REVIEW ARTICLE

The Treatment of Chronic Recurrent Oral Aphthous Ulcers

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SUMMARY

Background: Chronic recurrent oral aphthous ulcers are the most common type of inflammatory efflorescence of the oral mucosa, with a prevalence of 2% to 10% in Caucasian populations. To treat them properly, physicians should know their clinical appearance and course, conditioning factors, underlying causes, and differential diagnosis.

Method: This review is based on pertinent articles that were retrieved by a selective search in PubMed and in the Cochrane Central Register of Controlled Trials.

Results: Hard, acidic, and salty foods and toothpastes containing sodium lauryl sulfate should be avoided, along with alcohol and carbonated drinks. In Germany, the only drugs that have been approved to treat oral aphthous ulcers are corticosteroids, topical antiseptic/anti-inflammatory agents such as triclosan and diclofenac, and local anesthetics such as lidocaine. Antiseptic agents and local anesthetics should be tried first; if these are ineffective, topical corticosteroids should be used. In severe cases, local measures can be combined with systemic drugs, e.g., colchicine, pentoxifylline, or prednisolone. The efficacy of systemic treatment is debated. Other immunosuppressive agents should be given systemically only for refractory or particularly severe oral aphthous ulcers due to Adamantiades-Behçet disease.

Conclusion: The treatment of chronic recurrent oral aphthous ulcers is symptomatic, mainly with topically applied agents. It is tailored to the severity of the problem in the individual case, i.e., the frequency of ulcers, the intensity of pain, and the responsiveness of the lesions to treatment. Effective treatment relieves pain, lessens functional impairment, and lowers the frequency and severity of recurrences.

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Oral aphthous ulcers typically present as painful, sharply circumscribed fibrin-covered mucosal defects with a hyperemic border.

Chronic recurrent oral aphthous ulcers occur in three different clinical morphological variants and with two different time courses. Small ulcers of the minor-type (Mikulicz) are less than 1 cm in diameter (usually 2–5 mm) and heal spontaneously in 4–14 days. They account for 80–90% of all recurrent oral aphthous ulcers (1, e1). Scarring occurs in around 8% of cases (1, e2) *(Figure 1a)*. Large ulcers of the major-type (Sutton ulcers) are usually 1–3 cm in diameter, deeply indurated and can last for 10 days to 6 weeks or occasionally even longer (1, e3) *(Figure 1b)*. They account for around 10% of recurrent benign oral ulcers. About 64% of Sutton ulcers heal with scarring. Herpetiform aphthous ulcers are very small (1–2 mm) grouped lesions (1, e4) *(Figure 1c)*. They account for around 5% of recurrent oral aphthous ulcers, are extremely painful and persist for 7–10 days. As many as a 100 ulcers can be present; they may coalesce into larger erosive plagues and about 32% heal with scarring. The three morphologic variants can occasionally appear simultaneously (2).

Another classification is based on the time course. The simple chronic recurrent oral aphthous ulcers present with a limited number of small, quickly healing, minimally painful ulcers limited to the oral mucosa and recurring with 3–6 episodes annually. In complex aphthosis, there are a few or many slowly healing intensely painful ulcers on the oral and perhaps genital mucosa (3). The latter may also be perigenital, affecting the scrotum, vulva, anus, perineum and inguinal region. Complex aphthosis features frequently appearing ulcers with either short lesion-free periods or even repeatedly recurrent ulcers, severe pain and even systemic effects such as interference with eating and the resultant problems of inadequate nutrition (3).

Methods

A selective literature search concentrating on randomized controlled therapeutic trials was performed to prepare this review. The literature search employed PubMed and the Cochrane Central Register of Controlled Trials. Letters to the editor and meeting reports were ignored. Because of the small number of

