the diagnostic process related to the use of their products. • Permit and support the free exchange of information about real-time user experiences with health IT design and implementation that adversely affect the diagnostic process.	
Goal 4: Develop and deploy approaches to identify, learn from, and reduce diagnostic errors and near misses in clinical practice			
Recommendation 4A Accreditation organizations and the Medicare conditions of participation should require that health care organizations have programs in place to monitor the diagnostic process and identify, learn from, and reduce diagnostic errors and near misses in a timely fashion. Proven approaches should be incorporated into updates of these requirements.	Recommendation 4B Health care organizations should: • Monitor the diagnostic process and identify, learn from, and reduce diagnostic errors and near misses as a component of their research, quality improvement, and patient safety programs. • Implement procedures and practices to provide systematic feedback on diagnostic performance to individual health care professionals, care teams, and clinical and organizational leaders.	Recommendation 4C HHS should provide funding for a designated subset of health care systems to conduct routine postmortem examinations on a representative sample of patient deaths.	Recommendation 4D Health care professional societies should identify opportunities to improve accurate and timely diagnoses and reduce diagnostic errors in their specialties.
Goal 5: Establish a work system and culture that supports the diagnostic process and improvements in diagnostic performance			
Recommendation 5 Health care organizations should: • Adopt policies and practices that promote a non-punitive culture that values open discussion and feedback on diagnostic performance. • Design the work system in which the diagnostic process occurs to support the work and activities of patients, their families, and health care professionals and to facilitate accurate and timely diagnoses. • Develop and implement processes to ensure effective and timely communication between diagnostic testing health care professionals and treating health care professionals across all health care delivery settings.			

(*Continued*)

Table 28-1 (Continued)

Goal 6: Develop a reporting environment and medical liability system that facilitates improved diagnosis by learning from diagnostic errors and near misses			
Recommendation 6A The Agency for Healthcare Research and Quality (AHRQ) or other appropriate agencies or independent entities should encourage and facilitate the voluntary reporting of diagnostic errors and near misses.	Recommendation 6B AHRQ should evaluate the effectiveness of patient safety organizations (PSOs) as a major mechanism for voluntary reporting and learning from these events and modify the PSO common formats for reporting of patient safety events to include diagnostic errors and near misses.	Recommendation 6C States, in collaboration with other stakeholders (health care organizations, professional liability insurance carriers, state and federal policy makers, patient advocacy groups, and medical malpractice plaintiff and defense attorneys), should promote a legal environment that facilitates the timely identification, disclosure, and learning from diagnostic errors. Specifically, they should: • Encourage the adoption of communication and resolution programs (CRPs) with legal protections for disclosures and apologies under state laws. • Conduct demonstration projects of alternative approaches to the resolution of medical injuries, including administrative health courts and safe harbors for adherence to evidenced-based clinical practice guidelines.	Recommendation 6D Professional liability insurance carriers and captive insurers should collaborate with health care professionals on opportunities to improve diagnostic performance through education, training, and practice improvement approaches and increase participation in such programs.
Goal 7: Design a payment and care delivery environment that supports the diagnostic process			
Recommendation 7A As long as fee schedules remain a predominant mechanism for determining clinician payment, the Centers for Medicare & Medicaid Services (CMS) and other payers should: • Create current procedural terminology (CPT) codes and provide coverage for additional evaluation and management activities not currently coded or covered, including time spent by pathologists, radiologists, and other clinicians in advising ordering clinicians on the selection, use, and interpretation of diagnostic testing for specific patients. • Reorient relative value fees to more appropriately value the time spent with patients in evaluation and management activities. • Modify documentation guidelines for evaluation and management services to improve the accuracy of information in the EHR and to support decision making in the diagnostic process.		Recommendation 7B CMS and other payers should assess the impact of payment and care delivery models on the diagnostic process, the occurrence of diagnostic errors, and learning from these errors.	
Goal 8: Provide dedicated funding for research on the diagnostic process and diagnostic errors			
Recommendation 8A Federal agencies, including HHS, the U.S. Department of Veterans Affairs, and the United States Department of Defense, should: • Develop a coordinated research agenda on the diagnostic process and diagnostic errors by the end of 2016. • Commit dedicated funding to implementing this research agenda.		Recommendation 8B The federal government should pursue and encourage opportunities for public–private partnerships among a broad range of stakeholders, such as the Patient-Centered Outcomes Research Institute, foundations, the diagnostic testing and health IT industries, health care organizations, and professional liability insurers to support research on the diagnostic process and diagnostic errors.	

Source: Institute of Medicine (2015) Recommendations: improving diagnosis in health care. Washington, DC: National Academies of Sciences, Engineering, Medicine.

initiatives such as the "Choosing Wisely" campaign (www.choosingwisely.org), developed by the American Board of Medicine, and laboratory stewardship programs such as PLUGS (**P**atient-centered **L**aboratory **U**tilization **G**uidance **S**ervice), started by Seattle Children's Hospital and found in many hospitals (www.schplugs.org).[5,6]

In order to reduce or eliminate activities that have little benefit or can cause harm, Choosing Wisely focuses on what not to do rather than on positive advice about what to do. The recommendations from Choosing Wisely are helpful and, as a result, many medical specialty societies have adapted Choosing Wisely and include it as part of their medical specialty website.

In patient care, the first step in ordering the appropriate laboratory test is to determine whether a test should be ordered. In 1994, Dr. Catherine DeAngelis, the first woman editor of the *Journal of the American Medical Association,* made a pithy comment that summarizes the whole issue very succinctly: "Remember ordering a laboratory test is a bit like picking your nose in public: you must consider what you will do if you find something."[7] Hooper and his colleagues put the same sentiment in slightly different language: "Before ordering a test, decide what you will do if it is either positive or negative. If both answers are the same, then don't do the test."[8]

Lee in the 25th edition of *Goodman-Cecil Medicine* had the following comments about laboratory testing that provide more detailed advice about ordering laboratory tests:

> The interpretation of test results depends on what is already known about the patient.
>
> No test is perfect. Clinicians should be familiar with their diagnostic performance and never believe that a test "forces" them to pursue a specific management strategy.
>
> Tests should be ordered if they may provide additional information beyond that already available.
>
> Tests should be ordered if there is a reasonable chance that the data will influence patient care.
>
> Two tests that provide similar information should not be used.
>
> In choosing between two tests that provide similar data, use the one that has lower cost and/or causes less discomfort and inconvenience to the patient.
>
> Clinicians should seek all the information provided by the test, not just an abnormal or normal result.
>
> The cost-effectiveness of strategies using noninvasive tests should be considered in a manner similar to that of therapeutic strategies.[9]

Consideration of which laboratory test to order involves examination of parameters of the specific assay that determine the diagnostic usefulness of the test. In determining the usefulness of a test, the concepts of sensitivity and specificity come into play. In a population of patients in which the correct disease status is already known, sensitivity is the percentage testing positive in a population with disease (positive in disease), while specificity is the percentage testing negative in a population without disease (negative in health). For most commercially available assays, the sensitivity and specificity of a particular test are listed in the literature provided by the manufacturer. However, the sensitivity and specificity measures provided by the manufacturer are obtained under ideal conditions that are generally not found in clinical use. Generally, in "real-life" situations, the actual sensitivity and specificity of a particular assay are less than those indicated in the manufacturer's instructions for the test. As a general rule, a diagnostic assay should have performance characteristics that minimize false positives and false negatives. However, the clinical implications of a test result may determine which test is most useful in a specific situation. For patients who potentially have a serious, possibly incurable disease, the diagnostic test should have high specificity so as to minimize the number of false positive results. On the other hand, an assay that maximizes sensitivity should be used to diagnose serious but curable diseases. A second confirmatory assay may then be used.

When choosing between the sensitivity and specificity of a laboratory test for a condition, clinicians may find the mnemonic "SpIn and SnOut" helpful. Specificity, abbreviated as Sp, is used to rule in the condition (SpIn). Sensitivity, abbreviated as Sn, is used to rule out the condition (SnOut) (see Figure 28-1).

The actual usefulness of a laboratory test is better predicted by the positive and negative predictive values. The positive predictive value (PPV) of a test is the percentage of all positive results that are true positives and is calculated using the formula:

$$\text{PPV} = \left[\text{True positives} / (\text{True positives} + \text{False positives})\right] \times 100$$

The negative predictive value (NPV) is the percentage of all negative results that are true negatives and is calculated using the formula:

$$\text{NPV} = \left[\text{True negatives} / \left(\text{True negatives} + \text{False negatives}\right)\right] \times 100$$

A good test should have both high positive and negative predictive values. The predictive values for any test depend not only on the sensitivity and specificity of the test, but also on the prevalence of the disease for the diagnostic laboratory assay.

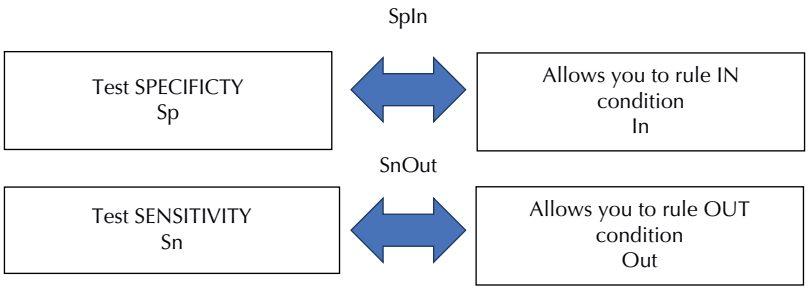

Figure 28-1 Mnemonic for Differentiating between Sensitivity and Specificity.

Using systemic lupus erythematosus (SLE) and the antinuclear antibody (ANA) test as an example:

> The sensitivity and specificity for ANA in the diagnosis of SLE are 95% and 90%, respectively; testing for SLE with ANA in all patients presenting to a primary care practice (assume prevalence of $\leq$1%), the PPV and NPV are 9% and >99%, respectively. In a rheumatology clinic in which only patients with clinical features of SLE (assume prevalence of 30%) are tested with ANA, the PPV and NPV of the test are 80% and 96%, respectively.

Understanding PPV and NPV is important for the dental healthcare team. Dental advertising and dental salespersons may try to sell tests for diagnosis of caries, periodontal disease, oral cancer, or other diseases and conditions to general dental practices. Moreover, these tests may be advertised for direct sale to the public. Whether the test is used for screening or diagnosis depends on the characteristics of the assay: high sensitivity for screening tests and high specificity for exclusion of a diagnosis. Preferably those characteristics should be obtained from published literature and not from the detail sheet accompanying the materials for performance of the assay. Dental practitioners using these tests need to be aware of the predictive value of these tests in their own patient populations and determine whether or not these tests are useful, and whether these assays are more appropriate for screening than for diagnostic purposes.

The diagnostic accuracy of a particular test is provided by knowledge of the sensitivity and specificity for that assay. However, these values do not give any indication about the effect the result has on the likelihood that the patient has the disease for which the test is performed. The relationship between the clinical suspicion—that is, the pre-test probability—that a patient has a disease compared to the chance that the patient has the disease after a particular test is performed—that is, the post-test probability—is given by the formula:

$$\text{Post-test probability} = \text{LR} \times \left(\text{pre-test probability}\right)$$

where LR is the likelihood ratio.

The pre-test probability is the clinician's estimate that the patient has the disease. This probability is estimated from the prevalence of the disease in the population from which the patient comes and the history and physical examination.

The LR of a positive result is calculated by the following equation:

$$\text{LR of a positive result} = \text{Sensitivity} / \left(1 - \text{Specificity}\right)$$

The LR of a negative result is calculated by the following equation:

$$\text{LR of a negative result} = \left(1 - \text{Sensitivity}\right) / \text{Specificity}$$

The diagnostic or testing threshold of a test is the point at which clinical suspicion for disease is so low that the results of the laboratory test will not alter that low probability. If the test has a low diagnostic threshold even if the test is positive, it is most likely a false positive result and the patient should not be treated for that disease. The therapeutic or treatment threshold is the point at which clinical suspicion is high enough that the results of the assay will not significantly increase the likelihood that the patient has the disease. Laboratory tests should be ordered when the pre-test probability of the patient having the disease lies between the diagnostic and the therapeutic threshold (see Figure 28-2). These thresholds are generally determined by published analyses. An example of determination of these break-points is seen in two papers dealing with Lyme disease testing.[10,11] In these papers, the diagnostic or testing threshold was 0.20 (a patient with nonspecific arthritis) and the therapeutic threshold was 0.8 (a patient from a geographic area endemic for Lyme disease with either erythema migrans or a combination of arthritis, history of a rash resembling erythema migrans, and a previous tick bite).

Diagnostic testing can be performed in a multitude of locations. Laboratories with a large menu of diagnostic tests generally include those laboratories found in larger hospitals, hospital systems, and commercial laboratories, such a Quest Diagnostics or LabCorp. Most hospitals and large healthcare centers have in-house laboratories. These in-house laboratories may offer a full spectrum of laboratory testing or may be limited to more routinely used assays, and the in-house laboratory may send out less commonly used

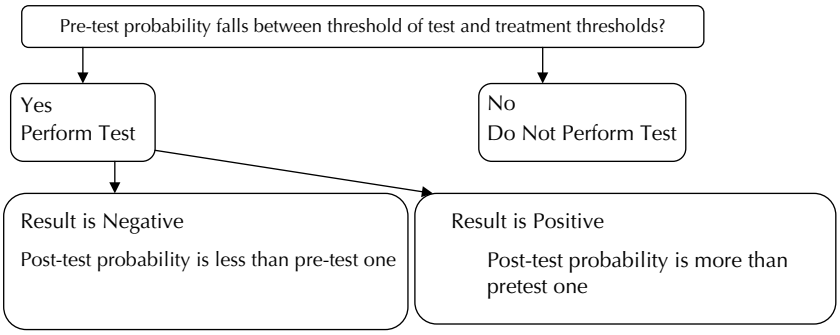

Figure 28-2 Diagnostic tree for ordering a test.

assays to a commercial laboratory. Diagnostic testing also occurs in smaller labs found in providers' offices, healthcare centers, urgent care centers, or other locations such as pharmacies. In the outpatient nonhospital setting, specimens are generally obtained from patients and sent to a centralized regional lab for analysis.

In the United States, diagnostic laboratories are required to be licensed and certified. On October 31, 1988, the US Congress enacted the Clinical Laboratory Improvement Amendments of 1988 (Pub. L. 100-578) (CLIA'88), codified at 42 U.S.C. 263.[12] This act, more generally known as CLIA, established quality standards for laboratory testing to ensure the accuracy, reliability, and timeliness of patient test results regardless of the location of the testing site, and requires laboratories to be CLIA certified. CLIA certification is important, as a clinical laboratory must be CLIA certified to receive reimbursement from Medicare or Medicaid. In the United States, Medicare payments for lab tests totaled $6.8 billion in 2016 and reimbursement for services provided is certainly an incentive for laboratories to obtain and maintain their CLIA certification.

Point-of-Care Testing

Office laboratories often use point-of-care (POC) assays as the basis for much of their testing. Point-of-care testing (POCT), defined as any testing that occurs outside of a central laboratory, is becoming a more common and accepted practice in the healthcare industry. POCT offers several advantages over traditional, more regulated laboratory testing, including increased accessibility to diagnostic testing for many populations, especially in rural and remote settings; minimal sample volumes required to perform the assay; real-time test results; and, most importantly, the ability of nonlaboratory personnel to perform these assays. However, the instructions for these POC tests must be followed precisely; and, as in more traditional laboratories, there must be documentation of training, performance of controls and instrument checks, and correct performance of procedures.

As useful as POC assays are, they may be inappropriate in certain clinical situations. An example is the use of a POC assay to determine glycosylated hemoglobin (HbA_{1c}) for the diagnosis of diabetes mellitus. HbA_{1c} is a measure of blood glucose over the life span of the red blood cell, which is approximately 120 days. While it may be appropriate to use POC HbA_{1c} assays to guide outpatient treatment of patients with diabetes, the analytic performance of these tests—that is, their accuracy relative to a reference laboratory's standard and precision—is such that patients who have true HbA_{1c} values close to the diagnostic cut-point may be misdiagnosed. A cut-point is a value at which subjects are classified as having or not having a condition. The World Health Organization (WHO) recommends an HbA_{1c} cut-point of 6.5% for the diagnosis of diabetes. A value of less than 6.5% does not exclude a diabetes diagnosis and further clinical investigation may be required.[13] Even in the same institution, there is often a difference between the results of an assay performed in an outpatient/clinic setting by one methodology and an assay for the same analyte performed by the reference method in the main hospital laboratory. When such differences are clinically important, such as in diagnosis of a disease, the main laboratory should append a comment to the results to indicate that such discrepancies exist and that correction factors have been applied to make the results compatible.

The American Dental Association (ADA) advocates for POCT of patient blood glucose levels on an ongoing basis or immediately prior to dental treatment as an appropriate activity for persons at risk for diabetes. In support of this recommendation, the ADA has established a billing code (D0142) for this test (Box 28-1).

Box 28-1 CDT Code for Point-of-Care Blood Glucose Testing

D0412 blood glucose level test—in-office using a glucose meter. This procedure provides an immediate finding of a patient's blood glucose level at the time of sample collection for the point of service analysis.

Box 28-2 CDT Code for Point-of-Care HbA1c testing
D0411 HbA_{1c} in-office point of service testing

Additionally, the ADA has established a billing code for testing for $HbA1_c$ (Box 28-2).

