Review Article

Practical aspects of management of recurrent aphthous stomatitis

A Altenburg,†¶ MB Abdel-Naser,*†¶ H Seeber,§ M Abdallah,‡ CC Zouboulis*†

†Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Dessau, Germany
‡Department of Dermatology and Venereology, Ain Shams University, Cairo, Egypt
§Department of Otolaryngology, Dessau Medical Center, Dessau, Germany

*Corresponding author, Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Auenweg 38, 06847 Dessau, Germany, tel. +49 340 5014000; fax +49 340 5014025; E-mail: christos.zouboulis@klinikum-dessau.de
¶These authors contributed equally to the manuscript.

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Abstract

Treatment of recurrent aphthous stomatitis (RAS) remains, to date, empirical and non-specific. The main goals of therapy are to minimize pain and functional disabilities as well as decrease inflammatory reactions and frequency of recurrences. Locally, symptomatically acting modalities are the standard treatment in simple cases of RAS. Examples include topical anaesthetics and analgesics, antiseptic and anti-phlogistic preparations, topical steroids as cream, paste or lotions, antacids like sucralfate, chemically stable tetracycline suspension, medicated toothpaste containing the enzymes amyloglucosidase and glucoseoxidase in addition to the well-known silver nitrate application. Dietary management supports the treatment. In more severe cases, topical therapies are again very useful in decreasing the healing time but fail to decrease the interval between attacks. Systemic immunomodulatory agents, like colchicine, pentoxifylline, prednisolone, dapsone, levamisol, thalidomide, azathioprine, methotrexate, cyclosporin A, interferon alpha and tumour necrosis factor (TNF) antagonists, are helpful in resistant cases of major RAS or aphthosis with systemic involvement.

Introduction

Common aphthosis is characterized by recurrent attacks of a single or multiple very painful small pin-head to several centimetres in size ulcers that are covered by fibrin and surrounded by hyperaemic rim on the mucous membrane of the mouth and rarely that of the genital region (figs 1–3). In general, the prognosis of recurrent aphthous stomatitis (RAS) is favourable and can undergo spontaneous remission after several years. They should, however, be differentiated from other causes of erosions and ulcers affecting oral mucous membrane.¹

The aetiology of benign aphthosis is not clear. One third of patients give a positive family history, and there is an association with certain HLA types. In addition, the occurrence of recurrent aphthosis could be due to an underlying definite disease, such as anaemia due to folic acid or iron deficiency or familial selective vitamin B12 absorption deficiency, or due to the so-called cyclic neutropenia. Other aetiological factors may be due to stress, trauma, cessation of tobacco smoking or celiac disease.²

fig. 1 Small oral aphthous ulcers.

Three types of RAS are recognized: minor RAS, the most common type; major RAS; and herpetiform RAS. Minor oral aphthae are less than 1 cm in diameter and usually heal within 4 to 14 days (fig. 1), whereas major
Management of recurrent aphthosis

Altenburg et al.

aphthae, also known as ‘Sutton’s’ ulcers or periadenitis mucosa necrotica, are larger than 1 cm and are often deeper than minor RAS and heal within 10 to 30 days (fig. 2). Herpetiform ulcers are grouped aphthae, 1 to 2 mm in size and extremely painful (fig. 3). Another classification differentiates simple aphthae with three to six attacks per year, which are few in number, heal rapidly, are not very painful and are restricted to the oral mucosa from continuously recurrent, few to multiple complex aphthae, which are extremely painful, heal slowly and can also occur in the genital region (figs 4, 5).¹

Differential diagnosis includes diseases that may result in similar lesions, such as Crohn's disease, erythema multiforme, and its variant Stevens–Johnson syndrome, Reiter's syndrome, syphilis, autoimmune bullous dermatoses (pemphigus, cicatricial pemphigoid, epidermolysis bullosa acquisita), viral infections (Herpes, Coxsackie, Echo, human immunodeficiency virus) or involvement of the mucous membrane in systemic lupus erythematosus. In case of the malignant aphthosis such as in Adamantiades–Behçet disease, there is a temporal increase of the frequency and severity of the attacks of aphthosis.⁴