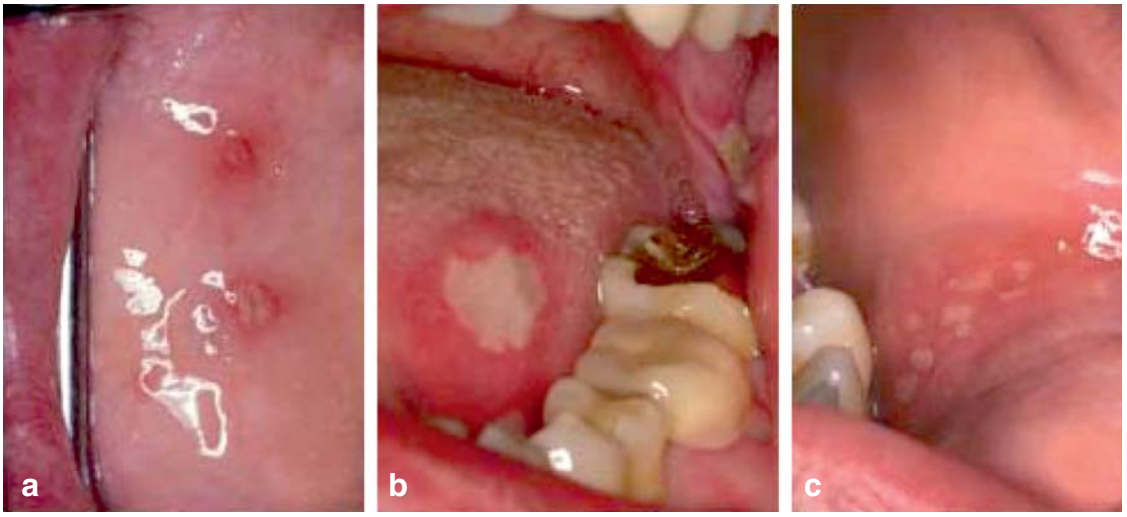


Figure 1: (a) Minor-type oral aphthous ulcers, (b) major-type oral aphthous ulcer, (c) herpetiform oral aphthous ulcers
(Figure 1a modified from[8] Altenburg A, Mahr A, Maldini C, et al.: Epidemiologie und Klinik des Morbus Adamantiades-Behçet in Deutschland: Aktuelle Daten. Ophthalmologe 2012; 109: 531–41.; Figure 1c modified from Altenberg A, et al. Klinik und Therapie chronic rezidivierender Aphthen. Hautarzt 2012; 63: 693–703). Figures 1a and c used with kind permission from Springer-Verlag, Heidelberg

published controlled studies, both studies without control groups and studies whose results correlate with our clinical experience were in exceptional cases included.

Epidemiology

Chronic recurrent oral aphthous ulcers are the most common inflammatory disease of the oral mucosa with a prevalence of 2–10% in Caucasian populations; women are more frequently affected (2, 4). A study evaluating 40 693 school children in the USA showed a point prevalence of 1.23% and a lifetime prevalence of 36.5% (5).

Pathogenesis

The etiology of chronic recurrent oral aphthous ulcers is still unclear. A variety of underlying disorders may predispose patients to develop oral aphthous ulcers; they include iron deficiency anemia, neutropenia, and folic acid or vitamin B12 deficiency, as well as a selective vitamin B12 resorption defect (e5–e7). Appropriate replacement therapy has reduced the severity of the disease as documented in case reports (e8) (evidence level [EL] 4). Local mucosal injuries are also possible trigger factors (6, e9). In addition, genetic factors may be important; the family history is positive in up to 40% of patients (7). No consistent association with an HLA haplotype has been shown (e10).

Differential diagnosis

Oral aphthous ulcers are clearly defined in a nosologic sense, but often hard to distinguish clinically from a broad group of similar (aphthoid) erosions and ulcers. The differential diagnosis includes a variety of diseases which can imitate the clinical picture of oral aphthous ulcers *(Box)*.

Adamantiades-Behçet disease (ABD) is a chronic recurrent systemic vasculitis (e11) in which oral and genital ulcers are major diagnostic criteria. Some include ABD among the autoinflammatory diseases. In ABD, 98.5% of patients have recurrent oral aphthous ulcers; this is the most common manifestation of the disorder (8). Recurrent genital aphthous ulcers are seen in 64.7% (8). In 84.5% of patients, the first manifestation is oral ulcers, while 3.5% start with genital ulcers, which are the second most frequent symptom (8). About 10% of the patients with complex aphthosis in Western Europe and North America develop ABD; the likelihood is higher in the eastern Mediterranean region, Middle East and Asia (9). In order to make the diagnosis, clinical diagnostic criteria are applied, such as those of the International Study Group for Behçet's Disease (e12), or the new International Criteria for Behçet's Disease (9) *(eBox)* which are based on epidemiological data.

Overview of therapy

The studies that we evaluated generally reached an EL 2A because of a variety of limitations including small patient number, reliance on self-reported information, unclear information on randomization, incomplete or lacking blinding, or inadequate information on the nature of the placebo.

Effects on the overall quality of life of the patients was not evaluated in the studies. Undesired effects of topical medications were either mild or not mentioned. In studies on systemic drugs, the undesired effects were not always discussed.