Further information on ADA recommendations for POC testing can be found on the ADA website.[14]

Laboratory Analysis

Laboratory analysis is based upon the idea that the material sampled will be collected in a standardized fashion to reduce the likelihood of undue variability of results. Since patients are not standardized, their physical status can significantly affect their hematologic profile and laboratory results. The patient's degree of hydration, level of anxiety, activity, medications, history of tobacco use, sex, and race may impact upon hematologic profile results. Additionally, the presence of certain medical conditions may impact laboratory test results. For example, $HbA1_c$ values are elevated in iron-deficiency anemia patients and decrease after the patients are treated with iron.[15]

Descriptive information regarding the patient is required when submitting a sample for laboratory analysis. This descriptive information may include pertinent medical history, sex, age, race, fasting status, and time of collection. Correctly labeling specimens that have been obtained is of the utmost importance. Samples must be labeled with appropriate identification to ensure the test results will be related back to the patient. The use of $\geq$1 unique patient identifiers such as medical record numbers or birthdate along with bar codes generated to identify that a sample was obtained from a specific known patient has become standard practice in clinics and hospitals. The barcode and unique identifiers are placed on the specimen container and attached to the laboratory requisition form.

In collecting blood for determination of specific analytes, there are different types of collection tubes whose purpose is generally indicated by the color of the top of the tube. Table 28-2 gives a representative sample of the common blood collection tubes and their uses.[16,17] However, the laboratory to which you send samples should provide a list of the blood collection tubes, specimen requirements, and any directions for use. If you are unsure about any of this information, you should contact the laboratory directly.

In order to aid in the draw of blood into the container, most of these tubes contain a vacuum. The tubes should be filled with a certain amount of blood with at least the minimum specimen volume designated by the laboratory. The tops of the tubes should not be removed to completely fill the container. In tubes that contain additives, under- or overfilling can yield in false results. Many of the collection tubes with additives should be inverted several times to allow complete mixing of the blood and/or any additive. Order of draw, when obtaining multiple samples for testing, is important, with the following sequence being recommended: sterile tubes for blood culture; tube for coagulation testing (light blue); gel separator tube (red); tube with heparin additive (green tube); tube with EDTA additive (purple/lavender tube); tube with oxalate/fluoride additive (gray tube).

Falsely high or low results for assays can occur due to materials that interfere with the accurate and precise measurement of the analyte in question. As many laboratory results are determined by spectrophotometric methods, any substance that colors the plasma and serum can interfere with the results. The three major interferences due to abnormal colors in a liquid are lipemia, causing a milky-white color; hemolysis, resulting in a red color; and increased bilirubin, turning plasma/serum orange, green, or brown. Besides altering the color of serum/plasma, many drugs produce significant interference by other means. Therefore, it is important to include medication information on a laboratory requisition slip when requested.

For most tests, blood can be drawn at any time during the day. However, there are exceptions to this statement. For therapeutic monitoring of drugs such as antibiotics, the medical professional needs to know if the drug concentration is within a certain therapeutic range. It is easier to draw a trough level, the lowest level of a drug before administration of the next dose, than a peak level for a drug. A peak level is the highest level of drug in the serum and is usually obtained 1 to several hours after the drug is administered. For an intravenously administered drug, blood is drawn for trough levels just prior ($\leq$30 minutes ideally) to administration of the next dose. Some biochemical assay results are biased by diurnal variations. Time of collection must be considered when interpreting these values in the clinical setting. For example, sampling of blood for distinction of pseudo-Cushing states from Cushing syndrome gives 96% accuracy. In Cushing's syndrome the loss of normal cortisol circadian rhythm and absence of a late-night cortisol nadir is typical. Midnight serum cortisol levels have been used to distinguish patients with Cushing's syndrome from those with pseudo-Cushing's syndrome. However, drawing blood at midnight is inconvenient for an ambulatory patient, so obtaining saliva for cortisol determination at bedtime or midnight is more convenient and just as accurate. For those readers who wish more information about laboratory medicine, including laboratory reference ranges, we recommend the third edition of *Laposata's Laboratory Medicine Diagnosis of Disease in the Clinical Laboratory*.[16]

Table 28-2 Selected examples of blood collection tubes.

Cap Color	Content(s)	Comments and Uses
Red	None	Clotted blood or serum Most routine chemistries, blood bank, serology
Light blue	Sodium citrate	Acts as anticoagulant, plasma coagulation testing
Purple (lavender)	EDTA	Acts as anticoagulant Unclotted blood for hematology, genetic testing, immunosuppressants, red blood cell folate, HbA_{1c}
Green	Sodium/lithium heparin	Acts as anticoagulant heparinized plasma, whole blood, and bone marrow specimens
Gold with gel	Clot activator	Gel for serum separation after centrifugation; shorter clot time Most routine chemistries Do not use for toxicology or drug testing
Gray	Sodium fluoride ± EDTA or potassium oxalate	Fluoride inhibits glycolysis, allowing optimum glucose measurements EDTA and oxalate are anticoagulants
Yellow	Acid-citrate dextrose solution Blood bank studies, human	Anticoagulates blood and preserves cells during processing leukocyte antigen phenotyping
Dark blue	EDTA or none	Trace element determination

Sources: Modified from Laposata M. *Laposata's Laboratory Medicine: Diagnosis of Disease in the Clinical Laboratory*, 3rd edn. New York: McGraw-Hill, 2019; Bakerman S, Bakerman P, Strausbauch P. *Bakerman's ABC's of Interpretive Laboratory Data*, 5th edn. Scottsdale, AZ: Interpretive Laboratory Data, 2014.

Although oral infections are common, bacterial cultures are of limited value in dentistry. Often, all that is needed is a direct smear of the infected tissue of interest, such as fluid from a vesicle, abscess aspirate, or scraping from tongue or mucosal sites. Microbiologic cultures of soft tissue infections of the head and neck are frequently not performed because there is a mixed aerobic/anaerobic flora that is difficult to sample and to culture. For these infections in which a culture has been submitted, most laboratories will either give a diagnosis of mixed aerobic/anaerobic flora and/or list the three most predominant organisms. However, for severe infections such as osteomyelitis, acute parotitis, and cellulitis, culture and sensitivity should be performed. If cultures are to be submitted to a diagnostic laboratory, pus or tissue is the best choice of sample materials. Microbiologic swabs are convenient, but inferior to tissue and fluid. Tissue and fluid are essential for fungal and mycobacterial cultures. Moreover, if there is a possibility that an anaerobic organism is the causative organism, materials for culture should be submitted in anaerobic transport containers. Unless the antibiotic susceptibility of a bacterium can be predicted from its identity, a standardized battery of antibiotic susceptibilities is performed as part of the culture.

However, unless fungal and mycobacterial cultures are sent to a large reference laboratory, often susceptibilities will only be performed with specific antifungal or antimycobacterial drugs upon specific request.

In the clinical pathology area, molecular methods have probably made their greatest inroads in the microbiology laboratory. In many virology reference laboratories, molecular methods with their greater sensitivity have replaced viral cultures. Many companies are marketing polymerase chain reaction (PCR) tests that can be performed in small laboratories. Many of these kits can detect multiple organisms (multiplex) from one sample. However, there is a growing awareness that detecting several organisms in one sample means that the clinical significance of these results is often hard to determine. In quantitative PCR assays, used most frequently for determination of viral loads in blood or tissue, the variability is such that a $\log_{10}$ difference between two different samples is necessary before it can be assumed that there is a true difference between results. In addition, the results of two different quantitative PCR tests performed in different laboratories cannot be compared.

Infectious diseases are one area in which correlation of laboratory results—that is, those from the microbiology laboratory with those from tissue biopsies of the same site—is absolutely essential. With increasing degrees of immunosuppression and more powerful drugs, it is now recognized that organisms that were formerly considered colonizers or of low virulence can invade tissues and be pathogenic. This is especially true of the majority of fungi, which are considered opportunistic pathogens. For example, sinus material from patients with chronic sinusitis often grows *Aspergillus spp*. In immunosuppressed patients the finding of *Aspergillus spp*. does not help the clinician determine if the diagnosis is chronic fungal sinusitis or invasive fungal sinusitis with the accompanying possibility of dissemination to other sites. Only a tissue biopsy will provide definitive evidence of sinus fungal invasion. There are other situations in which culture will provide a definitive identification of an organism, but tissue is necessary for determination of the clinical significance of the organism. Examples include active *Candida spp*. infection from a smear of involved epithelium demonstrating the presence of hyphae; the presence of characteristic viral inclusions in tissues for diagnosis of viral invasion; and the presence of the agents of endemic mycoses in histologic/cytologic material, as cultures may take weeks to grow or fail to grow.

For those organisms that cannot be detected by the methods we have previously discussed, serologic methods are often valuable. These methods detect the presence of a specific antigen in a body fluid or the presence of specific antibodies directed against the organism. Unfortunately, for many exotic pathogens, serologic diagnosis depends on assays available only in large, reference laboratories or at facilities such as the Centers for Disease Control and Prevention (CDC).

Theoretically, the most specific methods for measuring antibody production detected against a particular pathogen depend on the detection of immunoglobulin (Ig) M for documentation of an acute infection or measurement of an antibody, usually IgG, at two different time intervals, weeks apart. In many cases, these measures are not practical: either the peak of IgM has passed, or it is unlikely that the patient will return for a second visit to the laboratory for a blood draw weeks distant for the initial clinic visit. In such cases, the clinician must depend on an assay that detects the absolute magnitude of the antibody response at the time of the clinic visit.

Healthcare providers may order laboratory tests by completing an appropriate medical order for the test. Many of the major laboratories have online systems to request testing and to view the results. In order to use these online systems, the clinician must register with these laboratories. In the United States, the cost of laboratory tests may be billed to medical insurance and this billing process may make the process of ordering tests cumbersome for dental providers. For instance, the ordering dental healthcare worker may not be a preferred provider with the medical insurance company. The definition of a preferred provider is a provider who has a contract with the patient's health insurer or plan to provide services at a discount. For nonpreferred providers, the fees charged for laboratory tests ordered may be costlier and the patient may be responsible for a larger portion of the charges than if the provider had been a preferred provider (in the network). The laboratory charges to the patient in a situation such as this may be prohibitive, and the patient may not proceed with recommended dental treatment secondary to the laboratory costs, or may be upset with the dental team when the bill from the diagnostic laboratory is received. In such cases, it may be more efficient and less costly for a patient with medical insurance to have the necessary laboratory tests ordered by their primary care physician. The dental healthcare worker should communicate with the physician when requesting labs and discuss the planned dental procedure and need for the test. Similarly, the physician will need to update the patient's medical records with the reasons the tests were ordered and share those results with the dental healthcare worker.

POSTANALYTIC PHASE OF LABORATORY TESTING

Laboratory results are reported with reference intervals, which are more commonly known as reference ranges. Reference ranges aid in the interpretation of laboratory

results. Reference ranges for each test are determined using the demographics of the presumed healthy population from which specimens were obtained and the specific methods and/or instruments used to assay these specimens. The use of population reference ranges is an inexact science, and factors such as age, sex, and ethnicity are generally not considered. Reference ranges are usually defined as the set of values that 95% of the normal population falls within (also known as a 95% confidence interval). Reference ranges can be influenced by many factors.

Laboratory values that are within the reference range do not assure health. Likewise, laboratory values that fall outside of the reference range may not confirm disease or indicate a problem. When multiple tests on an individual are performed, there is an increased likelihood that an abnormal value may be due to chance. Lab values outside of the reference range should be investigated when clinically or statistically significant. Reference range values may differ among laboratories. Laboratories that are accredited by the College of American Pathologists (CAP) are required to establish and/or validate their own reference values at least annually.[18] Variance in reference ranges from laboratory to laboratory may occur for a variety of reasons, such as the equipment used in the analysis, reagents used, site humidity, temperature differences, and other conditions.

Blood

Formed elements of the blood arise from a common pluripotent hematopoietic progenitor cell, which matures and differentiates to form the various cellular elements. These cells include erythrocytes (red blood cells, RBCs), leukocytes (white blood cells, WBCs), and platelets.

Of these elements, RBCs are the most numerous. RBCs are required for the delivery of oxygen to tissues and use the iron-containing protein hemoglobin to transport oxygen and carbon dioxide. RBCs, unlike WBCs, have no nuclei (anucleate).

Analysis of RBCs includes the volume of packed red cells (hematocrit), concentration of hemoglobin (Hb), and concentration of red cells per unit volume (RBC count; see Table 28-3). Additionally, three indices are used to describe the quality of the red cells sampled. These indices are the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Table 28-3 Red blood cell count.

Specimen	Traditional Reference Interval	SI Reference Interval
Female whole blood	3.9–5.5 $\times 10^6$ µL	3.9–5.5 $\times 10^{12}$/L
Male whole blood	4.6–6.0 $\times 10^6$ µL	4.6–6.0 $\times 10^{12}$/L

Hemoglobin Concentration

Hb is measured through spectrophotometric methods secondary to its intensely colored nature. Its main function is to serve as an oxygen carrier and it is found in a variety of forms within the blood. These forms include methemoglobin, oxyhemoglobin, carboxyhemoglobin, and other minor components. In order to measure Hb, whole blood is mixed with Drabkin's solution. Drabkin's solution contains sodium bicarbonate, potassium ferricyanide, and potassium cyanide, which causes a conversion of the Hb forms to cyanmethemoglobin. The light absorbance of cyanmethemoglobin is then measured using a spectrophotometer at 540 nm and the concentration of Hb is determined in grams per deciliter of blood (g/dL) (see Table 28-4). Whole blood samples are collected in a purple/lavender-top tube using EDTA (see Table 28-2) as the anticoagulant and may be rejected by the laboratory if the sample has hemolyzed or clotted. Hemolysis (hemolyzed samples) is defined as a pathologic breakdown process in blood of the RBCs. Hemolysis is typically accompanied by varying degrees of a red-colored tinge in serum or plasma once the whole blood specimen has been centrifuged.

As discussed previously, a subfraction of normal Hb is glycosylated hemoglobin or HbA_{1c}, which is formed during the maturation of the RBC. HbA_{1c} is normally about 4.0% of all hemoglobin in adults, but may be elevated to two or three times normal level in individuals with diabetes mellitus. During the maturation process of RBCs, a glucose molecule is attached to the Hb β-polypeptide chains through a nonenzymatic reaction. The rate of synthesis of HbA_{1c} is dependent on blood glucose levels and therefore monitoring HbA_{1c} levels gives a good indication of average blood glucose levels of the preceding 2–3-month time period. As such, these values have become useful in evaluating long-term blood glucose levels in patients with diabetes mellitus (Table 28-5).

Table 28-4 Reference range values for hemoglobin (Mass Concentration).

	Traditional Reference Interval	SI Reference Interval
Male whole blood	13.5–17.5 g/dL	135–175 g/L
Female whole blood	12.0–15.5 g/dL	120–155 g/L

Table 28-5 Reference range values for glycosylated hemoglobin.

	Traditional Reference Interval	SI Reference Interval
Whole blood	4.0%–5.6% of total hemoglobin	4.0–5.6 mmol/L

Table 28-6 Reference ranges for hematocrit.

Specimen	Traditional Reference Interval	SI Reference Interval
Male whole blood	41%–50%	0.41–0.50
Female whole blood	35%–45%	0.35–0.45

Hematocrit

The hematocrit (Hct) may be measured either using an automated counter or manually. Manual measurement entails centrifugation of anticoagulated whole blood and this is generally an accurate measure of red cell status. Generally, the anticoagulant EDTA is used and a sample is drawn into a purple/lavender-top tube (see Table 28-2). There are certain inherent technique errors in manual determination, though, that may affect the results. Specifically, manual determination measures red cell concentration and not red cell mass. This factor may be important when dealing with a patient who is hemoconcentrated as a result of shock or volume depletion. In these patients, red blood cell volume may be normal or high, but red cell mass would actually be decreased.

Automated measurement of Hct usually does not depend on centrifugation and the automated values closely parallel the manual values. The automated technique directly calculates the Hct through determining the red cell number and red cell volume. In this technique, red cell number multiplied by red cell volume equals Hct (Table 28-6).

Hct values are used in calculating the MCV and the MCHC.

As the amount of RBCs contained within the body is volume dependent, there are differing reference ranges for ages and sexes. Specimens may be rejected from the laboratory if they do not contain enough of a sample or if the sample has coagulated or hemolyzed before analysis.

Red Cell Indices

Red cell indices are useful when evaluating patients for anemias. MCV evaluates for the size of the average RBC, MCH evaluates for the weight of Hb, and MCHC evaluates for the amount of Hb present compared to size.

Mean Corpuscular Volume

The average volume of the RBC is measured through MCV (Table 28-7). This index is used in the classification of anemias. MCV may be calculated using the following formula:

$$\text{MCV}\left(\text{fL}\right) = \text{Hct}\left(\text{proportion or}\%\right) / \text{Number of RBCs}\left(10^{12} / \text{L}\right)$$

where fL = femtoliter and 1 fL = 1×10^{-15} L.

Table 28-7 Reference ranges for mean corpuscular volume.

Specimen	Traditional Reference Interval	SI Reference Interval
Whole blood	80–100 μm^3	80–100 fL

Many condition can increase the volume of the red cells, including folic acid deficiency, vitamin B_{12} deficiency, cirrhosis, and chronic alcoholism. Certain medications may also induce an increase in red cell volume, including phenytoin and some cytotoxic drugs. RBC volume may be decreased with chronic iron-deficiency anemia, thalassemia minor, and other anemias associated with chronic diseases, such as uremia and collagen-vascular diseases.

Mean Corpuscular Hemoglobin

MCH is the measurement of the average weight of Hb per RBC (Table 28-8). MCH is proportional to the size of the RBC and amount of Hb. MCH can be calculated using the following formula:

$$\text{MCH}\left(\text{pg}\right) = \text{Hb}\left(\text{g / dL}\right) / \text{RBC count}\left(10^{12} / \text{L}\right)$$

where pg is picogram and 1 pg = 1×10^{-12} g.

