CLINICAL PRACTICE

Aphthous Ulceration

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 20-year-old woman has had recurrent painful mouth ulcers for the past 10 years. She is otherwise healthy and reports no genital or anal ulcers, skin lesions, gastrointestinal or joint problems, or fevers. Physical examination reveals several ulcers, 3 mm in diameter, on her buccal mucosae. She has no lesions on the skin or on other mucosal surfaces. How should she be evaluated and treated?

THE CLINICAL PROBLEM

Recurrent aphthous stomatitis (also referred to as aphthae, or canker sores) is one of the most common oral ailments. The disease is characterized by recurring painful ulcers of the mouth that are round or ovoid and have inflammatory halos. The ulcers typically appear first in childhood (patients often have a family history of recurrent aphthous stomatitis) and tend to abate around the third decade.[1,2] The term "recurrent aphthous stomatitis" should be reserved for recurrent ulcers confined to the mouth and seen in the absence of systemic disease. However, ulcers that resemble recurrent aphthous stomatitis in some respects, such as their clinical appearance, can be found in systemic disorders such as Behçet's syndrome, gastrointestinal diseases such as gluten-sensitive enteropathy or inflammatory bowel disease, and immunodeficiency syndromes such as infection with the human immunodeficiency virus (HIV) or cyclic neutropenia. If these ulcers do not have all the typical clinical characteristics or an onset in childhood, they are often termed "aphthous-like ulcers." This review focuses on the evaluation of patients presenting with recurrent oral ulcers and the management of such ulcers in the absence of systemic disorders.

Approximately 80 percent of patients with recurrent aphthous stomatitis present with minor aphthous ulcers. These are 2 to 8 mm in diameter, affect nonkeratinized mucosae such as the labial and buccal mucosae and the floor of mouth or the ventral surface of the tongue (Fig. 1), are rarely seen on the dorsum of the tongue or on the hard palate or gingiva, and heal spontaneously in 10 to 14 days.[3] Much less common are major aphthous ulcers (sometimes termed "periadenitis mucosa necrotica recurrens"). These ulcers are larger than minor ulcers — often 1 cm or more in diameter (Fig. 2). A third and even less common variety is termed "herpetiform ulceration" (unrelated to herpetic stomatitis) and comprises ulcers that are initially multiple and pinpoint. Both major and herpetiform ulcers are more likely than minor ulcers to lead patients to seek professional help, since these ulcers are particularly painful, last several weeks, and can affect the dorsum of the tongue and the hard palate, as well as the buccal and lip mucosae.

Cross-sectional studies suggest that recurrent aphthous stomatitis is more common in women, in people under the age of 40 years, in whites, in nonsmokers, and in people of high socioeconomic status.[4-6] Recurrent aphthous stomatitis affects

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Figure 1. Minor Aphthous Ulcer on the Lateral Margin of the Tongue.
The ulcer is small and round, with an erythematous halo (arrowhead).

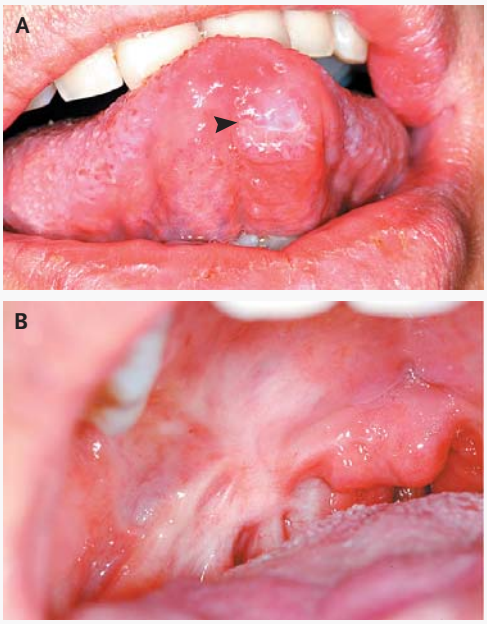

Figure 2. Major Aphthous Ulceration.
Panel A shows a large ulcer on the ventral surface of the tongue (arrowhead). Panel B shows pronounced scarring of the fauces.

up to 25 percent of the general population at some time.