With the exception of the corticosteroids, topical antiseptics and topical anesthetics, all tested substances

are used off-label for oral aphthous ulcers in Germany. Rebamipide, clofazimine and camel thorn distillate are not available in Germany.

Dietary and general measures

There are no reliable studies addressing the role of diet in managing aphthous ulcers. Substances that a majority of patients report frequently trigger ulcers should be avoided, especially if the patient in question has noticed an association. In general one should avoid hard, acidic and salty substances such as fruit juices, citrus fruits, tomatoes, and spices like pepper, paprika and curry, as well as alcoholic and carbonated beverages. Avoiding dental care products with sodium lauryl sulfate (SLS) is also desirable. Using a SLS-free toothpaste significantly reduced the healing period and pain of oral aphthous ulcers (10) (EL 1B).

Topical therapy

Topical anesthetics

Topical anesthetics often provide satisfactory pain relief (6). Options include lidocaine as 1% cream (randomized placebo-controlled study; EL2A [11]), 2% gel or spray; polidocanol as paste; and benzocaine lozenges. There is a pump spray that combines tetracaine 0.5% and polidocanol 0.1%. A mouth wash containing benzocaine and cetylpyridinium chloride is also available.

Antiseptics and anti-inflammatory agents

A mouth wash containing 0.15% triclosan in ethanol and zinc sulfate reduced the number of new aphthous ulcers in 43% of cases, the pain intensity in 45% and extended the ulcer-free interval (12) *(Table 1)* (EL 1B). Diclofenac 3% in a 2.5% hyaluronic acid gel was superior to a lidocaine 3% gel in reducing pain after 2–6 hours (13) *(Table 2)* (EL 2A).

Chlorhexidine mouthwash and chamomile extract both reduced the frequency, increased healing speed, and decreased the severity of aphthous ulcers in non-randomized studies (6, 14) (EL 2B). Chlorhexidine gels and sprays are also available. A useful adjuvant therapy is dexpanthenol in a variety of forms (spray, solution and tablets).

Cauterization

Topical application of hydrogen peroxide 0.5% solution or silver nitrate 1–2% solution significantly reduced the pain severity after one day, but did not increase the speed of healing (15) (EL2A).Treatment with a CO_2 (16) or Nd:YAG laser (17, e13) brought immediate pain relief which lasted for 4–7 days *(Table 2)* (EL 2A).

Topical tetracycline treatment

Using a mouthwash containing chlortetracycline 2.5% increased the number of ulcer-free or pain-free days significantly, by 40% compared to a placebo (18) *(Table 1)* (EL 2A). In regards to pain reduction, a minocycline 0.2% mouthwash was superior to a tetracycline 0.25% mouthwash (19, e13) *(Table 2)* (EL 2A).

BOX

Important differential diagnostic considerations for oral aphthous ulcers

- **Gastrointestinal, mucocutaneous disorders**
  - Ulcerative colitis
  - Crohn's disease
  - Celiac disease
- **Infections**
  - Herpes simplex and zoster
  - Infectious mononucleosis
  - Hand foot and mouth disease
  - Herpangina
  - HIV infection
  - Syphilis
  - Acute necrotizing ulcerative gingivitis
  - Candidiasis
- **Reactive changes**
  - Morsicatio buccalis
  - Traumatic eosinophilic ulcer
- **Malignant diseases**
  - Oral carcinoma
  - Non-Hodgkin's lymphoma
- **Mucocutaneous rheumatic diseases**
  - Lupus erythematosus
  - Sweet syndrome
  - Reactive arthritis
  - MAGIC syndrome (mouth and genital ulcers with inflamed cartilage)
  - Sarcoidosis
- **Bullous and lichenoid dermatoses**
  - Erythema multiforme and its variants, including Stevens-Johnson syndrome and toxic epidermal necrolysis
  - Bullous autoimmune disorders: pemphigus vulgaris, cicatricial pemphigoid, epidermolysis bullosa acquisita, linear IgA dermatosis
  - Lichen planus
- **Other oral disorders**
  - Allergic contact stomatitis
  - Drug-induced ulcerative stomatitis
  - Geographic stomatitis
  - PFAPA syndrome (periodic fever, aphthous ulcers, pharyngitis, cervical adenitis)

(from Altenburg A, et al.: Klinik und Therapie chronisch rezidivierender Aphthen. Hautarzt 2012; 63: 693–703; with kind permission from Springer Verlag, Heidelberg)