MCH is also used in classifying anemias. MCH is usually increased in macrocytosis and decreased in microcytosis and hypochromia.

Mean Corpuscular Hemoglobin Concentration

The average concentration of Hb in the average RBC is estimated through MCHC (Table 28-9). Thus, this value is dependent upon the amount of hemoglobin to the volume of RBC. MCHC is affected by conditions that affect the Hb or Hct values. The formula is:

$$\text{MCHC}\left(\text{g / dL}\right) = \text{Hemoglobin}\left(\text{g / dL}\right) / \text{Hematocrit}\left(\%\right)$$

Table 28-8 Reference ranges for mean corpuscular hemoglobin (Mass Concentration).

Traditional Reference Interval	SI Reference Interval
27–33 pg/cell	27–33 fmol/cell

Table 28-9 Reference ranges for mean corpuscular hemoglobin (Hb) concentration.

Traditional Reference Interval	SI Reference Interval
33–37 g Hb/dL	330–370 g Hb/L

Peripheral Smear

Evaluation of blood smears is important in determining whether hematologic disease is present. Alterations in the size, shape, and structure of individual cells can be noted. Peripheral smears have limitations, though, and cannot be used to diagnose anemias, but rather can be suggestive of anemias or other disease processes. Diagnosis of anemia must be made on Hb, Hct, or RBC counts. Additionally, visualization of sufficient quantities of normal platelets may help rule out certain disease states, such as myeloproliferative disease.

The cover-slip or wedge method may be used to prepare a uniform dispersion of blood for microscopic analysis. The blood smears are then stained with either Wright's or May–Grunwald–Giemsa stain. A properly stained slide will have a pink tint, with red cells showing orange and white cells showing purplish blue. The stained sample is then viewed under a light microscope under intermediate power.

Hypochromia or an increase in the central clear area of the RBC is due to poor hemoglobinization. Hypochromia is seen commonly in patients with chronic iron-deficiency anemia.

Polychromatophilia, caused by immature bluish cytoplasmic material and hemoglobin, is noted when there is an increase in the number of circulating RBCs. This activity is seen in patients with severe anemia secondary to blood loss, hemolysis, leukemia, myeloproliferative disease, and other diseases that cause immature forms of RBCs to be released into the systemic circulation. The presence of elevated numbers of macrocytes may suggest the presence of megaloblastic anemia or reticulocytosis—a release of immature forms of RBCs from the bone marrow.

Visualization of reticulocytes (Table 28-10) is not possible with Wright's or Giemsa staining and requires special staining techniques. Schistocytes, or broken RBCs, may also be seen in a peripheral blood smear of individuals with hemolytic anemias, malignancy, hypothyroidism, or alcoholism. Sickle cells are found in patients with homozygous sickle cell anemia.

RBC sedimentation rate and C-reactive protein (CRP) levels are useful in the presence or absence of inflammation. In inflammatory states, the concentration of certain plasma proteins, collectively known as acute-phase reactants, increases. CRP, a member of the pentraxin group of proteins, was the original acute-phase reactant. RBC sedimentation rate is useful in assessing certain patients. The erythrocyte sedimentation rate (ESR) is determined by measuring the rate of RBC sedimentation through a calibrated tube in a specified period of time, usually 1 hour (Table 28-11). The presence of certain acute-phase reactants, such as fibrinogen and haptoglobin, slows the sedimentation of the RBCs. Acute and chronic infections, malignancy, infarction, rheumatoid and collagen diseases, and physiologic stress cause increases in ESR and CRP. Although these tests are nonspecific, they are useful in the detection and/or monitoring of inflammatory conditions or to confirm the presence of organic disease.

Table 28-10 Reference values for reticulocyte count.

Traditional Reference Interval	SI Reference Interval
25–75 $\times 10^3/\mu L$	25–75 $\times 10^9/L$

Table 28-11 Reference values for erythrocyte sedimentation rate.

Traditional Reference Interval	SI Reference Interval
0–20 mm/h	0–20 mm/h

Platelets

Platelets assist in hemostasis through the release of serotonin and other vasoconstrictors and through the formation of a thrombus or temporary platelet plug. Abnormal number of platelets in circulation may result from chiefly productive or destructive forces.

Platelet counts are determined from whole blood (Table 28-12).

Thrombocytosis refers to a state of abnormally increased levels of platelets in circulation, usually above 400 $\times 10^3/\mu L$. Causes of thrombocytosis can be primary, reactive, or transitory. In primary thrombocytosis, platelet production may be increased up to 15 times normal and is due to the increased size and mass of megakaryocytes. Other cell lines may be involved and, when this occurs, the disease is characterized by clinical characteristics and the predominant cell line involved. An increase in predominantly megakaryocytes leads to essential thrombocythemia, with an increase in platelets but normal RBCs and normal to slightly increased WBCs.

Reactive thrombocytosis may involve increases in platelet production and release, and may be chronic or acute in nature. Acute reactive thrombocytosis may occur as a result of surgery, acute inflammation, or acute hemorrhage.

Transitory thrombocytosis occurs as a result of movement of platelets from the extravascular platelet pool. These

Table 28-12 Reference values for platelet count.

Traditional Reference Interval	SI Reference Interval
150–450 $\times 10^3/\mu L$	150–450 $\times 10^9/L$

extravascular pools include platelets from the spleen and lung.

The clinical findings in thrombocytosis are related to the underlying disorder and therefore patients are not predisposed to hemorrhage or thrombotic complications.

In patients with an acute recent reason for thrombocytosis, no treatment is generally necessary other than follow-up and observation. In patients with documented thrombocytosis of longer standing, an underlying disorder should be ruled out and the patient should be referred for an appropriate workup.

Thrombocytopenia is characterized by a decrease in the number of circulating platelets, usually below 100 $\times 10^3/\mu L$. Bleeding is the principal characteristic of this state, with patients having minimal symptoms with platelet counts of 50 $\times 10^3/\mu L$. Spontaneous bleeding can be observed in individuals with platelets at or below 20 $\times 10^3/\mu L$.

Thrombocytopenia may be caused by a decreased production of platelets, increased destruction, abnormal distribution, or through massive dilution.

Decreased production may be secondary to decreased megakaryocytes or ineffective erythropoiesis. Drugs, such as chemotherapeutic drugs, may also cause a decrease in platelet production. Diseases affecting bone marrow may also cause a decreased production of platelets. These diseases include leukemia and other malignancies, myelofibrosis, and viruses. Ineffective erythropoiesis may occur from suboptimal nutritional states, especially deficiencies of vitamins B_{12} and folate. Changes in other blood cell lines can also be seen when nutritional deficiencies are severe.

Increased destruction of platelets may occur from immune-related mechanisms. Typically, increased levels of immunoglobulin or complement can be found on these platelet membranes. These platelets are then removed by the reticuloendothelial system, largely the spleen. In certain cases, splenectomy is the treatment for immune-related destruction of platelets.

Abnormal distribution of platelets can occur when a significant portion of the circulating platelets are sequestered to the spleen. An enlarged spleen (hypersplenism) can be noted clinically. Lastly, thrombocytopenia may occur as a result of infusion of large quantities of whole blood in trauma or surgery patients. Additional platelet infusions are the treatment of choice in transfusion-related thrombocytopenia.

Analysis of White Blood Cells

WBCs defend the body against bacterial, viral, protozoal, and fungal invasion. WBCs are less numerous in blood and require less dilution to count after the predominant RBCs are lysed from the sample obtained. WBC counts may be falsely elevated in the presence of cryoglobins, aggregated platelets, and nucleated blood cells, or when there is incomplete lysis of RBCs. According to physiologic function, WBCs can be divided into granulocytic, monocytic, and lymphocytic categories. After WBCs have been counted, they are routinely analyzed to determine the percentages of individual cell categories (Table 28-13).

Granulocytes

Granulocyte production is influenced by a variety of factors, including interleukins, colony-stimulating factors, and growth factors. They arise from a progenitor cell line colony-forming units granulocyte/macrophage (CFU-GM), which differentiates into granulocyte (CFU-G) or monocyte (CFU-M) lines. Granulocytes are commonly differentiated according to staining techniques into three categories: neutrophils, eosinophils, and basophils.

Granulocytes undergo various stages of development within the bone marrow until they reach the metamyelocyte stage. In neutrophil maturation, the metamyelocyte nucleus forms a curved rod and this stage is called a "band" or "stab" neutrophil. Band neutrophils mature into segmented neutrophils, with a 4–8-day supply of segmented neutrophils called the marrow reserve. Metamyelocytes comprise approximately 45% of the maturation storage compartment of the bone marrow, while band neutrophils comprise 35% and segmented neutrophils comprise 20%. Eosinophils comprise 0%–5% and basophils comprise 0%–1%.

Table 28-13 Reference values for differential white blood cell count.

Traditional Reference Interval		SI Reference Interval
Differential count (absolute)		
Neutrophils	1800–7800/μL	1.8–7.8 $\times 10^9$/L
Bands	0–700/μL	0.00–0.70 $\times 10^9$/L
Lymphocytes	1000–4800/μL	1.0–4.8 $\times 10^9$/L
Monocytes	0–800/μL	0.00–0.80 $\times 10^9$/L
Eosinophils	0–450/μL	0.00–0.45 $\times 10^9$/L
Basophils	0–200/μL	0.00–0.20 $\times 10^9$/L
Differential count (number fraction)		
Neutrophils	56%	0.56
Bands	3%	0.03
Lymphocytes	34%	0.34
Monocytes	4%	0.04
Eosinophils	2.7%	0.027
Basophils	0.3%	0.003

Mature cells are released from the bone marrow sinusoids into the peripheral blood system. The blood system consists of equally large circulating and marginating pools. The marginating granulocytes adhere to the endothelial-lined walls of the blood vessels. Granulocyte reserves are also found in the spleen. Circulating granulocytes are in transit to a potential site of action within the tissues and travel from the circulatory system to the tissues through the process known as diapedesis. Both band and segmented (segs) neutrophil forms are found circulating in blood. Bands usually comprise approximately 3%–5% of total WBC count and segs comprise approximately 50%–70% of the WBC count. Although the presence of bands has been taken to mean the presence of infection, increased number of these cells are found in a variety of pathologic conditions. Moreover, there are a large number of technical problems associated with a precise determination of a band count. For these reasons, among others, many clinical laboratories no longer report band counts.

Segmented neutrophils are chiefly responsible for fighting bacterial infection.

Additionally, an increase in the number of neutrophils may be found associated with inflammation, myeloproliferative disorders, neoplasms, or hemolysis. Certain medications can also affect the number of neutrophils found in circulation and these medications include corticosteroids and lithium.

A decrease in the normal number of neutrophils may be associated with diseases of the bone marrow such as aplasia or hypoplasia. Medications such as antineoplastic agents or radiation therapy can also cause a decrease in the normal number of neutrophils. Sequestration of neutrophils can be caused by hypersplenism, while destruction of neutrophils may be caused by antigen–antibody reactions, antibody-mediated destruction, certain medications, and viral and bacterial infections.

When a larger number of immature neutrophils is found in the circulating blood (greater than 20% of normal value) it is termed a “shift to the left.” Immature neutrophil release may be indicative of a bacterial infection, toxemia, or hemorrhage. When a large number of mature neutrophils are present in the circulating blood, it is known as a "shift to the right" and may be indicative of megaloblastic anemia, liver disease, or iron-deficiency anemia. Once granulocytes and especially neutrophils reach affected peripheral tissues, they can begin the process of phagocytosis and trigger the immune system reaction. Eosinophils are granule-containing cells. The granules are of two types: azurophilic granules, which are nonspecific and found in all granulocytes, and specific granules. The specific granules are characteristically bright red when stained with eosin dyes. These granules, which contain major basic protein, eosinophilic cationic protein, and eosinophil-derived neurotoxin, have been implicated in the tissue damage observed in asthma and other allergic conditions. Elevation in the number of eosinophils is seen with allergic reactions, infections with roundworms and other parasites, and certain chronic mucocutaneous diseases such as pemphigus.

Basophils are also granule-containing cells. Their equivalent in tissue is the mast cell. Basophil granules have a high proportion of histamine and heparin. Loss of these granules (degranulation) occurs during antigen–antibody-mediated reactions. As a result of degranulation there is increased vascular permeability, vasodilatation, and smooth muscle spasm. Anaphylaxis is a severe life-threatening reaction associated with massive basophil degranulation. Leukotrienes mediate this degranulation process.

Monocytes

Mononuclear phagocytic cells are composed of monocytes, macrophages, and their progenitor cells. These cells all arise from CFU-GM, and CFU-GM cells then develop into either CFU-G or CFU-M cells.

Monocytes typically have a large indented or oval nucleus that is centrally located within the cell. When visualized utilizing Wright’s stain and a microscope, a monocyte will contain a large area of light-blue–gray cytoplasm and many fine granules. These granules contain peroxidase. Monocytes are found in the bone marrow and the peripheral blood. Peripheral monocyte cells have a circulatory half-life of 8.5 hours. Monocytes in the blood and connective tissue are capable of differentiating into macrophages. These macrophages are normally nonmotile, but may become activated as a result of the inflammatory process. When this occurs, these motile macrophages are known as free macrophages and they move to the area of inflammation through a process of chemotaxis. These macrophages then phagocytize particulate matter. This ability to become mobile and phagocytize particulate matter makes macrophages an important part of the cellular defense mechanism. They differ from neutrophilic granulocytes, the first line of defense against infections, in that monocytes and macrophages are seen as a second line of defense.

Lymphocytes

In addition to the nonspecific activities of monocytes, macrophages, and granulocytes, lymphocytes also play a role in defending the body. The lymphocytic defense system differs, though, in that it is specific; that is, it is acquired and involves the formation of specific antibodies and lymphocytes, which in turn attack specific invaders. Active immunity occurs when an individual recovers from a natural infection and

Table 28-14 Reference values for immunoglobulin (Adult).

	Traditional Reference Interval	SI Reference Interval
Immunoglobulin A	50–350 mg/dL	0.5–3.5 g/L
Immunoglobulin D	0.5–3 mg/dL	5–30 mg/L
Immunoglobulin E	10–179 IU/mL	24–430 μg/L
Immunoglobulin G	600–1560 mg/dL	6.0–15.6 g/L
Immunoglobulin M	54–222 mg/dL	0.5–2.2 g/L

has a reduced susceptibility to acquiring the disease again. Active immunity can also occur through vaccination, in which the body's immune system is stimulated into producing protective antibodies against the specific disease targeted. Passive immunity occurs when sensitized cells called lymphocytes or antibodies to the specific target disease are injected into a host.

In understanding specific immunity, it is necessary to review the humoral and cell-mediated branches of specific immunity.

Humoral Branch

Humoral immunity involves the development of circulating antibodies to a specific corresponding antigen, which is a substance that is capable of invoking an immune response. These antibodies are known as immunoglobin and consist of five subtypes (Table 28-14). IgG is the most predominant in the serum and is able to cross the placenta. As such, it is important in conferring passive immunity from mother to child. IgE is important in allergic reactions. Other immunoglobins are IgM, IgA, and IgD.

Antibodies combine with a specific antigen causing a specific reaction to occur, such as cell lysis, agglutination of the invading cells, or triggering of complement formation. These antibodies may also activate anaphylaxis, causing mast cells and basophils to release their contents in an effort to immobilize the invading cells. Most antibodies are produced by the plasma cells. Plasma cells may reside in the lymph nodes or spleen or may be found in lymphoid tissue in the gut. Plasma cells originate from B lymphocytes. B lymphocytes arise from cells in the bone marrow and undergo maturation in an unknown location in mammals, possibly the bone marrow itself. The maturing B lymphocytes are known as B lymphoblasts, and these cells may develop into either plasma cells or memory B lymphocytes. The memory B lymphocytes are involved in a stronger secondary immune response, which occurs when the antigen interacts with the host at a later date.

Cell-Mediated Branch

T lymphocytes are responsible for the cell-mediated branch of the immune system. T lymphocytes arise from a stem cell in the bone marrow and migrate to the thymus, where they mature. During this maturation process, T lymphocytes develop surface receptors, which makes them capable of reacting to a specific antigen.

T lymphocytes constitute about 80% of the lymphocytes found in circulating blood and have a long survival. Generally, these lymphocytes are found in the lymph nodes and spleen and recirculate between these areas and the blood. Approximately 5% of total lymphocyte mass can be found in circulating blood.

T lymphocytes are further classified into functional subgroups through the use of monoclonal antibodies against specific T lymphocyte–associated antigens. Two of the most commonly used markers for functional categorization are CD4 (cluster of differentiation) and CD8 markers.

CD4 cells have an inducer function and signal B lymphocytes to produce antibodies. CD4 cells also are the primary cells infected by the human immunodeficiency virus (HIV). During the course of HIV disease there is an absolute decrease and dysfunction in the number of CD4 lymphocytes. As such, CD4 cell count is widely used to assess disease management, prognosis, and staging of HIV. Certain opportunistic infections, including opportunistic infections of the oral cavity, are correlated with decreased CD4 cell counts.

CD8 lymphocytes have a cytotoxic function, which may suppress CD4 cells or may inhibit B-cell differentiation. Both these activities may inhibit antibody production.

A normal CD4:CD8 ratio is approximately 2:1 and may be reversed due to certain diseases.

The absolute lymphocyte value is the total number of lymphocytes over the total number of WBCs. The relative number of lymphocytes is determined from a blood smear and is reported as a percentage, with a normal range of 22%–40%.