Treatment of RAS is symptomatic and based mainly on empirical basis. It is mainly directed at relieving pain and diminishing functional disability, inhibition of the acute inflammatory reaction as well as the frequency and the degree of severity of the recurrences.
Dietary and general measures

Diet and food items that have been frequently reported by patients to be responsible for the causation or exacerbation of the aphthosis should be avoided. In general, patients are instructed to avoid hard food (e.g. hard toasted bread), all types of nuts (walnuts, hazel-nut, etc.) in addition to chocolates with nuts, acidic foods or drinks (fruit juices, citrus fruits, tomatoes), salty meals, strong spicy food (pepper, capsicum, curry) and alcoholic and carbonated beverages. In addition, patients are instructed to avoid teeth cleaning products and toothpastes containing sodium lauryl sulphate.7

Topical therapy

Local anaesthetics

Locally acting symptomatic preparations can relieve symptoms and decrease the duration of the attack. A satisfactory decrease of the pain can commonly be attained by the local application of anaesthetics.6 Lidocaine as a 2% containing gel (Dynexan mouth gel, Gelicaine 2% gel, Xylocaine 2% gel, Lidocaine 2% gel, lidocain and chamomile extract in Kamistad gel N), or as a spray (Xylocaine pump spray, Xylestesin pump spray, Wick Sulagil throat spray), polidocanol as a paste (Solcoseryl adhesive dental paste), and benzocaine in the form of lozenges (Anaesthesin or Dolo-Dobendan lozenges) can be used. There are also combination preparations, such as Mepivacaine 1.5% and Polidocanol 1% (Meaverin gel), Benzocaine and Benzalconium chloride (Zorac) or Tetracaine 5% and Polidocanol 1% (Acoint pump spray). Ready-made mouthwashes, such as Benzocaine and Cetyl pyridinium chloride (Dolo-Dobendan) or Cetyl puridin and Amine fluoride (Ezaffluor), are available. Solutions containing local anaesthetics can be carefully applied with an applicator directly on the lesions (Lidocaine in Xylocaine viscous 2% solution, Tetracaine in Gingoicaine D sol.).

Antiseptic/anti-inflammatory therapeutics

Treatment with local antiseptic and anti-inflammatory drugs can be tried to decrease the duration of the attack. Mouthwashes with mild inhibitors of inflammation are prescribed [e.g. chamomile extract in Kamillosan sol. or Chlorhexidine-containing mouthwashes (Corsodyl sol., Cidogel C sol., Chlorhexamide fluid, Chlorhexidine gluconate sol. 2%, Antiseptal, Hysoplac)]. In particular, for chlorhexidin mouthwashes, several controlled studies have shown the beneficial effect on the incidence, duration and the severity of the ulceration.2,8 Other application forms of chlorhexidine (e.g. CHX dental gel, DG-care oral gel, Ez-care, Elgyodium toothpaste or Fribulurgyl throat spray) can also be tried. As an adjuvant, dexamethasone in different application forms (Panthenol spray, Bepanthen sol., Bepanthen lozenges) can be applied.

Triclosan-containing toothpastes and mouthwashes (Rutisept extra 0.1%) are new local treatment applications. It is a local antiseptic substance that has also anti-inflammatory and analgesic characters.8 In a randomised study, locally applied diclofenac 3% in 2.5% hyaluronan resulted in a significant decrease of pain than that of 3% lidocaine gel.10

Local cauterization effect

Local cauterization by hydrogen peroxide solution 0.5% or with silver nitrate solution 1% to 2% or silver nitrate pen is an already known old and quite effective method to decrease the duration of the individual aphthae.6

Local therapy with tetracycline

Our experience and reports of several other studies have shown that therapy with tetracycline effectively decreases the duration and the pain of the aphthae.6,11-12 To avoid the stability problem in obtaining tetracycline hydrochloride in watery solution and consequently as a mouthwash, the required amount can be divided per use as a powder. We recommend here individual, already filled small containers or hard capsules each with 250 mg, which can be taken together with 5 mL drinking water as a mouthwash. Because of the acidic pH values, there may be a burning sensation that remains for a short time. This is generally followed by improvement of the condition. Chemical stability is achieved through neutralization of the tetracycline hydrochloride and the use of a specific base. A standardized preparation for the composition of this chemical stability is known in the Netherlands13 (Table 1).