TABLE 1

Therapeutic options to reduce the frequency of recurrence and/or the number of oral aphthous ulcers [*1]

Drug	Dose	Benefits	Controls	Number of probands	Length of study	Evidence level	Reference
Topical medications							
Triclosan 0.15% in 7.8% w/w ethanol/0.4% w/w zinc sulfate, triclosan 0.15% in 15.6% w/w ethanol/0.4% w/w zinc sulfate	10 mL for 30 s b.i.d.	Reduction of number of ulcers in 43%, of pain by 45%, increase in ulcer-free days vs. controls (p<0.0001)	Commercially available fluoride mouth wash. Triclosan 0.15% in propylene glycol	30	6 weeks (with each product)	2A	(12)
2.5% tetracycline solution vs. toothpaste with amyloglucosidase and glucose oxidase	Tetracycline solution 5 mL rinse in mouth for 1 minute q.i.d., toothpaste b.i.d.	2.5% tetracycline solution: increase (over 40%) in ulcer-free or pain-free days compared to placebo (p<0.05); toothpaste no significant differences from placebo	Placebo mouth wash or placebo toothpaste	57	10 weeks, then switch therapy	2A	(18)
Systemic medications							
Prednisolone vs. colchicine [*2]	Prednisolone 5 mg daily p.o., colchicine 0.5 mg daily p.o.	Reduction of pain and number of lesions after 3 months (p<0.001) without significant differences between agents; no placebo	–	17 (prednisolone), 17 (colchicine)	3 months	2A	(32)
Rebamipide	300 mg daily p.o.	ABD: Reduction in number of ulcers and pain in 65% vs. 36% in placebo group (p<0.01)	Placebo	35	12 to 24 weeks	2A	(e32)
Azathioprine	2.5 mg/kg BW daily p.o.	Reduction in frequency of oral aphthous ulcers from 43% to 11% (p<0.005)	Placebo	73 (only men)	2 years	2A	(35)

[*1] Except for azathioprine, all treatments are off-label. The recommendations are ordered based on disease severity.
[*2] evaluated as ineffective in (29).
w/w, weight by weight; s, seconds; min, minutes; p. o., per os; ABD, Adamantiades-Behçet disease; BW, body weight

Tetracycline hydrochloride powder 250 mg can be combined with 10 mL of tap water by the patient immediately before use to avoid stabilization problems. Because of the acid pH value, there may be temporary mucosal burning generally followed by clinical improvement. A stable mixture can also be prepared by neutralizing the tetracycline hydrochloride to create a basic product (6).

Both a standardized formulation—as well as the less-stable freshly prepared solution—can produce rapid healing in some patients, even in those with large ulcers resistant to topical corticosteroids.

Topical corticosteroids

If combined treatment with topical anesthetics and anti-inflammatory agents is not effective, then topical corticosteroids should be employed. In Germany, a registered oral paste containing prednisolone is commonly used, which is applied 1–2 times daily (20). The combination of topical anesthetics (for example, lidocaine gel) during the day with an oral paste containing triamcinolone in the evening is also effective (21). Studies indicate that triamcinolone oral paste is superior to phenytoin syrup (22) *(Table 3)* (EL 2A). Although both were equally effective in reducing pain, dexamethasone oral paste produced more rapid healing than triamcinolone oral paste (23) *(Table 3)* (EL 2A).

When topical corticosteroids are used regularly, one should be alert to the possibility of increased numbers of oral yeast infections (24). Especially painful, deep ulcers can be treated with intralesional triamcinolone suspension 0.1–0.5 mL per lesion (21).

Additional topical therapies

A double-blind, placebo-controlled study showed that 5-aminosalicylic acid 5% cream achieved pain reduction and more rapid healing of oral aphthous ulcers (25) *(Table 3)* (EL 2A). Amlexanox 5% paste or 2 mg tablets, when used in the prodromal stage, led to a reduction in the number and size of oral aphthous ulcers, as well as reduction in pain (26, 27) *(Table 3)* (EL 2A).