Both hereditary[7] and environmental causes of the disease have been suggested. Deficiencies of iron, vitamin B, or folate have been reported in some patients with recurrent aphthous stomatitis,[8-12] but the data are conflicting,[13] and neither iron nor vitamin supplements reliably increase the likelihood of ulcer resolution.[10,12,14] Infection with various microorganisms has been suggested but not proven to be a contributing factor, although cross-reactions between a microbial antigen and a homologous peptide within the oral epithelium may play a role.[15]

Various factors have been suggested to precipitate outbreaks of recurrent aphthous stomatitis in predisposed persons, including oral trauma, the cessation of smoking[4,16] (for reasons that are unclear), anxiety or stress,[17] sensitivities to food (e.g., to preservatives and agents such as benzoic acid or cinnamaldehyde), and hormonal changes related to the menstrual cycle.[18] However, evidence to support the causative role of these factors is scarce.

STRATEGIES AND EVIDENCE

EVALUATION

The diagnosis of recurrent aphthous stomatitis rests mainly on two features: a history of recurrent ulcers since childhood (though a small number of cases first appear at a later age) and the presence of the typical multiple round or ovoid ulcers on examination. The first episode of recurrent aphthous stomatitis is more difficult to identify than subsequent episodes, but a family history of the disease may suggest that diagnosis. In addition, although most cases of recurrent aphthous stomatitis are idiopathic, a careful history taking and physical examination should be performed to rule out a secondary cause (Table 1). This step is particularly important in atypical cases, such as those in which the ulceration begins after adolescence or if lesions affect sites other than the oral mucosa.

Features such as persistent diarrhea that are suggestive of systemic disease should raise the possibility of Crohn's disease or ulcerative colitis.[20] Weight loss or other signs of malabsorption may suggest gluten-sensitive enteropathy, although this disease was present in less than 5 percent of patients with recurrent aphthous stomatitis who attended a hospital clinic.[12,21] (In rare instances, patients with recurrent aphthous stomatitis have no detectable histologic evidence of gluten-sensitive enteropathy, yet they appear to have a response to the exclusion of gluten from the diet[22]; this apparent response may reflect a placebo effect.) The presence of genital ulceration should raise the suspicion of Behçet's syndrome or the possibly related condition, complex aphthous sto-

Table 1. Differential Diagnosis of Recurrent Mouth Ulcers.

Cause	Examples	Suggestive Findings	Basis of Diagnosis
Unknown	Aphthae	A history of recurrent round or ovoid mouth ulcers since childhood	Clinical presentation and the exclusion of systemic illnesses
	Periodic fever, aphthae, pharyngitis, and adenitis Tumor necrosis factor receptor–associated periodic syndrome	A history of recurrent mouth ulcers since childhood; recurrent fever, pharyngitis, lymphadenitis	Clinical presentation and the exclusion of other systemic illnesses
Infections	Recurrent infection with herpesvirus*	A history of recurrent localized ulcers, sometimes aphthous-like, usually on the palate or tongue, generally at the same site in each episode, often appearing after oral trauma; may be evidence of immunocompromised state	Clinical presentation and virologic studies
	HIV infection	Intraoral infections (candidiasis, hairy leukoplakia) or neoplasms (Kaposi's sarcoma, lymphoma); other clinical evidence of or risk factors for HIV infection	Clinical presentation and HIV testing
Rheumatic diseases	Behçet's syndrome	Aphthous-like ulcers occurring on genital or other mucosae; skin pustules, erythema nodosum, or other lesions; uveitis; joint involvement; central nervous system manifestations	Clinical presentation and serologic testing to rule out other conditions
	Reactive arthritis (Reiter's syndrome)	Urethritis; colitis; keratoderma blennorrhagicum; conjunctivitis; balanitis; joint and other involvement; usually found in men	Serologic testing to rule out other conditions
	Sweet's syndrome	Red plaques on skin; fever; aphthous-like ulcers on genital or other mucosae; often associated with other conditions (e.g., inflammatory bowel disease, leukemia)	Serologic testing to rule out other conditions
Cutaneous diseases†	Erythema multiforme	Lesions on mucosae other than oral or on skin or eyes; lip swelling	Clinical presentation and biopsy of perilesional tissue
Hematologic diseases	Cyclic neutropenia	Recurrent fevers; associated intraoral and other recurrent infections; onset in childhood or adolescence	Clinical presentation and complete blood count
	Leukemias	Infections; anemia; petechiae or purpura	Complete blood count
Gastrointestinal diseases	Gluten-sensitive enteropathy	Dental defects; malabsorption; bloating; diarrhea; weight loss	Clinical presentation; presence of antigliadin and transglutaminase antibodies; biopsy of small intestine
	Inflammatory bowel disease (ulcerative colitis, Crohn's disease)	Labial or facial swelling; bloody diarrhea; weight loss; occasionally, joint manifestations; hepatobiliary disease	Clinical presentation and colonoscopy or biopsy of ulcer tissue
Drugs	Nonsteroidal antiinflammatory drugs Beta-blockers Nicorandil (Ikorel) Alendronate (Fosamax)	Rash	History and response to drug withdrawal