In addition, the ready-formed preparation Aureomycin dental paste that contains 3% chlorotetracycline showed in a double-blind placebo-controlled study marked improvement in the duration and severity of pain.14 Tetracycline therapy is contraindicated in pregnancy.

Locally applied 5-aminosalicylic acid is an alternative to local tetracycline. A double-blind, placebo-controlled trial applying 5% 5-aminosalicylic acid in a cream form thrice daily showed marked improvement in 22 patients with oral aphthosis.15

Sucralfate

Sucralfate is a water-insoluble salt preparation of aluminium hydroxide and saccharosesulphate. It was originally used as an antacid for the treatment of peptic ulcers resulting
in an immediate pain relief. Local sucralfate (Sucrabest Granulat, Ulcogant – IC Suspension; e.g. 4 × 5 mL daily over 3 months) proved in several studies as an effective treatment in reducing the duration and pain of oral aphthosis.\(^{16,17}\)

**Local steroids**

Topical steroids are reserved for cases that show inadequate success from the combination of local anaesthetics and anti-inflammatory agents. Steroids inhibit the inflammatory reaction and can decrease the duration of the aphthosis. Traditionally, once or twice daily application of triamcinolone acetonide in orabase (Kenalog in orabase) or adhesive paste or prednisolone in mouth ulcer healing paste (Dontisolon D) in the mouth can be used. Betamethasone (Celestamine N 0.5 liquid) can be used as a mouthwash. The combination of a local anaesthetic during daytime (e.g. Dynexan A gel) and triamcinolone adhesive paste at night has been proved to be very effective.\(^{18}\)

Long-term use of local steroids may predispose to local candidal infection.\(^{19}\) The use of intraliesional injection of triamcinolone (10 mg/mL given 0.1–0.5 mL per lesion) is recommended only for painful deep aphthae.

Genital ulcers respond well to a combination of fluorinated steroids and antiseptics in a cream base form [e.g. dexamethasone 1% + chlorhexidine 1%, diflucortolone + chlorquinaldol (Nerisone C) and flumethasone + clioquinol (Locacorten vioform)].\(^{20}\)

**New local therapeutics**

A Swedish double-blind trial involving 33 patients showed that toothpaste containing the enzymes amylglucosidase and glucose oxidase was effective in reducing the number of attacks of aphthosis and pain.\(^{21}\)

Topical use of prostaglandin E2 gel prevented the appearance of new aphthae in a short duration (10 days) study.\(^{22}\) An association between smoking and the decrease of recurrence frequency of aphthae has been observed. Both number and frequency of lesions decreased during phases of smoking when compared with the phases of abstinence, and experimental data indeed confirmed the anti-inflammatory effect of nicotine and biochanin A on keratinocytes.\(^{23,24}\) Locally applied nicotine patches were not as effective as smoking (unpublished, personal observation). A very small study employing nicotine-containing chew tablets showed complete remission of recurrent aphthous ulcers,\(^{25}\) but results of larger studies are needed.