TABLE 2

Therapeutic options to reduce pain

Drug	Dose	Benefits	Controls	Number of probands	Length of study	Evidence level	Reference
Topical medications							
Diclofenac 3% in 2.5% hyaluronic acid gel	200 µL once	Less pain 2–6 hours after application of diclofenac-hyaluronic acid gel than after hyaluronic acid gel or lidocaine solution ($p = 0.01$)	2.5% hyaluronic acid gel, 2% lidocaine solution	60	8 hours	2A	(13)
Silver nitrate pencil	Once	Less pain at day 1 ($p<0.001$)	Placebo pencil; prior use of 2% lidocaine solution in both active and control groups	85	7 days	2A	(15)
CO_2 laser (2–5 mW)	Once	Reduction of pain immediately after treatment, relief lasting 96 hours ($p<0.001$)	Inactive laser	15	4 days	2A	(16)
Nd:YAG laser	Once	Less pain immediately and on days 4 and 7 with laser ($p<0.05$). Less exudation with laser ($p<0.05$)	Triamcinolone 0.1% in oral paste	14 (laser), 14 (triamcinolone)	7 days	2A	(e17)
Topical medications with systemic absorption							
Minocycline 0.2% in aqueous solution	5 mL q.i.d.	Less pain starting with day 2 ($p<0.05$)	Tetracycline 0.25% in aqueous solution	16 (minocycline), 17 (tetracycline)	10 days, then switch therapy	2A	(19)
Minocycline 0.2% in aqueous solution	5 mL q.i.d.	Less pain starting with day 2 ($p<0.05$)	Placebo solution	18 (minocycline), 15 (placebo)	10 days	2A	(e13)

An association between smoking and a reduction in the frequency of recurrences of oral aphthous ulcers has been observed. The number of lesions and the intervals between recurrences appear to be reduced during periods when the patient is smoking versus abstaining from tobacco (28, e14). Experimental evidence indicates that nicotine has an anti-inflammatory effect on keratinocytes (6, 14). Nicotine patches apparently cannot achieve the effects of tobacco smoke (own unpublished data). In a preliminary study with 3 patients, complete remission of recurrent oral aphthous ulcers was achieved with nicotine gum (e15) (EL 4). Neither cyclosporine (70 mg/g oral paste) nor interferon-α-2c gel was effective in treating oral aphthous ulcers (14).

Systemic therapy

A current review of the Cochrane Collaboration analyzed 25 studies (22 of which were placebo-controlled) on systemic therapy of oral aphthous ulcers and found no convincing evidence of efficacy (29) *(eTables 1, 2)*,

Colchicine

Colchicine (0.5–2 mg daily) is helpful for the majority of patients with chronic recurrent oral aphthous ulcers. An off-label trial is recommended for 6 weeks with 1–2 mg daily—followed by long-term therapy depending on how severe the ulcers are and how well-tolerated the medication is (20). In a large open study of Fontes at al. (30), colchicine produced clear improvement in 63% of cases over a period of 3 months and in 37% over many years. 22% of the patients were free of disease, while 41% had at least a 50% reduction in number and duration of aphthous ulcers. In 37% the improvement was maintained for 5 years. In additional controlled studies, colchicine 1–2 mg daily led to significantly fewer oral and genital aphthous ulcers in patients with ABD (e16, e17) (EL 2A). The aphthous ulcers frequently recurred when the treatment was stopped (20). Contraceptive measures after the conclusion of therapy are recommended for 3 months in women and 6 months in men. Up to 45% of patients experienced gastrointestinal symptoms.

TABLE 3

Topical therapeutic options to reduce the duration of illness and size of oral aphthous ulcers*

Drug	Dose	Benefits	Controls	Number of probands	Length of study	Evidence level	Reference
Amlexanox 5% paste	b.i.d.	Reduction in size and erythema (p<0.05)	Placebo paste	32	4 days	2A	(26)
Amlexanox 2 mg patch	q.i.d.	Smaller thermographically active area on day 4 (p<0.05)	Placebo patch	26 (amlexanox), 26 (placebo)	4 days	2A	(e30)
Amlexanox 2 mg adhesive tablets	q.i.d. to one aphthous ulcer for 5 days	Reduction in pain and size on days 4 and 6 (p<0.001)	Placebo adhesive tablet	104 (amlexanox), 108 (placebo)	6 days	2A	(27)
5-aminosalicylic acid 5% cream	t.i.d.	Reduction in duration of aphthous ulcers (7 vs. 11 days; p<0.01) and pain (p<0.05)	Placebo cream	22	14 days	2A	(25)
Sucralfate solution	Apply 5 mL solution with applicator q.i.d.	ABD: Reduction in frequency (p = 0.003) and duration (p = 0.03)	Placebo solution	40	3 months	2A	(34)
Camel thorn distillate (Iranian product)	Rinse mouth with 40 mL for one min q.i.d., then swallow	Size and pain reduced on days 3–7 (p<0.001) and 10 (p<0.02)	Placebo	49 (camel thorn distillate) and 44 (placebo)	2 weeks	2A	(e31)
Triamcinolone acetonide 0.1% in oral paste	t.i.d.	ABD: 86.7% response rate compared to 53.3% for phenytoin syrup (p = 0.01)	Phenytoin syrup as mouthwash for 4–5 min t.i.d.	30 (triamcinolone acetonide), 30 (phenytoin)	7 days	2A	(22)
Dexamethasone 0.1% in oral paste	q.i.d.	Quicker healing (dexamethasone) (p<0.001)	Triamcinolone acetonide 0.1% in oral paste	53 (dexamethasone), 37 (triamcinolone)	14 days	2A	(23)