Lymphocytopenia occurs when there is a decrease below the normal range in the number of lymphocytes. Typically, bacterial and viral diseases may cause lymphocytopenia.

Lymphocytosis occurs when the blood lymphocyte count increases above the normal reference range. This condition is also associated with viral, bacterial, and some parasitic infections. Additionally, it may occur as a result of drug reactions or tertiary or congenital syphilis. Malignant conditions such as lymphocytic leukemia, lymphoma, Waldenström's macroglobulinemia, and other neoplasms may also cause lymphocytosis.

DIAGNOSTIC ORAL PATHOLOGY

Lesion Description

When suspicious lesions are noted during a clinical examination and clinical diagnosis is not possible, diagnostic pathology is the gold standard for diagnosis. For soft tissue lesions, the specific location and distribution

(i.e., tongue—dorsal, lateral, ventral, gingiva, buccal mucosa, floor of mouth, keratinized vs. nonkeratinized mucosa), size and number of lesion(s) (greatest dimension of length, width, and surface elevation measured in centimeters), morphology (elevated, depressed, flat), color (red, white, pigmentation), texture (velvety, smooth), and consistency (soft, fluid-filled, firm) are documented. A clinical photo provided along with the description is beneficial for lesion documentation and also of use in evaluating lesion activity or the response to treatment. Each clinical photo is a snapshot in time and the lesion can change (regress, mature, elevate, or ulcerate). Photographs taken at recall or follow-up appointments afford the opportunity to monitor changes in the lesion or response to therapy. Soft tissue morphology, such as fluid-filled (vesicle, bulla, and pustule), elevated mass (papule, nodule, and tumor in order from small to large in size), and surface consistency (plaque, erosion, ulcer, and macule) should be included as lesion descriptors. Vesicles are small blebs or sacs with clear or amber-tinged fluid like serum. Bullae are larger, blister-like sacs that may contain fluid that is serosanguinous or tinged with blood.

Clinical Adjuncts to Diagnosis

To facilitate early diagnosis of malignant and potentially malignant oral mucosal lesions, a number of techniques and devices have become available. Exfoliative cytology, full-thickness (transepithelial) cytology, liquid cytology (taking advantage of the discohesive nature of epithelial malignancy and subsequent molecular diagnostics), lights of varied spectra (from blue to amber green to bright white) to assess either a better visualization, tissue reflectance, or light absorption, and autofluorescence techniques now exist.

Liquid-based cytology is a relatively new method of cytology. It has chiefly been used for the Papanicolaou (Pap) test, but is also used for detecting oral cancer. Typically, a collecting device or cytobrush is directed over suspicious oral mucosal sites. The collecting device is placed in a preservative and sent to the pathology laboratory. The benefits of using liquid-based cytology are that cellular debris such as mucous, blood, and other debris can be discarded more easily. Liquid-based techniques also reduce the proportion of unsatisfactory samples through carefully producing thin layers of the cell on the microscope slide. This reduces the number of false negative results.

Chemiluminescence is the emission of light of varying degrees of intensity and time from a chemical reaction. These properties of light are used to aid clinicians in detecting early asymptomatic precancerous and cancerous lesions in the oral cavity. ViziLite Plus with TBlue is a commercially available diagnostic tool that uses chemiluminescence to aid in detecting oral cancer. Patients rinse with an acetic acid solution before the clinician examines the mucosa for abnormalities using a special disposable mirror light device. MicroLux DL manufactures a similar system and also markets OraBlue Oral Lesion Marking System, a toluidine blue dye kit.

Autofluorescence occurs when certain biofluorophores found within tissue fluoresce upon exposure to a light source with a wavelength between 400 and 460 nm. Diseased tissue does not fluoresce and appears darker in color than nondiseased tissue. The VELscope Vx Enhanced Oral Assessment System is a commercially available device to visualize tissue autofluorescence in the oral cavity. OralID markets a similar light source device. OralID's fluorescence technology uses a blue light with a wavelength of 435–460 nm.

These adjunctive techniques, while designed primarily for early detection, have encouraged practitioners to look closely at suspicious lesions, and may convince the patient and often the clinician that a biopsy is appropriate or that the patient should be referred for biopsy. These techniques do not substitute for biopsy diagnosis. However, those adjuncts that employ molecular diagnostics are promising in assisting in early diagnosis. Loss of tissue autofluorescence in narrow-band imaging can indicate the full extent of a malignant mucosal lesion when planning the surgical biopsy.

In a report published in the *Journal of the American Dental Association*, an ADA expert panel suggests that adult patients with seemingly innocuous or nonsuspicious oral mucosal lesions of unknown diagnosis should be followed up on periodically to determine the need for further evaluation. Lesions that do not resolve should be biopsied or the patient should be referred to a specialist. Furthermore, the panel does not recommend cytologic adjuncts for seemingly innocuous or suspicious lesions. Clinicians may use adjunctive cytology for additional lesion assessment should a patient decline a biopsy, or they may refer to a specialist. The panel did not recommend autofluorescence, tissue reflectance, or vital staining adjuncts for the evaluation of potentially malignant disorders among adult patients with clinically evident, seemingly innocuous, or suspicious lesions.[19]

Patton and coworkers performed a systemic review of adjunctive techniques for oral cancer examination and lesion diagnosis. They concluded that, due the lack of data on the effectiveness of adjunctive cancer-detection techniques in general dental practice settings, clinicians must rely on a thorough oral mucosal examination, supported by specialty referral and/or tissue biopsy for oral premalignant and malignant lesion diagnosis.[20]

Clinical Assessment

Tissue biopsy is recommended when there is a concern for malignancy. It is also recommended when pigmented lesions are noted or these pigmented lesions have irregular borders. In some cases, the lesional characteristics of appearance, anatomic location, duration, and distribution, when coupled

with patient history, may be sufficient for clinical diagnosis. Examples of lesions that can be diagnosed and treated without a biopsy include pericoronitis, gingivitis, or periodontal abscesses. The response to therapy (or lack of response) is also informative as a lesional feature. There is the risk of modifying key diagnostic clues when therapy is rendered without a biopsy. If the lesion does not heal, and a subsequent biopsy is performed, histologic diagnosis can be more challenging due to the change in diagnostic features caused by the treatment. For example, a lesion that has inflammation as a critical diagnostic feature will be modified by a corticosteroid, but not necessarily adequately treated. There is value to the adage that you should be certain of what you are treating. However, benign-appearing lesions can share the clinical characteristics of other, more ominous entities. The persistence and change in size, color, or texture of a clinical abnormality warrant close follow-up and biopsy.

Ulceration (tissue loss that extends into the lamina propria of mucosa or dermis of the skin) and erosion (a superficial loss of epithelium) are quite common findings in the oral mucosa. Assessment of duration and distribution (keratinized attached mucosa versus nonkeratinized loose mucosa) of the ulcer has diagnostic implications. Clinical provocation that elicits a positive Nikolsky sign (the tissue slides laterally with sheer pressure applied to normal-looking mucosa adjacent to an erosion) characteristic of vesiculobullous disease requires a special biopsy technique. The biopsied tissue should be submitted in appropriate tissue fixative that preserves antigenicity (phosphate-buffered saline—Michel's/Zeus fixative) in addition to sampled tissue submission in 10% neutral buffered formalin. If tissue slippage/blade drag is noted during scalpel biopsy, use of a traction/stabilizing suture can assist in keeping tissue intact.

Areas of atrophic red mucosa and a white pseudomembranous covering on mucosa often represent variants of oral candidiasis, a diagnosis that should be considered in immunocompromise, diabetes mellitus, history of corticosteroid and other immunosuppressant use, broad-spectrum antibiotic use, xerostomia, and poor nutrition.

By informing/alerting the pathologist to the medical condition of the patient, fungal stains can be ordered at the same time as the standard hematoxylin and eosin (H&E).

Mucosal ulcers with rolled or umbilicated margins may represent entities as varied as squamous cell carcinoma, deep fungal infection (histoplasmosis, mucor/phycomycosis), syphilis, tuberculosis, or traumatic ulcerative granulomas. Any supporting history aids the pathologist in the selection of histochemical stains to highlight organisms when granulomatous inflammation is observed. Various polishing agents utilized in dentistry can be embedded in gingival tissue and the resulting granulomas will reveal polarizable material under polarized microscopy.

Anatomic Pathology Laboratory

The anatomic pathology laboratory provides consultative assistance when oral cytology and biopsy are required for diagnosis. The biopsy requisition form is the formal consult for a pathologic diagnosis. As such, as much supporting patient information (habits, medication/nutraceutical, family and medical history, imaging, and blood laboratory analyses when appropriate) should be included or accompany the requisition. Good-quality clinical photos are a plus when showing the anatomic location and lesion characteristics.

Oral cytology is commonly used to identify suspected fungal infections and herpetic infections. For exfoliative cytology, a moistened tongue blade, cytobrush, or moistened cotton-tipped applicator are scraped or rubbed over a leukoplakic, erythroblastic, or normal-appearing tissue (if burning mouth is evident). The collected material is placed on a microscopic slide and fixed with cytospray (or simply hairspray as an inexpensive alternative) and forwarded to the laboratory with a request for periodic acid–Schiff (PAS) staining for suspected fungal infection. Mark or label the surface where the specimen is placed with the frosted side up when placing the patient's name and oral site. Pencil marks are preferred for labeling, as they will not be dissolved (like ink) by lab preparation. PAS will stain viable organisms and Grocott–Gomori's methenamine silver (GMS) will stain nonviable organisms. The lab will report cell presence and fungal yeast and hyphal form presence if noted on microscopic examination.

A Tzanck prep or smear is used for suspected herpetic lesions when vesicles are noted clinically. For the smear, the vesicle is burst with a sterile anesthetic needle and the vesicle fluid and constituent cells are dispersed in the middle of an oriented microscopic slide. Cytospray is used to fix the fluid and cellular content. The slide is sent to the lab in a sleeve or carrier designed for slide transport to prevent breakage. A request for a Pap or Diff-Quik stain for a suspected viral lesion should accompany the slide on the requisition form. These stains will highlight ballooning degeneration and molded nuclei characteristic of herpetic viral infection. Tzanck smears will not distinguish between infections due to *Herpes simplex* and those due to *Varicella zoster*.

Biopsy

A biopsy is a surgical procedure undertaken to definitively diagnose abnormality or disease within a tissue. Biopsy is required when the clinical appearance and patient history are insufficient for clinical diagnosis. Biopsy involves sampling live tissue by scalpel, punch, or fine needle aspiration in an area of perceived deviation from normal. Accurate

diagnosis is dependent upon being able to discern a site that is outside of that considered normal, rather than random sampling of apparently normal-looking tissue. Normal-appearing oral mucosa is sometimes biopsied to diagnose minor salivary gland inflammation in Sjögren's disease and amyloid deposition around blood vessels in suspected amyloidosis. The surgical procedure involves prudent choice of anesthetic placement and careful manipulation of the sampled tissue to minimize introduction of anesthetic or surgical artifact (such as edema, crush, or clamp artifact by tissue forceps, or tissue cautery by electrosurgical and laser units). Traction or stabilization sutures minimize clamp and crush artifact. A suture is placed in the lesional tissue and tugged to facilitate the scalpel or sharp scissor biopsy. Stabilization sutures assist in keeping epithelium and connective tissue adherent in vesiculo- or immunobullous disease when the tissue slides (positive Nikolsky sign) during the scalpel biopsy (blade drag).

Tissue fixation is a means of preservation of the constituent cells in a "life-like" state for subsequent embedding and thin sectioning. Fixation limits autolytic processes and tissue necrosis that would alter the normal morphologic architecture of the cells. Fixation stabilizes the tissue for transport or storage. Many fixatives are available, but for routine H&E stained slides, 10% neutral buffered formalin is most commonly used. When antigen preservation is necessary in presumed immuno-bullous diseases (pemphigus, pemphigoid, erosive lichen planus), then phosphate-buffered saline fixatives such as Michel's or Zeus solutions are used to avoid antigen degradation by formalin. Optimal cutting temperature (OCT) fixative is utilized in frozen section preparation, as it limits freeze artifact that would be created by snap-freezing tissue. Frozen section is used in hospital settings and dermatology labs when a rapid diagnosis and margin adequacy are required in cases of suspected malignancy. The volume of the chosen fixative and specimen thickness are critical considerations in insuring adequate fixation pressure for appropriate tissue penetration. The volume of fixative should be at least 10 times that of the tissue specimen and the specimen thickness the size of a nickel coin (~2.0 mm).

Decalcification of hard tissue specimens (bone, teeth) is accomplished in the lab receiving the tissue. Hard tissue specimens require additional processing time because of the necessary decalcification. Oral and maxillofacial pathology laboratories and hospital laboratories have this capability.

Embedding in paraffin (hard wax) is done in the chosen lab. This will further preserve tissue and provide sufficient rigidity for ease of cutting thin tissue specimens on a microtome for subsequent staining and use of light microscopy.

H&E can be the singular stain or the initial scout stain. H&E will elucidate basophilic organelles (hematoxylin) and acidophilic (eosin) organelles within the cell. Abnormalities noted on H&E staining in collagen content, surface organisms, cytoplasmic content, and mucin production would necessitate additional special staining to highlight or decorate those abnormalities. The additional stains necessary for diagnosis take time and the diagnosis may be delayed a short while.

Biopsy Technique

A biopsy can be performed on soft tissue or hard tissue and is excisional or incisional, depending upon whether all or a portion of the lesion is removed. The biopsy technique will employ a scalpel, shave, punch, needle aspiration, or scissors when a pedunculated lesion is encountered.

The excisional biopsy is the technique for total removal of the lesion and is most often used when the lesion is less than 1.0 cm in size (see Figure 28-3A), while the incisional biopsy is a sampling of a portion of a lesion greater than 1.0 cm in size for diagnosis prior to more extensive surgery (see Figure 28-3B). These parameters are altered based on the skill of the clinician and the anatomic location of the lesion.

In the shave biopsy, a sharp instrument shaves the surface lesion. Shave biopsies are often performed on skin or mucosa as a "scout" procedure used to plan completion surgery.

The punch biopsy is akin to a "cookie cutter" technique done on broad, flat surfaces. The punch instrument was designed for small skin and mucosal biopsies, but is often used to uncover dental implant fixtures. The punch biopsy technique is effective for removal of small lesions for excisional biopsy. A core or needle biopsy can be used for tissue core cell collection (like a large-bore needle, or the biopsy gun used for breast and testicular lesions) and fine needle aspiration can be used for fluid content assessment and flow dynamics evaluation of vascular lesions. Fine needle biopsy is beneficial in diagnosing salivary gland and thyroid masses. The cells collected by the minimally invasive technique are assessed much like a cytologic smear. The fine needle insertion into the lesion can be guided by ultrasound or other imaging modalities.

Needle aspiration is required in radiolucent bone lesions in suspected vascular processes to assess whether the lesion is high flow or low flow, prior to attempting extractions or bone biopsy. Bone biopsies require surgical handpieces and burs, or Rongeur forceps and osteotomes for the removal of hard tissue.

The following description will focus on the soft tissue scalpel biopsy, as the principles are similar to many of the other sampling techniques.

After administration of anesthesia—block anesthesia is preferred—a gauze screen (like a hockey net at the back of the throat) is placed to prevent aspiration of the specimen. An elliptical incision is made with a #15 (small curved cutting

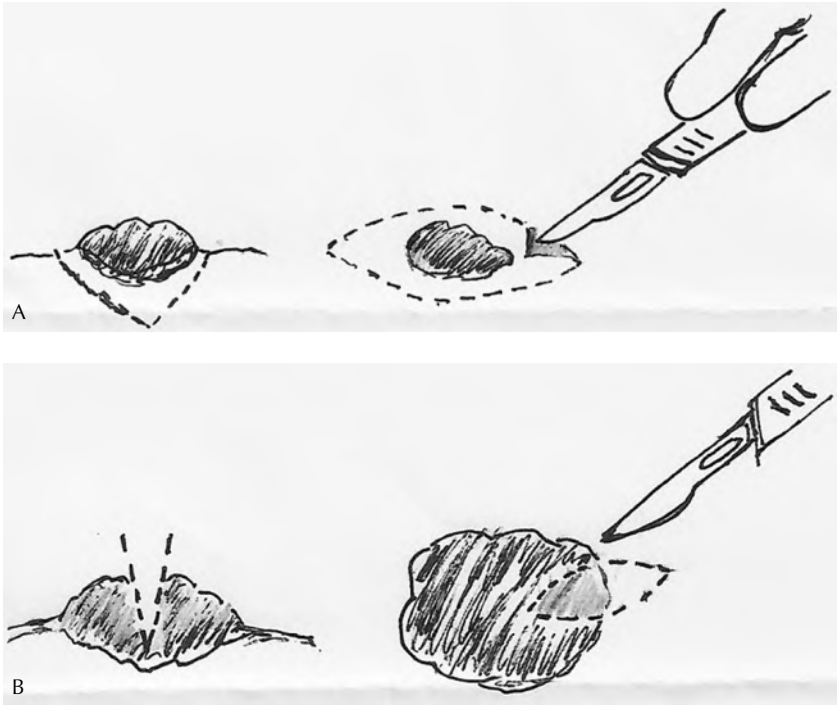

Figure 28-3 A. Excisional biopsy. B. Incisional biopsy.

edge) or #11 (elongated, triangular cutting edge) scalpel blade with tissue tension provided by tissue forceps, or to minimize crush artifact, a traction suture. The dimension of the incision is three times the length of the lesion and the same as the width of the lesion angled in toward the base like a "V." This helps facilitate wound closure. Curved Iris scissors can be used to free the tissue at the base. Hemorrhage control, wound cleansing, and suture closure completes the surgery. Silk suture is supple and less irritating than chromic gut, which is stiff and easily toyed with and often "untied" by tongue movement. Silk sutures do not resorb like chromic gut sutures and must be removed at a subsequent appointment.