**Systemic therapy**

**Cholchicine**

Cholchicine (Colchicin tablets) inhibits the chemotactic activity of neutrophils. Most patients with common aphthosis respond well to cholchicine by decreased number and duration of lesions, although it is not always effective.
in all types of recurrent aphthosis. Therefore, a therapeutic trial at least over 4 to 6 weeks in a dose of 1 to 2 mg/day orally is recommended, which is followed by long-term therapy according to tolerability and clinical response. In a large study of Fontes et al., colchicine markedly improved the symptoms of RAS in 63% of cases within 3 months of therapy and in 37% over several years. Recurrence of the aphthae is common following cessation of therapy and after a favourable therapeutic response. Colchicine should not be used during pregnancy. A contraceptive method should be applied in women for 3 months and in men up to 6 months after cessation of therapy. In severe cases, resistant to monotherapy with colchicine, combination with pentoxifylline, prednisolone, immunosuppressants or interferon alpha can be tried.28–30

**Pentoxifylline**

Pentoxifylline inhibits production of various pro-inflammatory cytokines, such as TNF alpha, and exhibits a suppressive effect on CD8-positive T cells. In uncontrolled studies, pentoxifylline (300 mg 1–3 times per day) and oxypentoxifylline (400 mg 3 times per day) have been shown to improve orogenital symptoms (e.g. in children). Response rates varied between 36% and 63% and were rapidly followed by recurrences as soon as the medication was stopped.28–30

**Systemic corticosteroids**

Oral and intravenous steroids are often used in acute exacerbation, generally in combination with other immunosuppressants, colchicine or dexamethasone. Dapsone (DADPS, Dapsone). Prednisolone or its equivalent (10–30 mg/day) is usually given during the attacks to decrease the duration of aphthosis. Steroids are usually used for a short period (up to 1 month), as appearance of new ulcers cannot be avoided. Steroids are one of the few systemically administered drugs that can be used during pregnancy.5

**DADPS**

DADPS (Dapsone, 100–150 mg/day) can also be used for oral and genital aphthae. A 12-month double-blind study treatment with Dapsone showed a significant improvement.31 Intermittent administration of ascorbic acid (e.g. Cebion, 500 mg/day) is advisable during treatment. Dapsone inhibits the elevated neutrophil chemotactic activity. Rapid relapse often occurs after discontinuation of therapy. Haemolysis, methaemoglobinemia and agranulocytosis are serious side-effects that may occur.

**Levamisol**

The effect of levamisol (150 mg/day on three successive days per week) against oral and genital aphthae, with or without combination with steroids (15 mg prednisolone), has been reported. Due to the risk of agranulocytosis, close patient monitoring is recommended.32,33

**Thalidomide**

Thalidomide, a cyclic derivative of glutamic acid, proved to be effective in low dose (50 mg/day) against major type RAS and orogenital ulcers. Usual doses are 100 to 300 mg/day. A dose-dependent effect is seen in general within 7 to 10 weeks. Recurrence occurs in about 3 weeks after cessation of therapy. Thalidomide reduces the production of TNF alpha, inhibits the chemotaxis of neutrophils and plays a role as inhibitor of angiogenesis. Expected side-effects include temporary cerebral symptoms such as headache and lethargy during the day and xerostomia and constipation. Thalidomide is not available in the market for the past four decades due to the severe congenital defects it produced. Informing patients about the potential risks, a written consent and adequate contraception are important. The therapy is restricted to particular cases due to teratogenicity and side-effects such as peripheral neuropathy.18

**Anti-metabolites: azathioiprine and methotrexate**

Azathioprine, a mercaptopurine derivative, inhibits purine ring synthesis. Azathioprine as a monotherapy or in combination with other immunosuppressants, administered in a dosage of 1 to 2 mg/kg/day (100–150 mg/day), has been shown in placebo-controlled studies to reduce the incidence, frequency and severity of severe orogenital aphthae.35 Possible side-effects include infertility, myelosuppression, opportunistic infection and liver damage, and it is contraindicated in the presence of these conditions as well as during pregnancy and lactation. During childhood, it may interfere with growth and is therefore not recommended for children. Blood picture should be monitored every month and liver function every 3 months.