*[1] All treatments are off-label. The recommendations are ordered based on disease severity. ABD, Adamantiades-Behcet disease; min, minutes

If aphthous ulcers fail to respond to colchicine monotherapy, combination approaches are possible. In patients with ABD, treatment with colchicine and benzathine penicillin was superior to colchicine alone in producing a slight improvement in the frequency of ulcers and a clear reduction in their healing time (more than 50%) (e18) *(eTable 1)* (EL 2A).

In our experience the off-label use of colchicine for chronic recurrent aphthous ulcers is generally approved and reimbursed by insurance companies.

Pentoxifylline

In case reports and older non-controlled studies, both pentoxifylline and oxypentoxifylline; 300 mg 1–3 times daily or 400 mg t.i.d. achieved good response rates (in children 36–50%) (6). In a more recent controlled study, pentoxifylline (400 mg t.i.d.) was only able to reduce the size of oral aphthous ulcers (p = 0.05) (31) *(eTable1)* (EL 2A).

Systemic corticosteroids

Systemic corticosteroids should be considered if colchicine and pentoxifylline do not produce improvement (20). Prednisolone or prednisone equivalents (10–30 mg daily) can be used on a short-term basis (up to one month) during a flare of the disease to speed healing. In a small controlled study, prednisolone 5 mg daily for 3 months was comparable to colchicine 0.5 mg daily. It produced a clear reduction in pain, as well as in number and size of oral aphthous ulcers (32) *(eTables 1 and 2)* (EL 2A). Prednisone (25 mg daily tapered over 2 months) was more effective than the leukotriene inhibitor montelukast in managing oral aphthous ulcers (33) *(eTable1)* (EL 2A).

Sucralfate

Sucralfate is used as an antacid in treating gastric and duodenal ulcers. Sucralfate suspension produced more rapid healing and reduced pain of both oral and

genital aphthous ulcers (34, e19) *(Table 3, eTable 1)* (EL 2A).

Dapsone

Dapsone significantly reduced the number and size of oral and genital aphthous ulcers in ABD (e20) *(eTable 1)* (EL 2A).

Antimetabolites: azathioprine and methotrexate

In a placebo-controlled study, azathioprine reduced the frequency and severity of orogenital aphthous ulcers in ABD; it is approved for this indication in Germany (35) *(eTable 1)* (EL 1B). In a case series, methotrexate 7.5–20 mg in a single weekly dose was helpful for severe orogenital aphthous ulcers (4) (EL 4).

Cyclosporine

There is information on over 350 patients with ABD treated with variable doses of cyclosporine (1–10 mg/kg body weight daily) for divergent periods of time (1–77 months) (36). In a controlled study up to 70% of patients experienced improvement in oral aphthous ulcers (37) *(eTable 2)* (EL 2A).There were more side effects in the cyclosporine group than in the colchicine control group. 92% of the women and 32% of men developed hirsutism, fever, fatigue, and gastrointestinal symptoms, all of which improved when the dose was reduced. In contrast to colchicine, cyclosporine led to increased creatinine and blood urea nitrogen levels. Cyclosporine is approved in Germany for treating uveitis associated with ABD.

Thalidomide

Thalidomide is considered effective against orogenital aphthous ulcers. In older open or retrospective studies, initial doses of 100–300 mg daily were tapered to 50 mg daily or the medication was discontinued after 3 months, in order to avoid a sensory neuropathy (e21, e22). Thalidomide in a dose of 100 mg daily for an average interval of 5 months was well tolerated by 8 patients with chronic recurrent oral aphthous ulcers (21). Thalidomide should only be used in exceptional cases. Because of its teratogenicity, it is absolutely contraindicated in pregnancy (e23). When it is discontinued, recurrences may develop rapidly (e22, e25). In Germany thalidomide is only approved for treating multiple myeloma.