* In rare instances, cytomegalovirus infection may have a similar presentation in immunocompromised patients.
† The early phages of pemphigus may be characterized by recurring ulcers.[19]

matitis; it is rare for patients apparently presenting with recurrent aphthous stomatitis subsequently to be found to have Behçet's syndrome.[23-26] Joint pain or swelling or urethritis suggests the possibility of a syndrome of reactive arthritis (formerly known as Reiter's syndrome), which is an associated condition. The history taking and examination should also focus on risk factors for or manifestations of HIV infection.[27] Table 1 lists several systemic conditions that may result in aphthous-like ulcers and features that suggest them.[19-33]

Medications should also be reviewed. A case–control study has shown that aphthous-like ulceration is associated with nonsteroidal antiinflammatory agents and various beta-blockers.[31]

Other drugs linked in observational studies to aphthous ulceration include those that damage neutrophils (such as cytotoxic agents), as well as nicorandil[32] and alendronate.[33] Sodium lauryl sulfate, a component of many toothpastes and other products, may also occasionally predispose people to aphthous ulceration; although some data have suggested a reduced incidence of ulceration when the patient stops using the product, a double-blind crossover trial showed no significant effect of excluding toothpaste containing sodium lauryl sulfate on the incidence or pattern of aphthous ulceration.[34]

Any ulcer that persists for three or more weeks, whether painful or not, requires further evaluation to rule out cancer, infection (e.g., with herpes simplex virus or cytomegalovirus, particularly in immunocompromised patients, and syphilis, tuberculosis, a deep mycosis, or leishmaniasis), and other serious disorders, such as vasculitis. Clinical signs suggestive of cancer include associated swelling or induration and a red or white lesion such as leukoplakia, especially if there is ipsilateral cervical lymphadenopathy.[35] Chronic ulceration may also indicate an underlying mucocutaneous disease such as lichen planus, pemphigus, or pemphigoid; on examination, these can generally be distinguished from recurrent aphthous stomatitis, since the ulcers tend not to have the characteristic ovoid or round shape or clearly defined outlines. Figure 3 shows examples of oral ulcers caused by conditions other than aphthous stomatitis.

INVESTIGATIONS

If the results of the history taking and examination are characteristic of recurrent aphthous stomatitis, routine laboratory testing is probably not warranted, since such testing is ineffective for identifying treatable disorders of this type. Some experts advocate the performance of a complete blood count and measurement of the levels of red-cell folate, serum vitamin B_{12}, and serum ferritin, although data in support of routine testing are lacking. This approach is more likely to be useful if other findings suggest a nutritional deficiency or a hematologic disorder.

A biopsy should be considered for solitary or multiple ulcers that last more than three weeks. Immunostaining is mandatory if a mucocutaneous disorder is suspected. The need for additional analyses, such as serologic tests for rheumatologic disease, cultures or other specific tests for infectious agents (such as herpes simplex virus, cytomegalovirus, or HIV), and evaluation for gastrointestinal disease, should be guided by the presence of features suggestive of these disorders.

TREATMENT

The treatment choices should be guided by the severity of the disease (the amount of pain), the frequency of ulceration, and the potential adverse