The biopsy specimen can be placed on a surgical tray and anatomically oriented with a suture to the sterile card the suture was wrapped around, or it may be oriented with India ink. The specimen is placed in the formalin container, labeled with the patient name, biopsy location, and date taken. The container will have a volume of 10% neutral buffered formalin at least 10 times the volume of the biopsy specimen. This insures adequate fixation pressure. A thick specimen may require dimensional reduction, following appropriate orientation for the same fixation volume requirement. Sometimes several containers are necessary to avoid confusion about lesion location, especially when multiple sites are sampled.

A specimen that has characteristics of an immunobullous (vesiculobullous) disease should also have a portion of the fresh specimen placed in a container of phosphate-buffered saline (Michel's or Zeus solution) for antigen preservation, as the lab will need to do immunofluorescence testing. The special fixative permits the immunofluorescent stains to highlight or decorate where autoimmune attack has occurred in the tissue.

Thorough completion of the biopsy requisition form will eliminate delay of specimen processing by the referral lab.

Salivary Diagnostics

Once viewed solely as a quantitative and qualitative measure of salivary output from the exocrine tubuloalveolar intraoral minor glands and the paired extraoral major salivary glands, salivary diagnostics now encompasses a varied array of tests of infectious, autoimmune, hormonal, and malignant diseases.

For salivary output, tests would report whether salivary flow was stimulated or unstimulated and whole versus gland specific (typically parotid). Sialometry was the term for the assessment of this salivary output. In the normal state, rigorous chewing produced more saliva as necessary to improve oral mucosal lubrication and for food bolus formation. Enzymatic content of saliva began the digestive process and hormonal activity facilitated subsequent digestion activity in the gut.

In the interest of rapid, POC testing, the ease of collecting oral fluids has resulted in a myriad of noninvasive diagnostic

tests. Specific biomarkers have become available to examine the components of saliva in health and disease states.

The biocomponents of oral fluids (i.e., saliva, gingival crevicular fluid, mucosal transudates) include microbial agents (viruses, bacteria, fungi), hormones, antibodies, cytokines, proteins, growth factors, drugs, electrolytes, metabolites, and various tumor markers. Nucleic acid derivatives are present from human and microbial sources. The significance of the oral biomarker findings can only be determined when paired with other clinical and laboratory data.

CONCLUSION

Laboratory medicine will continue to play a major role in the fluid, ever-changing environment of medical diagnosis. Salivary, serologic, and tissue assessments biochemically, molecularly, and microscopically provide insight into overall patient health. As genetic research-driven technology advances, and new, efficient, and cost-effective diagnostic methods continue to evolve, the complex healthcare environment demands up-to-date methods in high-quality patient management. Complete patient information linked with laboratory testing in a timely and economically feasible fashion will facilitate that management. Informed and appropriately requested diagnostic tests from complete and specialized diagnostic laboratories will serve the provision of healthcare delivery by enhanced capability in diagnosing, treating, and preventing disease. Dental healthcare workers can achieve the recommendations of the 2015 Institute of Medicine on improving diagnosis in healthcare through effective teamwork in the diagnostic process, and through enhancement of healthcare professional education and training in diagnosis.

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29

How to Identify, Interpret and Apply the Scientific Literature to Practice

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More than ever, we are inundated with biomedical and other scientific information from varied and sundry sources. Such material is readily available and can today be retrieved by anyone with access to the internet. However, this type of access comes with a certain responsibility. The traditional publishing landscape is rapidly changing, with an increasing number of journals and websites purportedly providing trustworthy and reliable information.

There has been a rapid rise in the number of predatory journals—journals that will publish any article for a fee without proper peer review, claim to be indexed on different publishing databases, and assert that they have a system of measurement that implies scientific rigor, for example high impact factors, which turn out to be of their own creation or from dubious sources—and books that offer miracle cures and recommend strange and often dangerous medical practices and interventions. Many individuals get much of their medical information from health apps and social media postings, where pseudoscientific beliefs can gain a large following and be reinforced, which generates a culture of suspicion and distrust of recognized medical norms and healthcare professionals.

In order to provide faster exchange of research ideas and research findings, several websites have emerged where articles can be posted prior to being accepted or even prior to being peer reviewed (medRχiv: www.medrxiv.org; bioRχiv:

Burket's Oral Medicine, Thirteenth Edition. Edited by Michael Glick, Martin S. Greenberg, Peter B. Lockhart, and Stephen J. Challacombe.

www.biorxiv.org; Preprints: www.preprints.org). Information found on these websites must be evaluated, like all non-peer-reviewed materials. There obviously also exists access to trustworthy and reliable biomedical information, much of which can be retrieved for free (see below).

This changing publishing landscape puts the onus on the users of biomedical information, including oral healthcare professionals, to be able to formulate focused and precise clinical queries, utilize good and efficient search strategies to find pertinent information, and, last, be able to assess and synthesize the retrieved information in order to acquaint themselves with the best available evidence and put it into practice.

DEFINING AND ASKING THE RIGHT QUESTION

There are two facets to addressing the "right question": one when articulating a research question in order to identify an existing knowledge gap and generate research that can bridge this gap; and the other when searching for an answer to a clinical query in order to inform practice. This chapter will address the second aspect: how to formulate a clinical query to perform a thorough literature search and assess the trustworthiness and reliability of the available evidence to enhance patient care.

PICO Questions

A focused question should be relevant to a particular clinical scenario and articulated in a manner that can inform an appropriate search strategy. One approach, often utilized when performing a systematic review, is to parse a question into four different parts:

- The **p**atient, population, or health problem being addressed.
- The **i**ntervention or exposure being considered.
- The **c**omparison intervention or exposure.
- The clinical **o**utcome(s) of interest.

Framing a question in this manner is often abbreviated as a "PICO" question, where the "P" represents a patient, a population, or a health condition; "I" represents an intervention or an indicator; "C" represents a comparison or control; and "O" represents an outcome. Sometimes a "T" is added—PICO(T)—representing a **t**ime element or even a **t**ype of study.

A simple example that illustrates a PICO(T) question is assessing the outcome of treating patients with aphthous ulcers with systemic glucocorticosteroids (GCS). Patients with major aphthous ulcers (Patient) that are treated with systemic GCS (Intervention) are compared to patients not receiving systemic GCS (Comparison) to assess the healing of the aphthous ulcers (Outcome) during a time period ranging from 10 to 14 days (Time). This question can be made even more granular by, for example, including only male patients, who receive only a specific dose of systemic GCS, and comparing these patients with patients who receive oral mouth rinses containing GCS (Table 29-1).

PICO and similar frameworks need to be tweaked according to the type of question being asked. For example, clinical questions concerning therapy, prevention, diagnosis, prognosis, or etiology may have to be framed differently (Table 29-2). Utilizing a PICO(T) framework is also helpful when treating patients in order to formulate differential diagnoses.

Table 29-1 Example of PICO(T) questions and framework.

PICO(T) Item	Specifics	Example
P— patient, population, or problem being addressed	Patients' demographics, such as age, gender, and ethnicity, and overall health status Possible subcategory of the problem	Presence of major aphthous ulcers
I—intervention or exposure	What type of intervention is being considered? In case of medication, what is the dosage? How is the medication being dispensed and used (systemically or a mouth rinse)?	Treatment of major aphthous ulcers with systemic glucocorticosteroids
C— comparison intervention or control	The comparison may be no intervention, or an intervention with the same medication but with a different dosage	No medication
O— clinical outcome(s) of interest	What is the desired outcome? Are there undesired outcomes? Who will assess the outcome (the patient or the clinician)?	Healing of the major aphthous ulcer
T—time frame	Time from dispensing the medication to clinical examination	Patient is being examined by a calibrated examiner every 3 days

Table 29-2 Changes in the PICO framework depending on the type of query.

Question Type	P patient, population, or problem	I intervention or exposure	C comparison intervention or control	O clinical outcome(s) of interest
Diagnosis— discriminate patients with a disease or conditions from those without the disorder	Specific disease or condition	Diagnostic test or procedure, diagnosis by exclusion	Accepted reference standard for that disease or condition	Sensitivity, specificity, predictive values, accuracy, odds ratio, proportion of true positives, true negatives, false positives, and false negatives, likelihood ratio
Therapy—determining the effects (desirable and undesirable effects) of an intervention on relevant outcomes	Patient's disease or condition	Therapeutic intervention	Active intervention, standard of care, no intervention, or placebo	Resolution of the disease or condition, impact on quality of life, disease frequency and incidence rate
Harm and prevention— determining the effects of an intervention or exposure considered potentially harmful on outcomes relevant to patients (e.g., downsides or adverse effects)	Patient's general health condition and risk factors	Preventive measure, e.g., minimize drinking sugar-sweetened beverages	Another preventive measure, no intervention	Disease frequency and incidence rate, harmful effects
Prognosis— predicting the future course of a patient's recovery or aggravation from a disease	Patients with a disease or health condition	Presence of one or multiple prognostic factors	Absence of one or multiple prognostic factors	Survival rates, mortality rates, rates of disease progression
Etiology or causation— determining the origin of a disease or condition	Patients at risk of a disease or condition, or comorbidities	Presence of risk factors and the duration of exposure	Absence of risk factors or shorter duration of exposure	Disease frequency and incidence rate, rates of disease progression

PICO questions are often referred to as foreground questions, as these are more specific than background questions that address more general knowledge. Differentiating between foreground and background questions facilitates formulating a search strategy.

SEARCHING THE LITERATURE

When answering clinical inquiries, it is necessary to conduct an evidence-based literature search. Below is an outline of search strategies that will help the oral medicine practitioner retrieve the most useful information, as well as descriptions of the commonly used evidence-based resources.

The practice of evidence-based oral medicine begins with articulating a clinical question (see above), and then moves to conducting a literature search for relevant information, evaluating the evidence, and using that evidence to answer the clinical question in order to make a decision in a clinical setting.

The exponential growth of complex health information is why it is essential not only to learn how to search for the best evidence-based literature in effective and efficient ways, but to be able to evaluate that literature as well. In order to conduct complex literature searches (such as the literature searches required to conduct systematic reviews), it can help to work with a librarian or other information professional.

Search Strategies

Begin with a broad search, using only a few terms, and do not apply any search filters. There are several databases and resources available that are populated with clinical practice guidelines, synopses, systematic reviews, primary studies, and other information (Table 29-3). (Tip: Use nouns as search terms rather than adjectives to retrieve literature that contains quantifiable results.) If researching a clinical question, the PICO framework (see above) components of population and intervention are useful in determining initial search terms. To narrow results, add additional terms using Boolean logic (Figure 29-1). Next, employ search filters to limit results to relevant material—useful search filters include limits such as language, publication date, and study design type. If the search is retrieving too many results or too many irrelevant results, narrow the search by searching a specific field (e.g., title or abstract). Finally, if the results of the initial search are not relevant, try using Boolean logic to include synonyms (e.g., "pregnancy" for "pregnant women")

Table 29-3 Databases and other resources for searching the literature.

		Databases and Other Resources	Website	Cost	Specialty of Resource
Summaries and Guidelines	Comprehensive Resources	Epistemonikos	www.epistemonikos.org	Free, with limited full-text availability	Clinical practice guidelines, synopses, systematic reviews, primary studies, other
		Trip	www.tripdatabase.com	Free. A premium version is available to individuals via subscription	
	Point-of-Care Resources	UpToDate	www.uptodate.com	Only available via subscription. Access to the patient content is free	Summaries
		ClinicalKey	www.clinicalkey.com	Only available via subscription	
		Lexicomp	http://www.wolterskluwercdi.com/lexicomp-online	Only available via subscription	
	Guidelines	ECRI* Guidelines Trust	https://guidelines.ecri.org	Free; must sign up for free account to use	Clinical practice guidelines, guideline summaries
		ADA Center for Evidence-Based Dentistry	https://ebd.ada.org/en/evidence/guidelines	Free, with limited full-text availability	Clinical practice guidelines
	Preappraised Resources	Cochrane Library	www.thecochranelibrary.com	Only available via subscription	Primary research, systematic reviews
		PubMed	http://www.ncbi.nlm.nih.gov/pubmed	Free, with limited full-text availability	
		MEDLINE	http://www.ncbi.nlm.nih.gov/pubmed or http://www.ovid.com/site/catalog/databases/901.jsp	MEDLINE records are available within PubMed for free with limited full-text availability, or available via subscription on several different platforms	
		Embase	www.embase.com	Subscription based	
		Web of Science	https://apps.webofknowledge.com	Subscription based	
		Scopus	https://www.scopus.com	Subscription based	

*ECRI, formerly the Emergency Care Research Institute.

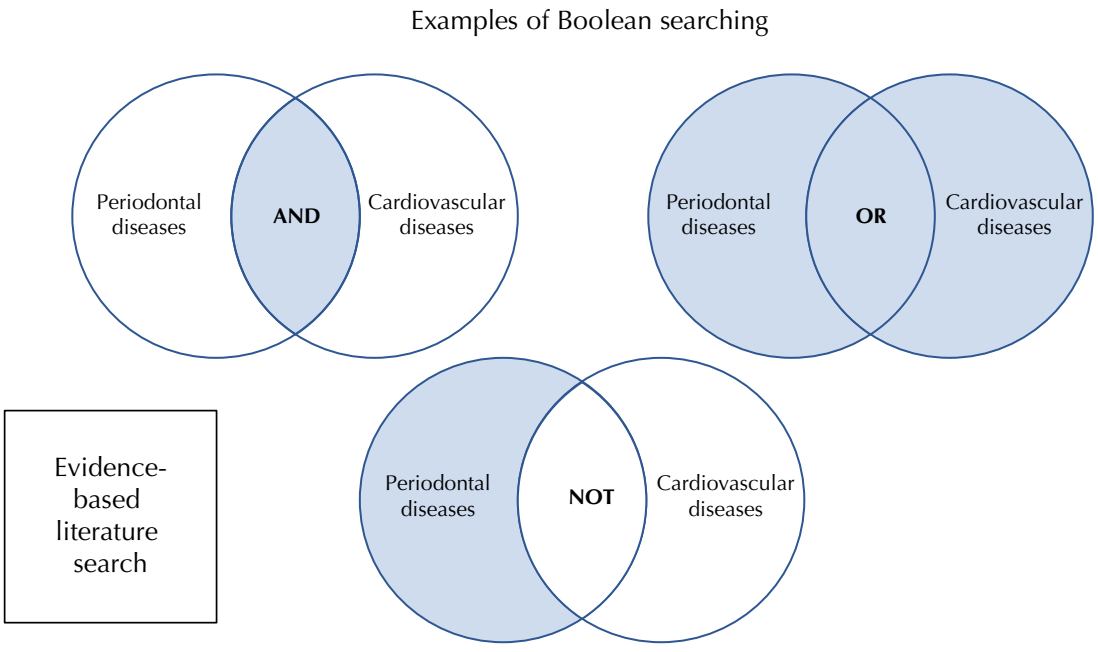

Figure 29-1 Boolean search.

and alternative spellings (e.g., UK and US spellings) for search terms.

Many medical databases use controlled vocabulary—the preferred terminology used within a particular database to describe and index materials. When conducting extensive searching, examine the databases' thesauri to identify synonyms for search terms. (Note: most medical databases will correct common misspellings, recognize abbreviations, and automatically search plurals.)

Databases and Other Resources

In order to conduct a thorough search for relevant information, search a combination of databases. Although the determination of which databases to search depends on the topic/question at hand, at a minimum search Cochrane (the gold standard for evidence-based information), Trip (the best "preappraised" resource), and PubMed (the most comprehensive medical literature search engine; see below for database descriptions and individual search tips). Search all three of these major databases in order to avoid missing relevant material; there is less overlap among these resources than one would assume, because they cover different types of materials and the material in each is updated on different cycles. Each of these databases has a unique underlying architecture, vocabulary, and results algorithm, and therefore will return different results.

A search strategy for evidence in order to decide a course of action within a clinical setting or answer a clinical question will differ from a search strategy for conducting a literature review or a systematic review. The latter are comprehensive, the former is not. If a search is being conducted to answer a clinical question, include high levels of evidence (e.g., guidelines or systematic reviews).

If an initial search results in too many irrelevant items, the following strategies may be useful:

- Limit the search to the title and abstract.
- Limit the results to secondary, preappraised literature such as clinical practice guidelines, summaries, critical summaries, and systematic reviews.
- If the search does not result in secondary literature, one strategy to narrow down the result of primary studies is to limit the search to randomized controlled trials (RCTs).
- If a search retrieves too many irrelevant results, searching using subject headings (rather than keywords) might prove to be a more efficient search strategy. Searching by subject headings will narrow the result of the search to only those items for which the subject heading in question has been considered (indexed) as the main topic of the item. Most of the databases listed here include specialized thesauri that list the subject headings used to index articles contained in the databases.
- At least preliminarily, set aside results published a decade or more ago.
- Add additional PICO components to your search terms, beginning with the outcome category.

Table 29-4 contains a list of databases that contain oral medicine–related information. An effective search strategy would begin with a search in Cochrane, followed by a search of Trip (particularly if Cochrane does not return relevant results), and then a search of PubMed to cover any potential gaps in results. Cochrane contains materials with high levels of evidence, such as systematic reviews, and is therefore an effective starting place. Because Cochrane only includes secondary materials, however, it is a smaller database than many of the others listed, and therefore may not contain all the information relevant to the topic being searched (including the most recent information). PubMed, by contrast, is the largest database listed, and will always retrieve the most results.