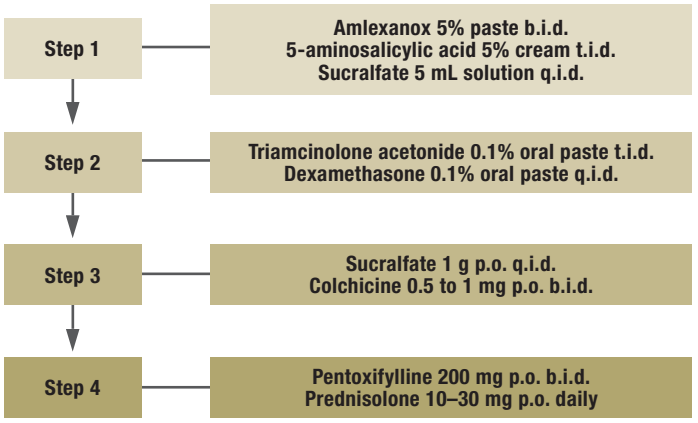
Interferon-α

Interferon-α can achieve complete or partial remission (reduction in pain, duration and frequency) of recurrent orogenital aphthous ulcers in ABD within 1–4 months (14, 38, e26) *(eTable 2)* (EL 2A). A low-dose (3 million IU 3 times weekly) maintenance therapy is recommended after 6 months for ABD patients (14). Combination therapy with corticosteroids, colchicine, or benzathine penicillin is possible (e27).

Other systemic agents

In a controlled study, sub-antimicrobial doses of doxycycline (40 mg daily) prolonged the interval between aphthous ulcers (e28) *(Table1)* (EL 2A). Zinc sulfate 300 mg daily reduced the number and size of aphthous ulcers in comparison to placebo (e29) *(eTable1)* (EL 2A). In patients with pre-menstrual flares of oral aphthous ulcers, once yearly subcutaneous injections of testosterone helped in some cases (39). Estrogen-dominant oral contraceptives can also be employed (14, 21) (EL 4). An effect is first to be expected after 3 to 6 months.

FIGURE 2



Algorithm for the treatment of chronic recurrent oral aphthous ulcers to reduce the duration of illness and the size of the ulcers

Summary

Until the etiology of chronic recurrent oral aphthous ulcers is determined, all therapeutic measures are aimed at symptomatic relief. Topical measures should be preferred as first-line therapy because of their low risk for systemic side effects *(Figure 2)*.

Systemic measures should only be considered in addition to topical treatment in patients with a severe course and complex aphthosis; options include sucralfate, colchicine, pentoxifylline or prednisolone and combinations thereof. Systemic therapy with other immunosuppressive agents should be reserved for refractory or especially severe aphthous ulcers in patients with ABD.

Conflict of interest statement
The authors declare that no conflict of interest exists.

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KEY MESSAGES

- The prevalence of chronic recurrent oral aphthous ulcers is 2 to 10%. Women are somewhat more frequently affected.
- Iron deficiency anemia, neutropenia, folic acid deficiency, vitamin B12 deficiency, local trauma and other factors all can facilitate the development of oral aphthous ulcers
- Hard, acidic and salty food, alcohol and carbonated beverages should be avoided.
- In Germany only corticosteroids and topical antiseptics and anti-inflammatory agents are approved for therapy.
- In severe cases, topical treatment can be combined with systemic therapy, e.g. with colchicine, pentoxifylline or prednisolone.

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eBox, eTables:
www.aerzteblatt-international.de/14m0665

REVIEW ARTICLE

The Treatment of Chronic Recurrent Oral Aphthous Ulcers

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eBOX

International criteria for the diagnosis of Adamantiades-Behçet disease (2014) (9)

Recurrent oral aphthous ulcers	2
Skin lesions (papulopustules, erythema nodosum, thrombophlebitis)	1
Vascular involvement (arterial or venous thromboses, aneurysms)	1
Recurrent genital aphthous ulcers	2
Ocular involvement (hypopyon-iritis, uveitis)	2
CNS involvement	1
Positive pathergy test	1

Adamantiades-Behçet disease: 4 or more points

eTABLE 1

Systemic therapeutic options to reduce duration of illness and size of aphthous ulcers