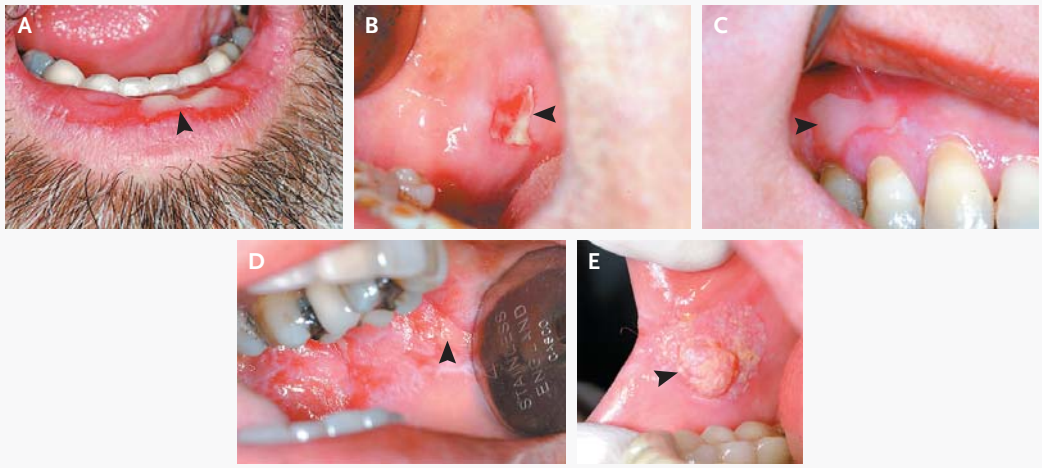

Figure 3. Oral Ulcers Caused by Conditions Other Than Aphthous Stomatitis.
Panel A shows lichen planus with a superficial irregular erosion on the lip (arrowhead). Panel B shows pemphigus on the buccal mucosa, with irregular ulceration (arrowhead). Panel C shows pemphigoid on the gingiva (arrowhead), causing erosion. Panel D shows lupus erythematosus with irregular ulceration on the buccal mucosa (arrowhead). Panel E shows squamous-cell carcinoma on the buccal mucosa in the form of a mass that has ulcerated (arrowhead).

effects of the medications. In the absence of a clearly defined cause, the treatment is aimed primarily at pain relief and the reduction of inflammation. If an underlying disorder is present, effective treatment of the condition may result in the remission or amelioration of the ulcers, but the interventions discussed below may help in the interim before diagnosis. Referral to a specialist is indicated if cancer is suspected, if there is evidence of an associated systemic disease, or if ulceration is severe (particularly painful, frequent, or disabling).

Minor Ulcers

For the management of minor aphthous ulcers, patients should avoid oral trauma (for example, from hard toothbrushes or foods such as toast) and acidic foods or drinks that may exacerbate pain or perhaps precipitate ulcers.[1] Although nicotine-replacement therapy may help people whose ulcers arise on smoking cessation, only a small open-label trial showed a benefit.[36] Clinical experience suggests that topical analgesics (such as benzydamine or lidocaine) and protective bioadhesives (such as carmellose or cyanoacrylate[37]) can help relieve pain,[1] although data from clinical trials are limited.

Randomized clinical trials support the use of some topical treatments to speed healing and reduce pain[38] (Table 2). These therapies are mainly used for aphthae that recur more often than monthly and for any ulcers that are bothersome. However, much of the evidence in support of these interventions is from small and incompletely blinded trials, and the efficacies of the interventions are generally modest.

Topical corticosteroids may speed the healing of ulcers and reduce pain. The Food and Drug Administration (FDA) has approved 1 percent triamcinolone dental paste (Adcortyl or Kenalog in Orabase) for the relief of symptoms of any inflammatory condition in the mouth. Other, more potent topical corticosteroids or other related preparations (such as a 2.5-mg lozenge of hydrocortisone, taken four times daily for two weeks[1,39]) may be useful, although they are not specifically approved for this indication. In a single-blind trial, patients with recurrent aphthous stomatitis who were randomly assigned to receive topical 0.05 percent fluocinonide in Orabase up to five times daily for 6 weeks had a mean ulcer duration of 4.9 days, as compared with 7.8 days in the placebo group.[40] A randomized, double-blind trial demonstrated a significant reduction in the duration of multiple ulcers with the use of betamethasone aerosol four times daily for 4 to 8 weeks (means, 8.5 days in the active group vs. 15.0 days in the placebo group).[41] However, these and other, more potent topical corticosteroids are not readily available in oral pastes (and thus are unlikely to remain on the oral mucosa). A risk of any of these therapies is oral candidiasis, and a concern is the systemic absorption of the drug through ulcerated oral mucosa.