Begin with a search using a combination of keywords and subject headings in order to gather a sense of the results and to capture results that might be so new that they have not been assigned subject headings at the time of the search. Cochrane and PubMed share a thesauri of index terms—both databases use MeSH (Medical Subject Headings) for subject headings (see below for a detailed explanation of MeSH). Trip does not use a specialized thesaurus. After conducting the initial search, note any useful related terms and synonyms, and revise the search using all relevant search terms.

SELECTING THE RIGHT ARTICLE

Type of Clinical Information

Clinicians informing their practice using scientific literature are interested in answering questions directly related to their day-to-day activities. As mentioned before, such questions are classified according to their nature in four clinical areas:[1,2]

- *Diagnosis*: establishing the ability of a test to discriminate patients with a disease or conditions from those without the disorder.
- *Therapy or prevention*: determining the effect (desirable and undesirable) of an intervention on relevant outcomes (e.g., patient-centered outcomes).
- *Harm/etiology*: determining the effects of an intervention or exposure considered potentially harmful on outcomes relevant to patients (e.g., downsides or adverse effects).
- *Prognosis*: predicting the future course of a patient's recovery or aggravation from a disease.

Table 29-4 Workflow for searching for evidence.

Type of Question/Situation	Resources to Consult	Level of Evidence Available
Consider first: Does a guideline for the question/situation exist?	1) Epistemonikos 2) Trip 3) ECRI Guidelines Trust 4) Point-of-care resources	Guidelines, guideline summaries
Therapy/prevention question (general)	1) Cochrane Database of Systematic Reviews 2) Trip 3) PubMed	Critical summaries, meta-analyses, systematic reviews, randomized controlled trials (RCTs)
Therapy/prevention question (drug therapy)	1) Cochrane 2) Trip 3) Embase 4) PubMed	Critical summaries, meta-analyses, systematic reviews, RCTs
Harm/etiology question	1) Cochrane 2) Trip 3) PubMed	Critical summaries, meta-analyses, systematic reviews, observational studies
Diagnosis question	1) Cochrane 2) Trip 3) PubMed	Critical summaries,* meta-analyses,* systematic reviews,* cross-sectional studies, case report/series
Prognosis question	1) Cochrane 2) Trip 3) PubMed	Critical summaries,* meta-analyses,* systematic reviews,* observational studies, case report/series

* Indicates that this type of evidence may not be available for this type of question.

Table 29-5 Type of clinical questions and preferable type of study design.

Type of Question	Example	When Feasible, Preferable Study Design	Preferable Source of Information for Clinicians
Harm or etiology	What is the association between receiving dental radiographs and the occurrence of any type of meningioma?	Cohort *or* case–control studies	Systematic review including the appropriate type of study design for a clinical question
Diagnostic	What is the diagnostic test accuracy of autofluorescence devices when triaging a seemingly innocuous oral mucosa lesion for biopsy?	Cross-sectional diagnostic test accuracy studies	*or*
Prognostic	What is the impact of different radiation dose exposures of the parotid and submandibular glands in salivary flow 3 months post radiation?	Cohort studies	Evidence-based clinical practice guideline informed by systematic reviews, including the appropriate type of study design
Therapy or prevention	What is the effect of using a hyperbaric chamber for preventing osteonecrosis of the jaw in a patient's head and neck cancer undergoing radiation therapy?	Randomized controlled trials	

It is recommended that users of the literature correctly determine the type of question to address, as achieving this step will allow the question to be linked to the most appropriate study design (Table 29-5). When addressing therapeutic questions, experimental designs using chance (analogous to tossing a coin) rather than convenience to allocate participants to a treatment of interest that is compared with another active intervention, placebo, or no treatment are preferable (RCTs). In the absence of such experimental types of study, clinicians can also use nonexperimental or observational types of design. In this type of study, not chance but clinicians, patients and their preferences, or simply the circumstances determine the allocation of participants to treatment arms or an exposure.

In theory, one can also answer harm questions using RCTs; however, when a potential hazard is apparent (e.g., a serious, initially unintended adverse event), the intentional assignment of participants to the potential harmful intervention is not ethical. In this case, observational studies (cohort and case–control studies) are helpful to learn about the eventual harmful effect of an exposure or intervention that has occurred or will occur, without the need for the investigator to assign participants to the study arms.

As no diagnostic test is perfect, clinicians who want to learn about the performance or accuracy of diagnostic strategies for replacing a preexisting test because it is cheaper or less invasive, for triaging subsequent test applications (e.g., a positive result warrants further investigation to confirm diagnosis, while a negative result rules out the disease), or for adding on a new test to a preexisting diagnostic workout will choose a particular type of study design. Diagnostic test accuracy studies recruit participants with a suspicion of having the condition of interest and undergo an index test or new test, while also receiving a reference test or gold standard. Then, investigators report how often the index test is in agreement and disagreement with the reference test.[3]

Questions of prognosis examine the presence of factors that can positively or negatively influence the future course of action of a disease or condition, with the purpose of increasing the chance of achieving better outcomes. These studies include patients with and without a particular feature or prognostic factor (e.g., age, comorbidity, educational status, etc.) and examine the extent to which this factor influences a particular outcome in the future.

It can be inferred from the variety of clinical questions and study design indications presented here that the idea of a single "evidence pyramid" placing RCTs at the top of the hierarchy as the most suitable study to inform all clinical decisions is an oversimplification, as such a depiction ignores the idea that study design on its own is not a fair indicator of trustworthiness.[4] The traditional evidence pyramid is more appropriate for being applied to questions about therapy. Thus, it is strongly recommended to abandon the use of this evidence pyramid and replace it with a broader perspective, in which not a single primary study but rather a body of evidence (i.e., the group of studies informing the effect of an intervention of exposure on a particular outcome) is considered for decision-making. The certainty that clinicians can place in this evidence then not only focuses on the risk of bias of the studies at hand, but also the consistency across their findings (i.e., studies showing similar results), the precision of their estimates (i.e., width of confidence intervals), the relevance or directness of the study to the question at hand (i.e., appropriate generalizability or applicability), and the possibility for publication bias (i.e., the extent to which all studies conducted are made available irrespective of their results).[1,5,6] (For more details on study design, see Chapter 1: Overview of Clinical Research).

It is not uncommon that a new and somewhat controversial primary study attracts clinicians' and patients' attention, including presentations of the findings in media channels. However, clinicians should favor systematic reviews and evidence-based clinical practice guidelines over a single study, as systematic reviews and evidence-based clinical practice guidelines provide the full picture of all available evidence regarding a clinical question, making them more informative for the busy practitioner. In the same way that "one swallow doesn't make a summer," a single study outcome must be put in the context of the totality of the evidence before it is decided that a change in practice is warranted.

Causation, Association, and Correlation

Causation is important for clinical practice. Any practitioner trying to determine what is the best therapeutic strategy to treat a condition or disease, or looking for risk factors and studying their influence in the occurrence of a future event, is framing a causal question. Despite seeming simple, causal inferences are complex. In a hypothetical world where anything is possible, an investigator interested in studying the effect of the human papilloma virus (HPV) vaccine on the incidence of oropharyngeal squamous cell carcinoma (OSCC) will administer the vaccine to a group of participants, preferably a few thousand of them, and then perform follow-up assessments to determine how many did and did not develop OSCC. In this hypothetical world, the investigators would now time-travel back to the time before the vaccine was initially administered and enroll the same people who, in the first scenario, were vaccinated against the HPV virus and this time not administer the vaccine. The investigators would again perform follow-up assessments and determine how many did and did not develop OSCC. Thus, in these hypothetical scenarios, the same people were both vaccinated and not vaccinated and were essentially acting as their own control group. However, in the real world where one only has access to one side of the story at a time and the alternative scenario is missing and unobserved, this is called the "counterfactual dilemma."[7]

Since time-traveling remains possible only in theory, researchers will try all sorts of methodologic strategies to access that inaccessible alternative scenario. One strategy is to have a control group that could stand in for the second (unobserved) scenario. As inferred from the time-traveling idea, it is necessary to have a second observation—a control group—that is as similar as possible to the group receiving the experimental intervention. Hence, any time that two groups under comparison differ, the trustworthiness of an

association or causality claim weakens. Additional information on causality and its frameworks can be found elsewhere.[8]

The terms "causation" and "association" are often used interchangeably, but while causation implies association, the opposite is not true. For example, people who consume four or more cups of coffee a day have a lower risk of presenting with actinic cheilitis (AC). This does not mean that consuming coffee provides a protective effect from suffering from AC; rather, an alternative explanation would be that those consuming a larger amount of coffee a day usually work in indoor environments, such as an office, which dramatically reduces their exposure to direct sunlight, a known risk for AC. In this scenario, sunlight exposure is a confounder—that is, an alternative explanation for both the exposure (sunlight) and the outcome (AC)—for the association between coffee consumption and AC. Thus, a causal connection cannot be claimed, and the hypothesized association is spurious.

Nor can the terms "association" and "correlation" be used interchangeably. An association refers to one variable or clinical feature providing information about another variable or clinical feature. A correlation refers to one variable or clinical feature increasing or decreasing a fixed amount for a unit of increase or decrease of the other variable or clinical feature (Figure 29.2). Thus, "correlation implies association, but not causation. Conversely, causation implies association, but not correlation."[9]

A question for this section remains: Why do causation-related issues matter at the moment of selecting an article? When answering a question of therapy, for example, clinicians would prefer RCTs over analytic observational studies (e.g., cohort and case–control designs), and those analytic designs over case series, case reports, and other forms of anecdotal information. Thus, the ranking offered above (i.e., the traditional evidence pyramid) relates to the strength of those types of study design to establish causality. Study design by itself, however, is not sufficient as an indicator of validity or trustworthiness. It is necessary to determine the extent to which the authors appropriately implemented the methodologic measures required to minimize the effect of bias and confounding, while obtaining results with sufficient precision to draw meaningful conclusions.

BIAS, CONFOUNDING, AND RANDOM ERROR

Science is used to understand the world around us and attempts to predict outcomes or consequences of people's actions. To achieve these goals, answers from the literature must reflect an underlying reality or truth: a truth that can never be completely known, but one that can be surmised and approximated by using estimates and inferences. There are two main issues that deviate estimates from clinical studies from the truth: (1) bias and confounding; and (2) random error.

Bias and Confounding

Both bias and confounding result from systematic errors. Bias is the term used to describe reasons for studies deviating from the underlying truth (i.e., misguided estimation of the true effect of an intervention or exposure in an outcome) due to limitations in their planning and design, participant recruitment, conduct, data gathering, and analysis. The ways in which suboptimal methods distort clinical study results are numerous.[10] For example, in 1979 Sackett described more than 35 types of bias that may affect RCTs and 56 potential biases affecting analytic observational study designs (e.g., cohort and case–control studies).[11]

The presence of bias in the different study designs cannot be disregarded. For example, in studies answering questions of therapeutic or preventive interventions, one may claim

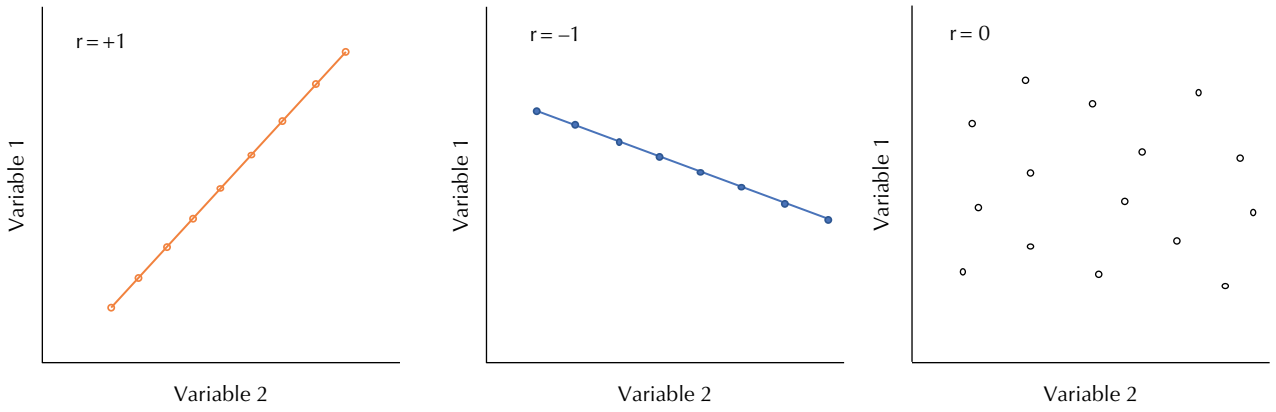

Figure 29-2 Illustration of correlations.

that a specific therapy is effective for managing or preventing a certain condition and implementing it. In reality, imbalances in prognostic factors at the moment of recruitment (e.g., the control group has more severe cases of the disease compared to the experimental intervention arm), while the study progresses (e.g., lack of blinding), or even at the end of the study (e.g., participants in the intervention arm lost to follow-up due to an adverse effect of the experimental intervention) can result in an overestimation of the treatment effect. In studies answering questions of prognosis, the presence of bias and confounding can lead to misguided predictions, which may induce either an overly optimistic or overly pessimistic assessment of a patient's fate. In the presence of a high risk of bias, studies answering questions of harm can conduce to an overestimation or, even more concerning, an underestimation of the adverse effects of an intervention or exposure causing deleterious consequences. Finally, studies implementing poor methodologic strategies and answering questions of diagnosis often report an overestimation of their accuracy.

These misleading estimates can cause two main problems in practice. The first problem is when test results define the patient as sick, while in reality they are not, exposing the patient to all the additional undesirable and unnecessary consequences associated with the cascade of clinical strategies resulting from establishing a definitive diagnosis and further treatment. The second problem is when the test results suggest that a patient does not have a disease, when in fact they do have it, delaying urgent treatment, allowing the disease to naturally progress, severely affecting prognosis, and in the case of an infectious disease resulting in not using strategies to mitigate contagion. (See Chapter 1: Overview of Clinical Research to learn more about the methodologic strategies implemented to reduce bias and confounding.)

Random Error

Even a study conducted with high methodologic rigor to minimize the influence of bias and confounding can still suffer from the play of chance, or random error. In previous sections of this chapter it has been mentioned that irrespective of how well-designed or powerful (i.e., large sample size and number of events, high signal-to-noise ratio) a study is, one will never be able to fully access the true effect of an intervention or exposure. This is the case because "chance is directionless, and it is equally likely, for instance, to overestimate or underestimate treatment effects."[2] In practical terms, this means that when two treatments or two exposure statuses are compared, any difference that the researchers find may simply be a reflection of the play of chance (e.g., by chance that day most patients recruited in the study were sicker than those recruited on other days, or they tended to report more adverse outcomes when asked about their health status). Investigators minimize the probability of being misled by random error by increasing the number of events and the sample size. Issues related to precision and random error will be covered in subsequent sections in this chapter.

INTERPRETING STUDY RESULTS

Outcome Measures in Clinical Research

According to Relevance

Patient-Important and Patient-Reported Outcome Measures

Conference speakers, investigators, and clinicians often refer to research findings as "clinically relevant" to distinguish them from "statistically significant" but "clinically irrelevant" results.[1] The term "clinically relevant," however, remains ambiguous. Does the use of the word "clinical" mean that such an outcome is important to the clinician or to the patient? The daily activities of a clinical practitioner can help us to better understand whose perspective may be of more value. Clinicians treat patients to achieve three broad goals: (1) increase longevity (at both person and tooth level); (2) decrease symptoms and the impact of a disease in people's life; and (3) to prevent future disease.[2] When evaluating whether clinicians have achieved these three goals, one may consider measuring outcomes that effectively reflect the degree of clinician success.[12]

Outcomes like mortality, survival, and the presence and absence of morbidities are of high relevance for both patients and clinicians, and likely as well as to society as a whole. These "patient-important outcomes" are often linked to diagnostic means and measures that make them fairly reliable, and also objective. This type of outcome is usually measured when defining success for goals 1 and 3 (i.e., increase longevity and prevent future morbidity). However, when trying to measure success for goal number 2 (i.e., decrease symptoms and impact of a disease), the patient perspective becomes particularly relevant.

One proposal to define such success is by using a type of "patient-important outcome" called a "patient-reported outcome measure" (PROM). PROMs are defined as "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else."[13] In other words, PROMs are a specific type of outcome that attempts to reflect the patient experience, and the patients' perspective is a construct or attribute to which only they can have access, and therefore only they can report. The evidence suggests that PROMs exhibit poor correlations with biomarkers,

clinician-reported outcomes, physiologic parameters, and laboratory tests.[12] The relevance of PROMs becomes more apparent when studying the latest definition of oral health by the FDI World Dental Federation: "Oral health is multifaceted and includes the ability to speak, smile, smell, taste, touch, chew, swallow, and convey a range of emotions through facial expressions with confidence and without pain, discomfort, and disease of the craniofacial complex."[14] Many components in this definition reflect abilities and functions that can only be understood and measured by directly accessing the patient experience and the impact that oral health has in their daily life (e.g., ability to speak, smile, smell, taste, touch, chew, swallowing, experiencing pain and discomfort).