Drug	Dose	Benefits	Controls	Number of probands	Length of study	Evidence level	Reference
Sucralfate	1 g q.i.d.	More rapid healing and less pain in 80% of patients compared to 13% with placebo and 38% with antacids (p<0.001)	Placebo solution and antacid solution	21	2 years	2A	(e19)
Colchicine	1 mg daily p.o.	ABD: fewer oral aphthous ulcers in men and women compared to placebo (p<0.005)	Placebo	169	4 months, then switch therapy	2A	(e16)
Colchicine	1–2 mg daily p.o.	ABD: no significant difference from placebo	Placebo	50 (48% women)	24 weeks	2A	(e17)
Benzathine penicillin plus colchicine	Benzathine penicillin 1.2 IU monthly i.m. plus colchicine 1–1.5 mg daily p.o.	ABD: Reduction in frequency and duration of disease compared to colchicine alone (p<0.005)	Colchicine	154	24 months	2A	(e18)
Pentoxifylline*	400 mg daily p.o.	Reduction in aphthous ulcer size (p = 0.05)	Placebo	14 (pentoxifylline) and 16 (placebo)	2 months	2A	(31)
Prednisone vs. montelukast*	Prednisone 25 mg daily for 15 days, 12.5 mg daily for 15 days, 6.25 mg daily for 15 days, 6.25 mg q.o.d. for 15 days p.o.; montelukast 10 mg daily for 1 month and then q.o.d. for 1 month p.o.	More rapid healing and reduction in frequency of flares with prednisone vs. montelukast and montelukast vs. placebo (p<0.0001), with both fewer oral aphthous ulcers than with placebo (p<0.01)	Cellulose placebo	20 (prednisone), 20 (montelukast), and 20 (placebo)	2 months plus 2 month follow-up	2A	(33)
Dapsone	100 mg daily p.o.	ABD: Reduction in number, duration (p<0.001) and frequency (p<0.01)	Placebo	20	3 months	2A	(e20)
Zinc sulfate vs. dapsone	Zinc sulfate 300 mg daily p.o.; dapsone 100 mg daily p.o.	Zinc sulfate and dapsone: smaller and fewer lesions compared to placebo	Placebo	15 (dapsone), 15 (zinc sulfate) and 15 (placebo)	3 months	2A	(e29)

* evaluated as ineffective in (29). ABD, Adamantiades-Behçet disease

eTABLE 2

Systemic therapeutic options to reduce frequency of attacks or number of aphthous ulcers

Drug	Dose	Benefits	Controls	Number of probands	Length of study	Evidence level	Reference
Cyclosporine	Cyclosporine 10 mg/kg BW daily p.o., colchicine 1 mg daily p.o.	ABD: Oral aphthous ulcers improved by 70% with cyclosporine vs. 20% with colchicine (p<0.001)	Colchicine	47 (cyclosporine), 49 (colchicine)	16 weeks	2A	(37)
Thalidomide	100 or 300 mg daily p.o.	ABD: Reduction in frequency of oral aphthous ulcers after 4 weeks (p<0.001)—same effects with 100 and 300 mg daily	Placebo	96 (only men)	24 weeks	2A	(e24)
Interferon-α-2a	6 million IU 3 times weekly s.c.	ABD: Reduction in duration (p = 0.02) and pain (p = 0.01) vs. placebo	Placebo	50 (38% women)	3 months	2A	(e26)
Interferon-α-2b plus colchicine plus benzathine penicillin	Interferon-α-2b 3 million IU q.o.d., colchicine 1.5 mg daily p.o., benzathine penicillin 1.2 million IU every 3 weeks	ABD: fewer flares of aphthous ulcers (p = 0.007) in the interferon-α-2b group compared to controls	Colchicine plus benzathine penicillin	65 (interferon-α-2b, colchicine and benzathine penicillin), 65 (colchicine and benzathine penicillin)	1 year	2A	(e27)
Etanercept	25 mg twice weekly s.c.	ABD: Reduction in number of lesions and greater likelihood of being free of disease (p = 0.0017)	Placebo	40 (only men)	4 weeks	2A	(e33)
Doxycycline*	20 mg b.i.d. p.o.	Reduction in days with new aphthous ulcers (p = 0.04)	Placebo	25 (doxycycline), 25 (placebo)	2 months	2A	(e28)
Clofazimine*	Clofazimine 100 mg daily p.o. for 30 days, then 100 mg p.o. q.o.d.	More ulcer-free intervals (in 17–44%) than in the other groups	Placebo and colchicine 0.5 mg daily	23 (clofazimine) , 23 (colchicine), and 20 (placebo)	6 months	2A	(e34)

* evaluated as ineffective in (29). BW, body weight; ABD, Adamantiades-Behçet disease