Antimicrobial mouthwashes may also benefit patients with recurrent aphthous stomatitis. Mouthwashes containing chlorhexidine gluconate (Peridex, Periogard, Corsodyl) or triclosan (Plax, Total) inhibit the accumulation of bacterial plaque on teeth and improve oral hygiene; they are approved for use in the treatment of periodontal disease but not for aphthous stomatitis. The data from some, but not all, randomized trials support the benefit of such mouthwashes. In one trial, for example, patients using a 0.2 percent chlorhexidine gluconate mouthwash three times daily for 6 weeks had significantly longer ulcer-free periods (mean, 22.9 days) than patients who received a placebo (mean, 17.5 days).[42] Chlorhexidine gluconate mouthwashes interact with tannins to stain the teeth brown, although patients can reduce this staining by brushing their teeth before using the mouthwash and by minimizing their intake of tea, coffee, and red wine. In a double-blind crossover trial, 0.15 percent triclosan mouthwashes (three preparations differing in the solubilizing agent) used twice daily over a period of six weeks resulted in significantly fewer new ulcers (166 to 211 total) in the three triclosan groups than in the placebo group (290 total).[43] One double-blind trial also suggested that the use of Listerine mouthwash reduced the duration of lesions and associated pain.[44] Tetracycline mouth rinse (for example, the contents of a 100-mg doxycycline capsule dissolved in 10 ml of water by the patient and used as a rinse four times daily) may also benefit patients; its adverse effects may include tooth discoloration — if swallowed by a child — or local discomfort from candidiasis, particularly with prolonged use.

Five percent amlexanox paste (Aphthasol, Aphtheal) is a topical antiinflammatory treatment that is approved by the FDA for aphthous ulceration. In one small placebo-controlled, double-blind trial, patients receiving amlexanox (applied by the investigators twice daily for three days)

Table 2. Therapies to Consider for Recurrent Aphthous Stomatitis.

Drug	Route of Administration	Examples		Possible Adverse Effects, Contraindications, or Comments
		Preparation	Application or Dose	
Mild disease*				
Topical anesthetics†	Topical	0.15% Benzydamine oral rinse (Difflam, Tantum) 5% Lidocaine gel or viscous Xylocaine	Applied to ulcers 4 times daily for 2 wk or until ulcers heal	Occasional numbness or stinging; rare hypersensitivity reactions
Protective bioadhesives	Topical	Carmellose (Orabase: pectin plus gelatin)	Applied to ulcers 4 times daily for 2 wk or until ulcers heal	Possible religious objections to the use of gelatin in carmellose
Corticosteroids‡§	Topical, in adhesive base (carmellose), or as spray, cream, or pellet	1% Triamcinolone dental paste (Adcortyl or Kenalog in Orabase) Hydrocortisone, 2.5 mg pellets (Corlan) 0.05% Fluocinonide cream (Metosyn)	Applied to ulcers 4 times daily for 2 wk or until ulcers heal	Oral candidiasis (addition of antifungal agents to more potent corticosteroids recommended because of this possible risk) Possible religious objections to the use of gelatin in carmellose
Antimicrobial mouth rinses‡¶	Topical	0.12% or 0.2% Chlorhexidine gluconate aqueous mouthwash (e.g., Peridex) or 1% chlorhexidine gluconate gel	4 times daily for a variable duration (2 wk to months or longer)	Superficial tooth staining (mitigated by reducing intake of coffee, tea, and red wine)
Amlexanox (Aphthasol)‡	Topical	A 5% preparation in an adhesive base	Applied to ulcers 4 times daily for 2 wk or until ulcers heal	Stinging
Severe disease*				
Corticosteroids	Systemic	Tablet or capsule	Orally 30 to 60 mg for 1 wk, followed by a 1-wk taper	Increased blood pressure; hyperglycemia; other effects of corticosteroid excess
Thalidomide (Thalomid)‡‖	Systemic	Tablet	Orally 50 to 200 mg daily for 4 to 8 wk	Teratogenesis (contraindicated in pregnancy); neuropathy (monitoring of sensory-nerve action potentials every 3 mo recommended); drowsiness