Circling back to the initial question in this section, outcomes that are important to inform practice should be patient important, and the expression "clinically relevant" should reflect outcomes that are relevant to patients.[15] Thus, note the importance of moving from the use of clinician-centered terminology in favor of a patient- or person-centered perspective.[16]

Surrogate Outcomes Surrogate outcomes are indirect measures observed sooner than the definitive or patient-important endpoint. Researchers often use surrogate measures to make extrapolations about the impact of an intervention or exposure on a clinically meaningful endpoint.[17] For example, a significant reduction in plaque among patients using oscillating powered compared to side-to-side powered toothbrushes could be used by researchers to conclude that oscillating brushes may be more effective in reducing a patient-important outcome, such as periodontal disease. Measuring surrogate endpoints can be advantageous for researchers as they are typically observed quicker and are easier to measure than the patient-important outcomes. Thus, researchers can conduct shorter, smaller, and less expensive studies.[17,18]

Although measuring surrogate endpoints can be advantageous from an investigator perspective, there are some drawbacks associated with using them in clinical research. Many statistical methods have been developed to help researchers make extrapolations from surrogate outcomes; however, the impact of these extrapolations is still unknown.[17,19] Surrogate outcomes are typically measured in Phase II or proof-of-concept clinical trials, in an attempt to assess whether an intervention is biologically active, making them useless for day-to-day clinical decision-making. By contrast, Phase III trials are designed to provide definitive assessments of the effectiveness of an intervention. If Phase III trialists want to use surrogate endpoints as a valid substitute for patient-important outcomes, there must be evidence that the effects of an intervention on the surrogate outcome can reliably predict clinically meaningful effects on the final patient-important endpoint.[20]

Composite Outcomes Composite outcomes are a single measure of effect that combines two or more outcomes. Investigators may find these measures useful to avoid making an arbitrary choice among several available primary outcomes.[21] Additionally, the use of composite outcomes allows for increasing statistical power and precision owing to more events (i.e., increasing the occurrences of the outcome) and increased trial efficiency (e.g., smaller sample size, fewer resources). Another application of composite endpoints is in the presence of competing risks.[22] Last, from a clinical point of view, composite outcomes may be easier for patients to understand when participating in shared decision-making, by considering many relevant outcomes at the same time.[22]

The use of composite outcomes also comes with limitations. This is verified when the result from the composite outcome (i.e., overall result across outcomes) tells a different story than its individual components (i.e., suboutcomes contributing to the composite result).[21] Imagine a trial assessing the effectiveness of a chemotherapeutic drug compared to placebo for managing oral cancer. The researchers report a significant decrease in the composite outcome of "death and tumor shrinkage" in those receiving the drug compared to the placebo group. However, when examining each individual component of this composite outcome, it is clear that there is a reduction in tumor shrinkage, but no impact on death. The presentation of the research findings in a composite manner could be misguided, as it would imply that the drug had a significant impact on both tumor shrinkage and death, when in fact it showed no impact on death at all. Thus, clinicians using composite outcomes to inform practice need to take into consideration not only the aggregated composite outcome, but also each component.[23]

According to Type of Data

The data collected and used for research purposes can come in many forms, with binary, ordinal, continuous, counts and rates, and time-to-event data being the most common types. The study design and research question(s) defined by the investigators will usually dictate the type of outcome data that they will collect (Table 29-6).

Measures of Association Measures of association or effect are calculated using the different types of data listed above. Their purpose is to provide a quantitative estimation of the effect or association between an intervention or exposure and an outcome. Measures of association are usually expressed in relative and absolute terms.

Table 29-6 Type of outcome data.

Type of Data	Definition	Example
Dichotomous	Dichotomous or binary data is a type of categorical (grouped) data in which responses can take on one of two possible states.	Mucositis: yes or no Xerostomia: yes or no
Ordinal	Ordinal data is a type of categorical (grouped) data in which the categories have an inherent order.	Cancer grade (grade 1, grade 2, grade 3, grade 4) Caries lesion status (sound, initial, moderate, advanced)
Continuous	Continuous data is a measurement of numeric quantity and can take on any value in a specified range. The number can take on any value and be reported with any number of decimal places.	Weight Age Blood pressure
Counts and rates	Counts are the collective number of times that an event or outcome occurs in a population. Rates are a way of relating these counts to the amount of time that the population was at risk for the event. A rate is calculated by dividing the count by the total amount of time the people at risk for an event contributed to the study.	In a study of a novel surgical technique for treating oral cancer, the count or number of hospitalizations post surgery in patients who underwent the novel surgery was 20. The patients in this group contributed a total of 430 years of follow-up to the study (i.e., person-years).The rate of post-surgery hospitalizations among these patients was 20/430 = .047 per person-year or 4.7 per 100 person-years.
Time-to-event (TTE)	Time-to-event data captures the time it takes for an outcome to occur in a population.For each patient in a study, the event-free time is recorded. If that person experiences the event, this time is also recorded.	Time to infection with human papillomavirus among patients who received the human papillomavirus vaccine Cancer-free survival among patients treated for oropharyngeal cancer

- *Relative effects* (e.g., Risk Ratio [RR], relative risk difference (i.e., relative risk reduction [RRR] or relative risk increase [RRI]), odds ratio, hazard ratio), or the proportional effect of an intervention compared to another intervention or exposure and the lack of it on a health outcome, tend to remain consistent across populations and outcomes (Table 29-7).[26] For example, a recent systematic review evaluated the effect of corticosteroids for treating patients with symptoms of oral lichen planus.[27] In relative terms, their findings suggest that using topical corticosteroids in an adhesive base compared to a placebo may increase the risk of resolving pain complaints by 91% (RR 1.91, 95% confidence interval [CI] 1.08–3.36). This can also be presented as a twofold increased chance to resolve pain complaints when corticosteroids are compared to placebo. Topical corticosteroids offer this benefit to any patient presenting with lichen planus irrespective of the country of origin or setting around the world. Does the same hold true, however, when applied to more versus less severe cases? This is when the concept of absolute measure of an effect becomes relevant.
- *Absolute effects*, in a way, help clinicians to better contextualize the relative treatment effect to their practice, which makes them more relevant and, at the same time, less universal and yet more context specific (Table 29-8). Following the previous example in patients with lichen planus, it is known that 306 out of 1000 (or 30.6% baseline risk for reporting spontaneous pain resolution) of patients not treated with corticosteroids will experience spontaneous pain resolution. When applying the relative effect (RR 1.91) to that 30.6% baseline risk, a new risk is obtained, reflecting the potential benefit of using corticosteroids (30.6% multiplied by 1.91= 58.4%). Thus, we know that 584 out of 1000 patients receiving corticosteroids will also experience pain resolution. In absolute terms, the intervention would allow 278 more patients out of 1000 to achieve pain resolution compared to placebo after 8–9 weeks follow-up.[27]

Using relative and absolute estimates allows patients and clinicians to better inform care-related decision by providing the magnitude of the potential benefits and harms. The extent to which the magnitude of desirable or undesirable effects means something to a patient, to a point where an intervention or test is considered worthwhile or useless, is a matter of interpretation of that magnitude in the face of patients' values and preferences. In the next section, some of the strategies proposed to assist in the interpretation of the significance of research findings are discussed.

Clinical versus Statistical Significance

In an initial hypothetical study, researchers attempted to determine the rate of potentially malignant disorders (PMDs) in the oral cavity in two communities: community A and community B. They obtained statistically significant

Table 29-7 Relative measures of association.

Measure	Definition	Dental Example
Relative risk or risk ratio (RR)	The relative risk or risk ratio provides participants with an exposure or receiving a therapy with a measure of risk for developing a preidentified outcome. It does this by quantifying the proportion of participants who develop the outcome in the intervention group over all at risk in this group in comparison to, or divided by, the proportion of participants who develop the outcome in the comparison group over all at risk in this group. Risk ratios are presented in clinical trials and cohort studies, where the intervention is exchanged for an exposure. Relative risks cannot be presented in case–control studies because, in addition to other factors, there are no participants that are truly at risk in case–control studies and therefore the formula's denominator cannot be built.	When using therapeutic application of aloe vera (28 out of 31 total patients improved) versus placebo (21 out of 24 total patients improved), the relative risk of patients with lichen planus experiencing clinical improvement is RR = 1.03. This means that patients with lichen planus receiving aloe vera have 1.03 times the risk of experiencing a clinical improvement compared to patients not receiving aloe vera. Alternatively, this can also be presented as a relative risk difference (RRD), in this case, a relative risk increase (RRI) in the chance of experiencing clinical improvement. This means that patients with lichen planus receiving aloe vera can experience a 3% increase in the risk of having a clinical improvement compared to the patients not receiving aloe vera as an intervention.[24]
Odds ratio (OR)	Odds ratios are presented in clinical trials and observational studies, including both cohort and case–control studies. In clinical trials and cohort studies, the odds ratio quantifies the proportion of participants with the odds of experiencing a preidentified outcome in an exposed or intervention group over the odds of the outcome in an unexposed or comparator group. In case–control studies, the odds ratio is a proportion of the odds of participants with the outcome having an exposure compared to or divided by the odds of participants with no outcome, the comparison group, having the exposure.	When using therapeutic application of aloe vera versus placebo, the odds of patients with lichen planus experiencing clinical improvement is OR = 1.33. This means that there is 1.33 increased odds of clinical improvement in lichen planus using aloe vera as compared to placebo.[24]
Preventive Fraction (PF)	The preventive fraction corresponds to the proportion of the disease or other undesirable outcome that would be prevented or avoided if an entire population receives an intervention or exposure of interest. The preventive fraction is obtained by subtracting the incidence (or event rate) of the disease or undesirable outcome of interest in the population (I_p) from the incidence (or event rate) if the entire population were exposed or received the intervention of interest (I_e). Then this difference is divided by the incidence (or event rate) of the disease or undesirable outcome of interest in the population (I_p). Thus, the preventive fraction is expressed as follows: (I_p-I_e/I_p).	In a study assessing the effect of topical aloe vera compared to placebo for resolving lichen planus lesions, PF = 3%. In other words, 3% of lichen planus lesions that would have remained unresolved were resolved by applying topical aloe vera instead of applying the placebo.[24]
Hazard Ratio (HR)	A hazard is the event rate at an instant in time. A hazard ratio quantifies the proportion, at any point in time during the follow-up period, of participants experiencing an event in the intervention group compared to those experiencing an event in the control group.	Patients receiving placebo experienced 74% 3-year oral cancer-free survival compared to patients receiving erlotinib, who experienced 70% 3-year oral cancer-free survival. This corresponds to HR = 1.27, meaning that patients in the placebo group are 27% more likely to experience oral cancer-free survival over 3 years when compared to patients in the erlotinib group.[25]

results showing that the PMD rate in community A is higher than in community B—50% of people in community A have PMDs, but in community B 48% of people have PMDs. Clinically, one could say that these are comparable rates, and a 2% difference may not lead to further inquiry. In a second hypothetical study, researchers found results that were not statistically significant, in which the data suggested that 75% of people in community A had PMDs, while only 25% of people in community B presented with PMDs. This difference should trigger additional questions, and possibly further studies to ascertain the reason for it. People in community B might be doing something that has improved the rate of PMDs, or maybe they are less exposed to a carcinogenic substance, or the lack of statistical significance is

Table 29-8 Absolute measures of association.

Measure	Definition	Example
Risk difference (RD) [absolute risk reduction (ARR) or absolute risk increase (ARI)]	Risk differences or [absolute risk reduction (ARR) or absolute risk increase (ARI)] are absolute measures, as compared to relative measures, which are proportions. They are calculated using the absolute risk (i.e., the risk of patients developing an outcome in each group of a study) expressed as a number or a percentage. The RD is the difference between the absolute risk between two groups.	When using therapeutic application of aloe vera versus a placebo, the relative risk of patients with lichen planus experiencing clinical improvement is RR = 1.03. Via the data used to calculate the relative risk, we can estimate the effect as an absolute risk. 28 patients in the aloe vera arm (total N = 31) experienced clinical improvement. The absolute risk of improving with aloe vera can be presented as 900 out of 1000 patients receiving aloe vera improved, or 90% of patients receiving aloe vera improved. Similarly, 21 patients in the placebo arm (total N = 24) experienced clinical improvement. Therefore, the absolute risk for improving using placebo can be presented as 880 out of 1000 patients improved, or 88% of patients receiving placebo improved. The RD can also be calculated by subtracting the absolute risk of the control group from the intervention group, for an RD/ARR = 2%. This means that patients receiving aloe vera gel were 2% more likely to experience clinical improvement compared to the placebo group. Or, aloe vera gel will improve clinical appearance in 20 additional patients out of 1000 compared to the placebo group.[24]
Number needed to treat for an additional benefit (NNTB)	In a randomized controlled trial (RCT) comparing an intervention to placebo, the NNTB is the number of patients that need to receive the intervention rather than placebo for one person to experience a beneficial outcome in a given time frame.[28] This measure is calculated by taking the inverse of the risk difference (i.e., 1/RD). Small NNTBs are indicative of a favorable intervention.	In a study assessing the effect of topical aloe vera compared to placebo for resolving lichen planus lesions, 28 out of 31 patients in the aloe vera group experience clinical improvement compared to 21 out of 24 patients in the placebo group, resulting in an NNTB of 35. This means that 1 person will experience resolution of their lichen planus for every 35 people treated with aloe vera after 12 weeks.[24]
Number needed to treat for an additional harmful outcome (NNTH)	In an RCT comparing an intervention to placebo, the NNTH is the number of patients that need to receive the intervention rather than placebo for one person to experience a harmful outcome in a given time frame. This measure is calculated by taking the inverse of the risk difference (i.e., 1/RD). Large NNTHs are indicative of a favorable intervention.	In an RCT comparing the effectiveness of pimecrolimus cream with vehicle cream for the treatment of erosive lichen planus, investigators measured the incidence of adverse events in each group. After 60 days, 5 out of 10 patients who received pimecrolimus cream experienced an adverse event compared to 1 out of 10 patients in the vehicle cream group. This corresponds to an NNTH of 3, meaning for every 3 people treated with the pimecrolimus cream, 1 person will experience an adverse event throughout 60 days of follow-up.[29]
Mean difference (MD)	The mean difference is a measure that quantifies the difference in the mean value or average of a continuous outcome between the two groups. When there is no difference in the treatment effect between the two groups, MD = 0. When conducting additional statistical analysis such as a meta-analysis, it may also be necessary to standardize measures of association by calculating a standardized mean difference. This summary statistic will not be discussed in depth here.	A study assessed the effect of systemic prednisone compared to a placebo drug in patients with recurrent aphthous stomatitis. The mean days to resolution of the ulcer was measured in both groups. The mean days to resolution was 4.55 and 10.85 in the prednisone and placebo groups, respectively. MD = –6.3 days (4.55 – 10.85 = –6.3). On average, the patients who took prednisone experienced resolution of their ulcer 6.3 days earlier than patients who took the placebo pill.[30]

simply a matter of study power (i.e., sample size and number of people with PMDs). Thus, whether results are or are not statistically significant have no bearing on the clinical significance of the findings.

There is a large consensus in the research community advocating for discontinuing the use of statistical significance (e.g., emphasis on significant P-values) as a measure of relevance for study findings. Their concerns are backed by evidence, suggesting that research is more likely to get published if it demonstrates statistically significant results.[31] In order to improve their chance of publication, investigators might be tempted to manipulate the data, for example by implementing something called P hacking.[32] This practice is a form of data manipulation that results in statistically

significant P-values. With significant P-values, researchers may be more likely to get published, get awarded a grant, or enjoy other positive outcomes in the research community. A recent article summarized data manipulation strategies as follows: "These practices are akin to the Texas sharpshooter fallacy, in which an incompetent shooter sprays the side of a barn with bullets and then draws a target around the bullet holes to show how accurate of a shot he was."[33] For the novice practitioner of evidence-based clinical practice, it is not always possible to identify when manipulation of data is occurring. At the very least, when using evidence to inform practice it is important to maintain vigilant skepticism and avoid being persuaded by every "almost too good to be true" positive outcome that one encounters in the literature or presentations by gurus at prestigious conferences.

What Is the Null Hypothesis?

When conducting a scientific study, it is very difficult to prove that an observation is true and deserves attention. For example, it would be difficult to prove the following: "All people in the community who smoke get oral cancer." The likelihood that one could examine every single person in the community would be extremely difficult, if not impossible. Even if 99% of the community who smoked are examined and all had cancer, there is still a remaining 1% of the community who smoked whose cancer status remains uncertain. As is commonly noted in research, an absence of evidence is not evidence of absence.[34] In other words, just because something is not seen does not mean it does not exist. In research, rather than stating that something is the case (referred to as the "alternative"), researchers instead present the "null" and then try to find evidence to refute it or not refute it: "All the people in the community who smoke do not have oral cancer." This statement is easier to refute, as it will be sufficient to find just one person in the community who smokes and has oral cancer to reject such a statement. While it is not the primary goal of investigators to conduct research to report something to be false, by principle and philosophy, research methodology makes disproving/refuting easier than proving. And this is where the null hypothesis comes in. Researchers' goal when designing a project is to provide evidence as to what extent an observation of the world is compatible with a preconceived statement (i.e., assuming that the null hypothesis is correct).