Methotrexate, a folic acid analogue, in a dose of 7.5 to 20 mg weekly proved to be effective in severe orogenital aphthosis. Intermittent folic acid administration should be given after methotrexate intake. Pregnancy, lactation, severe bone marrow depression, liver function abnormalities, peptic ulcers and renal insufficiency are the main contraindications. Long-term therapy requires monthly monitoring of blood picture and liver function.36
Management of recurrent aphthosis

Immunomodulators/calcineurin inhibitors (cyclosporine A)

Cyclosporine A therapy in a dose of 3 to 6 mg/kg/day was effective in about 50% of patients with recurrent aphthosis either as a monotherapy or in combination with steroids to achieve a higher anti-inflammatory effect. Cyclosporine A is a cytostatic agent that primarily inhibits T-cell activation and recruitment. Rapid dose reduction or abrupt withdrawal can lead to rebound phenomenon. Serum levels of 100 to 150 ng/mL are desirable. Its use is absolutely contraindicated in nursing women. Pregnancy and renal insufficiency are considered relative contraindications. Local cyclosporine A in oral paste is ineffective.18

Alkylating agents: chlorambucil and cyclophosphamide

Therapy with alkylating agents (i.e. chlorambucil and cyclophosphamide) should be reserved for severe cases of aphthosis. Chlorambucil interferes with cross-linking during DNA replication and inhibits B- and T-cell function and marked improvement of orogenital ulceration in Adamantiades–Behçet disease has been frequently reported. In general, chlorambucil (leukeran) is given initially in a dose of 6 to 8 mg/day.19 With a less maintenance dose (2 mg/day), complete absence of lesions with chlorambucil as a monotherapy could be achieved.19 Severe cases of Adamantiades–Behçet disease, which have been treated with cyclophosphamide due to affection of the internal organs (e.g. nervous system manifestation), showed also marked improvement of the orogenital aphthae.20

Interferon alpha

Interferon alpha 2a (Roferon A) and b (Intron A) have been successfully used in the treatment of mucocutaneous forms of the disease, resulting in the majority of cases in complete or partial remission of oral and genital lesions.19,40 Intermediate (e.g. 6 × 106 IU thrice a week) or high doses (e.g. 9 × 106 IU thrice a week) are principally more effective than low doses (3 × 106 IU thrice a week). Low doses are recommended as a maintenance therapy when treatment is successful in the first 1 to 4 months. A combination therapy with steroids or colchicine is also possible; however, an antagonizing effect with immunosuppressants may occur. In most studies, there is a rapid recurrence following stoppage of interferon therapy, although there is also a rapid response following re-administration. Paracetamol (500 mg orally 1 h before and after the injection) is usually given to decrease the initial dose-dependent flu-like symptoms as a side-effect. Mild leucopenia and or alopecia may occur. Interferon alpha 2c (10 × 106 IU/g) in a locally applied gel is ineffective in the management of oral aphthae.

Biologics: infliximab and etanercept

Recently it has been shown that infliximab (Remicade), a chimeric anti-TNF antibody, is very effective in the management of refractory and recurrent oral and genital ulcers. It is usually given in a dose of 5 mg/kg body weight intravenously in different schemes (e.g. 2, 6 and 32 weeks after the first injection). Few days following the first dose, there is rapid healing of the lesions with no evidence of recurrence for 6 to 8 weeks.41

Etanercept, a dimer fusion protein of 75-kDa TNF alpha receptor and the Fc portion of human IgG1 is subcutaneously injected twice weekly. A recent study showed that etanercept (Enbrel 2 × 25 mg/week subcutaneously) has a favourable effect on oral aphthae, whereas it seems that it has no effect on genital ulcers.42

Other systemic therapies

Minocyclin was found effective in a dose of 100 mg/day for 6 months regarding the number and recurrence rate of genital ulcers in a study involving 13 patients but had no effect on oral aphthosis. Subcutaneous testosterone injected yearly can be effective in premenstrual erupted aphthae in some cases.43 In addition, high oestrogen containing contraceptive pills can be used; however, the effect is to be expected after 3 to 6 months.18

References