* Mild disease refers to minor aphthous ulcers recurring frequently or considered sufficiently bothersome to warrant intervention. Severe disease refers to painful persistent ulcers — typically major ulcers.
† Alternatives include Maalox (a suspension containing aluminum hydroxide, simethicone, and magnesium hydroxide) used as swish and spit.
‡ The value of this agent is supported by data from randomized trials.
§ Triamcinolone dental paste can be effective if applied to a dried ulcer, but it rarely adheres to ulcers on the tongue; in the latter cases, another formulation should be used, such as hydrocortisone pellets. More potent corticosteroids — such as 500 μg of betamethasone (Betnesol) in a soluble tablet dissolved in 10 ml of water and used as a mouthwash four times daily — are alternatives but are not approved for this use.
¶ An alternative in more refractory cases is tetracycline–doxycycline mouthwash (e.g., the contents of a 250-mg capsule of tetracycline or a 100-mg capsule of doxycycline dissolved into 10 ml of water and used as a rinse four times daily for three days). The risks include tooth discoloration, if swallowed by a child, and candidiasis. This alternative should not be used by children under eight years of age, pregnant women, or women who are breast-feeding.
‖ This drug is not approved by the FDA for this use and should be considered only in extreme cases of recurrent aphthous stomatitis or aphthous-like ulcers (particularly in association with HIV infection or Behçet's syndrome).

had a significantly greater reduction in ulcer size on day 5 than did patients receiving placebo (median reduction, 76 percent vs. 40 percent) and their ulcers were more likely to be rated by the investigators as having improved, although changes in pain ratings did not differ significantly between the two groups. Another randomized trial compared the use of amlexanox (applied four times daily to the affected area) during the prodromal phase of ulcer symptoms with its use once an ulcer was evident. The likelihood of having an ulcer by day 3 was significantly lower in the early-use group (35 percent) than in the late-use group (97 percent). Early treatment with amlexanox also reduced the size, associated pain, and duration of the ulcers, as compared with late therapy or with a no-treatment run-in phase. However, the study was limited by the lack of a placebo group.[45,46]

Head-to-head comparisons of different agents are limited[38] and have failed to demonstrate the

superiority of a particular agent over others. For example, one small study comparing topical cyanoacrylate alone and cyanoacrylate applied over 0.025 percent triamcinolone acetonide or 0.012 percent chlorhexidine gluconate showed no differences in ulcer duration among the treatment groups.[47] These agents have not been well studied in combination.

Severe Aphthous Stomatitis

For patients with severe recurrent aphthous stomatitis, possible therapies include systemic corticosteroids or thalidomide.[26] A one-week course of 30 to 60 mg of oral prednisone or oral prednisolone (tapered over a second week) has been used in practice, although data that demonstrate a greater efficacy than with topical corticosteroids are lacking and there is an increased risk of adverse effects. In a randomized trial of patients with severe recurrent aphthous stomatitis, 45 percent of those treated with 100 mg of thalidomide daily for two months had fewer ulcers or none at all (but only while taking the medication), as compared with 3 percent of patients given placebo.[48] Thalidomide (200 mg daily) was likewise effective in a randomized trial of patients with HIV infection who had aphthous-like ulcers.[49] Open-label studies suggest that thalidomide may also be effective at a lower dose (50 mg daily).[50] Serious adverse effects — including neuropathy and teratogenesis — are possible, however, and thalidomide is not approved by the FDA for the treatment of aphthous ulcers, so it should be used cautiously and only in extreme cases.

AREAS OF UNCERTAINTY

The cause of recurrent aphthous stomatitis remains unclear. Randomized, controlled trials of the interventions are limited. Other medications (such as levamisole, colchicine, and pentoxifylline) have been suggested for the treatment of more refractory cases, but limited data are available to support their effectiveness. Further study is needed to guide the management of this disease better.

GUIDELINES

Recommendations for the management of recurrent aphthous stomatitis are available from Prodigy Guidance of the U.K. Department of Health (www.prodigy.nhs.uk/aphthous_ulcer) and from the U.S. National Guideline Clearinghouse (www.ngc.gov). The recommendations in this review are consistent with these guidelines.

SUMMARY AND RECOMMENDATIONS

The presentation of the patient in the vignette is consistent with recurrent aphthous stomatitis, based on the history of recurrent ulcers since childhood, the examination showing typical round or ovoid ulcers, and the lack of clinical evidence of any drug-related or systemic cause. I would recommend the avoidance of oral trauma and acidic foods and drinks. Topical therapy such as lidocaine or protective bioadhesives might be helpful. On the basis of the data available from randomized, controlled trials, I would also recommend treatment with topical corticosteroids in a paste, or 5 percent amlexanox paste (typically for two weeks or until the ulcers heal), or treatment with a mouth rinse such as chlorhexidine gluconate, since these may speed healing and reduce pain. I would repeat this treatment as needed if the ulcers recur.

No potential conflict of interest relevant to this article was reported.

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