P-Values, What They Are, and What They Are Not

Probably one of the most cited statistics and the one upon which most journal reviewers focus when considering an article for publication is the P-value. Researchers will often aim to reach that critical value of $P \leq 0.05$; this accomplishment leads them feeling validated for their research with findings that can be considered statistically significant. Yet there are times when the illustrious P-value gets more credit than is due. Given that critically appraising the research literature requires a broad understanding of statistics, it is necessary to have a solid understanding of science's most ubiquitous statistic. A broader and valid understanding of P-values contextualizes them as one piece in a "statistical model." A model is the group of assumptions, methods, and steps (e.g., definition of selection criteria, study recruitment process, implementation of allocation concealment, blinding for outcome adjudicators, analysis planning, null hypothesis formulation statistical test of choice, selection of data to report) that investigators plan and execute when trying to get an understanding of a phenomenon.[35]

A P-value is defined as "a statistical summary of the compatibility between the observed data and what we would predict or expect to see if we knew the entire statistical model (all the assumptions used to compute the P-value) were correct."[35] Thus, the role of statistical tests is to provide a numeric value that reflects the distance or degree of compatibility between the data observed in the study and a predefined statistical model. As mentioned above, such a model includes all the assumptions, decisions, and steps for the execution of a study from which a phenomenon was observed, and not merely the comparison of the P-value against a predetermined level of significance or "alpha level"—by convention set at 0.05. A small P-value, equal to or lower than the alpha level, can be attributed to a number of potential explanations. One possible explanation is that the observed data are not close to or not compatible with the predefined statistical model (i.e., all aspects of the research, including the null hypothesis), warranting a rejection of the null hypothesis, under the condition that all assumptions to obtain the P-value were correct. Another explanation can be that methodologic issues, confounding, residual bias, or reporting issues contributed to the computation of a small P-value, making the data look "unusual" with regard to the model. Unfortunately, hypothesis testing is incapable of differentiating between these two scenarios: "$P \leq 0.05$ only means that a discrepancy from the hypothesis prediction (e.g., no difference between treatment groups) would be as large or larger than that observed no more than 5% of the time if only chance were creating the discrepancy (as opposed to a violation of the test hypothesis or a mistaken assumption)."[35]

Clinicians must be careful not to put emphasis on the P-value out of proportion to what it represents. For instance, it offers no insight into the magnitude of the effect of the observed phenomenon: a P-value of 0.04 is no weaker than a P-value of 0.02. A smaller P-value does not automatically imply more statistically significant results, nor more

substantial outcomes. In addition, P-values do not represent the extent to which the observed differences in a study are due to chance alone, nor do they reflect the probability of the null hypothesis being true (the computation of P-values assumes that the null hypothesis is true).

Interpreting Confidence Intervals

CIs have emerged as an alternative to P-values for examining the relevance and implications of study results for practice. They provide a range of plausible results in the same units as the outcome measure of interest (including direction and magnitude), and represent progress toward making research findings more accessible and understandable for decision-making. A CI has upper and lower boundaries, as well as a point estimate representing the best estimate that reflects the observed data.[1] When researchers present 90%, 95%, or 99% CIs obtained from a single study, they are always representing a range of results, which may or may not contain the true value, irrespective of the percentage of confidence. The "confidence" aspect of the interval refers to a coverage probability that is applicable to a long sequence of repeated calculations of CIs.[35] For example, if an investigator computes many 95% CIs repeatedly for the phenomenon of interest, on average 95% of them will contain the true effect size, and, by extension, 5% of the CIs will not contain the true value. As the concept of confidence is applicable to the series of CIs and not to a single observation, one would never know whether the single CI reported in a clinical study belongs to the 95% that contains the true value or the 5% that does not contain the true value. This observation emphasizes the need for replication of study results in scientific research, an aspect often ignored by the research community, which frequently prioritizes novelty and uncommon findings over replication of initial results that were "too good to be true."

The width or precision of a CI is determined by sample size and the number of observed events of interest, and has important implications for its ability to inform practice and policy decisions. Picture, for example, a study testing a new surgical technique that promises to reduce the incidence of dental implant failures (Table 29-9). If the same study is repeated over time, increasing the sample size and number of events for both experimental and control groups (implant failure) while keeping the absolute risk constant across both arms in increments that double the risk, it can be verified that a 20% relative risk reduction (RRR) is present across all scenarios (people who received the new surgical technique experienced a 20% reduction in implant failure compared to those who received the conventional technique). However, the width of the 95% CI and the ability to inform the effect of the new surgical technique on implant failure varies. In the second to last scenario in Table 29-9, the lower boundary of the 95% CI only suggests a 5% reduction in the risk of experiencing implant failure, an effect in implant failure that many can consider negligible, especially if the new technique requires the adoption of different equipment, additional training, and other expenses. In other words, changing practice and adopting the new technique in the face of a 5% RRR in the outcome may not be worthwhile. On the other hand, the upper boundary of the CI suggests a 33% reduction in implant failure, a treatment effect that many clinicians would consider large enough to change practice and adopt the new technique. When in the presence of a CI whose boundaries provide evidence that would determine different clinical actions (e.g., adopting the new technique would not be worthwhile vs. adopting the new technique seems to be appropriate), one can claim that such a CI is imprecise or

Table 29-9 Sample size, absolute risk reduction, relative risk reduction, and width of a confidence interval *Sample size and width of a confidence interval (CI).*

Experimental group			Control group					
Implant failures	Total number of implants	Absolute risk	Implant failures	Total number of implants	Absolute risk	Absolute risk reduction (ARR)	Relative risk reduction (RRR)	RRR; 95% CI
8	20	0.40	10	20	0.50	0.10	0.20	0.20; –60 to 60%
16	40	0.40	20	40	0.50	0.10	0.20	0.20; –31 to 51%
32	80	0.40	40	80	0.50	0.10	0.20	0.20; –13 to 43%
128	320	0.40	160	320	0.50	0.10	0.20	0.20; 5 to 33%
320	800	0.40	400	800	0.50	0.10	0.20	0.20; 11 to 28%

The five different studies illustrate that an increase in sample size will result in a narrower confidence interval constructed around the relative risk reduction (RRR); that is, it will provide more confidence that the "true" RRR for the implant failure rate is close to the observed 10% ARR and 20% RRR.

has a width that is not narrow enough to effectively inform practice. Let's focus now on the last scenario presented in Table 28-9. Here, the 95% CI suggests an 11% increase in the incidence of implant failure (lower boundary) as well as a 28% increase in the same outcome. With both boundaries suggesting an increase in implant failure by using the new technique, and the lower boundary still reflecting a reduction that many clinicians would consider relevant enough to warrant a change in practice (i.e., the adoption of the new surgical technique), one can claim that this CI is precise and narrow enough to inform practice.[1]

After being presented with these scenarios, one question remains unanswered: How can patients and clinicians define thresholds to evaluate the extent to which a treatment effect can be judged as important? What is the smallest magnitude of a treatment effect that patients can identify as a meaningful improvement or deterioration in a particular outcome?

Use of Thresholds to Interpret Evidence: The Minimal Important Difference

A concept called minimal important difference (MID) addresses the challenges in interpreting outcomes (including PROMs), and in particular the need to establish a threshold between an unimportant versus a small but important impact. An MID corresponds to the smallest change in score of an outcome of interest, either beneficial or harmful, that patients would perceive as important.[36,37] Since it was first described, there has been an exponential growth in the number of publications in the medical literature referring to the concept. There are two main approaches in the literature for estimating an MID: (1) distribution-based and (2) anchor-based methods. Distribution-based methods evaluate a change in a PROM by estimating statistical parameters (e.g., pared t-statistic, effect size, standard error of measurement, standard deviation of 0.5, etc.).[38–40] These methods have been questioned as they rely on the statistical characteristics of the PROM, and do not reflect the patient perspective, highly desired when interpreting the impact of healthcare interventions.

In anchor-based methods, PROM results are compared against an external independent criterion—the anchor—that is in itself understandable and relevant for patients and exhibits at least a moderate correlation with the PROM.[41,42] Examples of anchors are healthcare utilization, response to treatment, disease severity, and presence of symptoms. Investigators establish the MID by relating the results of the anchor to those of the target PROM.

Investigators can apply anchor-based methods in a longitudinal or cross-sectional fashion.[39] The global rating of a change or transition item is one of the most frequently used longitudinal anchor-based methods (e.g., "Are you feeling better or worse, and if so, what is the extent of the change?").[41] Other examples of anchor-based methods use a comparison to disease-related criteria, preference ratings, and comparison to a known population.[39] The main advantage of anchor-based methods over distribution-based methods is the inclusion of criteria that are relevant for patients.

APPLYING THE RESULTS TO PRACTICE AND POLICY

After identifying the best available evidence to inform practice, assessing its validity (i.e., risk of bias or the extent to which methodologic strategies were appropriately implemented to minimize effect bias and confounding), and examining the study results, including the magnitude of a treatment effect and the strength of an association between an exposure and an outcome, clinicians and policy-makers still need to answer a subsequent question: "Is this evidence relevant for my decision-making needs?"

Consideration of All Patient/Person-Centered Outcomes

One of the hallmarks of any study, systematic review, or clinical practice guideline is that all patient/person-centered (or important to patients or people) outcomes should be defined, measured, and included for analysis, regardless of whether the evidence-collection process resulted in no studies reporting these outcomes. In fact, when defining the basis for decision-making, it should be clinical judgment and patient input that inform the set of desirable and undesirable outcomes needing to be documented, not their availability in the research literature. What this tells clinicians and policy-makers is that the authors looked for all relevant studies and outcome data relevant for decision-making, irrespective of the data actually reported in the literature, which represents an approach to basing healthcare decisions in "what matters from a patient's point of view" rather than "what it is reported in the literature" with no discretion of relevance. Though there is inherent uncertainty in the evidence-based decision-making process in the absence of data, the presentation of all patient-important outcomes allows users to be confident that decisions are being made using the best available evidence. The fact that for many relevant clinical questions more definitive patient/person-centered outcomes are not available is in itself a valuable piece of information for those facing a choice. In contrast to surrogate outcomes, patient/person-centered outcomes will best inform decisions in the clinic and in policy-making, as they directly relate to how patients and, in turn, clinicians perceive the benefits and harms of a therapy or diagnostic test.

Additionally, it is an integral part of the evidence-based decision-making process to consider patients' values and preferences. A patient's and, sometimes, caregiver's preferences may dictate whether the undesirable effects associated with an intervention outweigh the potential benefits or vice versa, a contrast that is commonly seen in value-sensitive decisions.[43]

Balancing Benefits and Harms (Magnitude of Desirable and Undesirable Effects)

In addition to a therapy's desirable effects, or benefits, clinicians and policy-makers should weight those against the undesirable effects or harms, and associated costs and burden. In the context of implementing shared decision-making, it is important to present all desirable and undesirable effects to the patient when considering a clinical decision, as the relative importance of these outcomes and the appreciation for their magnitude may vary from patient to patient, particularly in highly value-sensitive decisions (Figure 29-3).

Shared decision-making involves patients and clinicians working together to articulate patients' values and preferences, which ultimately should inform the clinical decision. Patients need information to work with their clinician to make an informed decision that is best for them. This is a conversational, bi-directional approach, not a clinician to patient–directional approach.[44]

When conducting evidence-based clinical practice guidelines, a guideline panel solicits feedback about the scope and recommendations from the public and stakeholders as an essential methodologic step in the development of quality clinical practice guidelines. This step ensures that all considerations from the general public or society, patients, and key stakeholder organizations or agencies are included in the panel's final recommendations. It is expected that guideline panels define the relative importance of outcomes based on patients' values rather than their own. This process also provides guideline developers additional information on how patients perceive the therapy and its alternatives. That informs users on how the typical patient may perceive the benefits and harms of a therapy, providing further information to the patients in the context of shared decision-making. Defining to what extent the use of an intervention produces "more good than harm" is a challenging activity that clinicians nevertheless must perform on a daily basis. Informing such a balance with trustworthy data that contextualizes the magnitude of the desirable and undesirable consequences makes a decision truly evidence based.

Patients Similar to the Ones in My Practice

Clinical studies often focus on generating—by using strategies like randomization, allocation concealment, blinded adjudication of outcomes in the groups, or with the application of the intention-to-treat principle—two groups that are comparable. However, these strategies frequently fail to address the extent to which the characteristics of the patients recruited reflect the general population or the typical patient suffering from the condition under investigation. Applicability or generalizability represents "the degree to which the results of a study can be generalized [or applied] to settings or samples other than the ones studied."[2] The National Institutes of Health (NIH) released policy guidelines in 1994 (updated in 2017) that ensure NIH-funded research includes subjects of all genders, sexes, ages, and racial or ethnic groups.[45] But not all research is NIH funded, so it is important to be prudent when evaluating the literature before applying the findings to practices. There are three key questions when assessing the extent to which the results of a study conducted in certain sample can be applied to another setting:[2]

- Have biologic factors that might modify the treatment response been excluded? Biologic factors including sex, age, race, presence of comorbidities, and specific features of the disease can modify the effects observed from studies

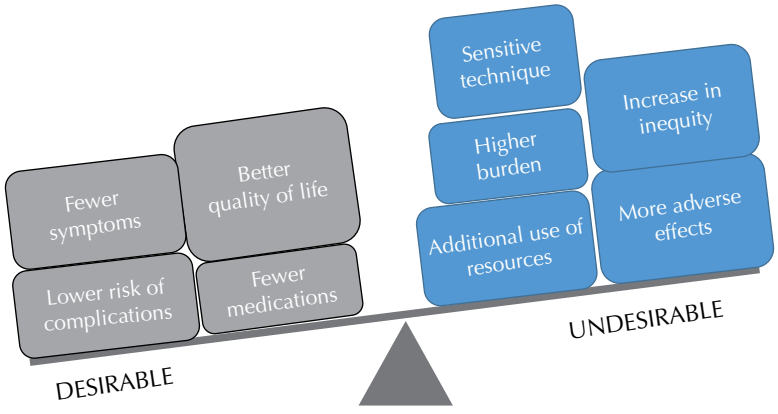

Figure 29-3 Balancing benefits and harms.

when compared to an individual patient in the community. Experienced clinicians will be able to identify the role that these factors may play in modulating the disease process and defining whether a given therapy would be an unsuccessful treatment in an individual patient with any of these modulating factors.

- Can the patients adhere to treatment requirements? Investigators often attempt to recruit participants who have demonstrated a high level of adherence and commitment to the study and the therapy under testing. On the one hand, this is a desirable feature of clinical studies to minimize the effect of missing participant data, making sure that all patient outcomes are accounted for in the analysis, and therefore minimizing risk of bias. On the other hand, these over-adhering participants may well not represent the ability of people in the community or the general population to effectively stick to the treatment, especially in the face of high burden, costs, significant adverse events, and so on. It is reasonable to assume that real patients outside a research setting would exhibit lower levels of adherence, negatively affecting the observed treatment effect in the study informing a decision. Interventions that carry little burden would suffer less from adherence issues compared to highly intense and demanding therapies.
- Can the clinicians adhere to treatment requirements? Clinicians' ability to appropriately diagnose, ask relevant questions during the medical history recollection, apply their technical skills, and use supportive equipment according to specifications are essential considerations when determining to what extent a practitioner would be able to replicate the therapy from the study in their practice. This point is of particular importance in dentistry as a profession that relies heavily on surgical procedures. The more sensitive an intervention in a clinical study is to technique and experience, the less likely it is that a regular general practitioner in the community will be able to obtain treatment results close to the ones reported in the research literature. In the presence of large discrepancies between clinicians' expertise in a trial compared to another clinician attempting to apply the evidence from that trial, the more serious the issues of applicability or generalizability that would emerge.

In summary, when assessing the applicability of a study to clinical practice, valuable information can be found in the methods section of the article; definition of selection criteria (inclusion and exclusion criteria) should be critically appraised and assessed for similarity between the research subjects and the clinical patients of interest. Should one completely ignore the evidence when patients in the setting of interest do not match the study subjects? The answer is probably no, as in many cases the only available information is coming from a study with issues of applicability. A clinician with a deep understanding of applicability will be cautious when a study reporting a highly effective therapy is outside their level of surgical or technical expertise, too distant from the patients of interest, or too burdensome, therefore negatively affecting patients' adherence.

One special point of interest is the determination of whether a particular clinical practice guideline can be truly helpful in the hands of a clinician.

Utilization of Clinical Practice Guidelines and Clinicians' Expertise

The evidence-based practitioner will have reviewed the possible outcomes of a treatment, balanced harms and benefits, and considered whether the patients in a study match the patients in their clinic. The last question a clinician should be prepared to answer is: "Am I prepared to conduct the treatment indicated in the clinical guideline?" For example, the American Academy of Pediatrics has developed guidelines for sedation before, during, after a dental procedure.[46] After reading these guidelines, one will be well informed in the considerations for and practice of sedation for pediatric patients. But the guidelines make clear that practitioners need to be knowledgeable about a variety of areas; for example, they must be trained in advanced pediatric airway management. Therefore, these guidelines cannot be adopted by every clinician, as not every clinician has been trained in this area.

While these guidelines point out the required training to utilize them, others may not be as clear. In these situations, it is important that the clinician be ready to self-assess and follow the ethical principles laid out in dentistry.[47] If a clinician were to implement a guideline without the appropriate training, there is a risk that they would be violating the principle of nonmaleficence, or "do no harm." Without proper training, a clinician may not be prepared for the adverse outcomes of a treatment or procedure. It is up to each clinician to constantly self-assess, and when faced with a lack of training to help patients, appropriately refer or determine that time to retrain is warranted.

Another key question within the implementation discussion is how to resolve contradictions between guidelines and training. For example, recent guidelines regarding antibiotic use recommend antibiotics in a limited number of situations, contradicting the general practice of generous antibiotic prescribing practices.[48–50] Many dentists and physicians may not feel comfortable with these new guidelines, as the latter contradict what they were taught in school or learned in a continuing education course. Some prefer to prescribe an antibiotic under the misguided assumption that doing it

"just in case" is appropriate. Studies examining why guidelines are not implemented cite lack of agreement, lack of training, and lack of skills.[51] Unfortunately, there is no one simple resolution to this issue. Changing attitudes and behaviors is a difficult process. It is therefore important that evidence-based practice continues being taught broadly to those early in their career, as well as those well versed in their fields. Learning how to practice evidence-based dentistry is a skill, just like learning how to do a filling. It takes time and requires repetition.

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