Recurrent aphthous stomatitis (RAS) is one of the most common oral diseases worldwide. Although the exact etiology of RAS remains unknown, a variety of topical and systemic preparations may be used for palliation or prevention. In most patients with RAS, topical agents, including over-the-counter preparations such as amlexanox, prescribed corticosteroids, or antimicrobial agents, are sufficient to control the disease. Patients with frequent exacerbations or those with a severe form of RAS that is unresponsive to topical treatments often require systemic agents to control their disease. These include corticosteroids, colchicine, dapsone, pentoxifylline, and thalidomide. All therapies are palliative, and none result in permanent remission.

Recurrent aphthous stomatitis (RAS), or canker sore, is the most common form of oral ulcerations in both children and adults. The clinical characteristics of RAS and differentiation
from ulcerations caused by intraoral herpes simplex virus infection are outlined in Table 1. RAS is a multifactorial process, with the development of oral lesions influenced by trauma, smoking, stress, hormonal state, family history, food hypersensitivity, and infectious or immunologic factors. Fortunately, most cases of RAS can be managed palliatively with topical agents. A variety of over-the-counter preparations containing one or more active ingredients, including anesthetics, antimicrobials, wound cleansers, coating agents, and occlusive dressings, is widely available. Although many of these products reduce the pain and/or shorten the duration of the disease, benefits are modest and attained typically in patients with RAS whose ulcers are shallow, relatively painless, and short in duration.

A significant number of patients with RAS develop painful ulcerations that result in difficulty when speaking, eating, drinking, and performing routine oral hygiene (Figure, A and B). Over-the-counter preparations are relatively ineffective for these patients; however, multiple topical and systemic therapeutic modalities, which may provide symptomatic relief, are available (Table 2).

**Topical Treatments**

Amlexanox is a topical preparation that is effective in the treatment of RAS. The drug was approved by the US Food and Drug Administration in 1996 as the first treatment for aphthous ulcers in immunocompetent patients. Amlexanox is an anti-inflammatory that inhibits leukotrienes and histamines, although its exact mechanism of action in the treatment of RAS is unknown. In several double-blind, controlled, multicenter studies involving more than 1100 patients, amlexanox was shown to statistically accelerate complete ulcer healing and reduce the time of pain resolution. Specifically, application of amlexanox as a 5% paste to ulcerations resulted in complete resolution of pain 1.3 days sooner than no treatment and 0.7 days sooner than vehicle alone. Similarly, amlexanox reduced complete healing by 1.6 days compared with no treatment and by 0.7 days compared with vehicle alone.
Like corticosteroids, amlexanox should be applied 4 times daily (after meals and at bedtime). Topical preparation, applied at the first sign of ulceration, significantly reduces pain and accelerates healing. Patients may complain of burning or stinging at the site of application, but this adverse reaction is transient. The vehicle, an oral paste specifically formulated to adhere to the oral mucosa, is well accepted by patients and often preferred to other topical agents.

Although rigorous controlled studies are lacking, the efficacy of topical corticosteroids in the treatment of RAS is indisputable based on their favorable and widespread use. Furthermore, the lack of observed or reported adverse effects of topical corticosteroids in the treatment of RAS and other oral inflammatory diseases supports their safety.5,6 Several generalizations about topical corticosteroid use in the oral cavity may be made. Patients should be warned about the off-label use of these agents and the accompanying package inserts, which all state “for external use only.” As demonstrated in an open label study, superpotent topical corticosteroids are more effective and rapid in onset than weaker preparations.7,8 Because efficacy studies comparing corticosteroids in various vehicles have been performed only on the skin, choosing a vehicle for oral-cavity use is an inexact process that should include patient preference. Ointments, unlike gels or creams, do not burn or sting when applied to ulcerations, although they adhere poorly to mucosa. Elixir forms of corticosteroids such as dexamethasone can be used as an oral rinse for patients with multiple ulcerations. Corticosteroids are commonly compounded with the occlusive dressing Orabase® (Colgate-Palmolive, New York, NY), despite findings of a controlled study that suggests that topical steroids in adhesive bases are no more effective than the base preparation alone.8 Patients should be instructed to apply topical corticosteroids 3 to 5 times daily and to initiate therapy during the early stage of lesion development. Prolonged contact of the corticosteroid with the ulcerated mucosa appears to significantly increase the effectiveness of treatment. Therefore, patients should massage the medication on the ulceration for 30 to 60 seconds with their fingers or coat a cotton-tipped applicator and hold it against the ulceration for up to a minute. Eating and drinking should be avoided for a minimum of 30 minutes after application. Chronic topical corticosteroid use in the oral cavity can facilitate overgrowth of Candida and requires careful monitoring.

Although their benefits have not been substantiated in multicenter trials, many antimicrobial compounds may be used to treat RAS with various degrees of success. For example, topically applied antibiotics such as tetracycline and cephalexin may be helpful because of their anti-inflammatory effects.9 A solution containing a 250 or 500 mg antibiotic capsule dissolved in 30 to 50 mL of water may be used as a rinse or to saturate gauze, which can be applied directly to the ulcer. Other antimicrobial compounds including the mouthwash Listerine® (Warner-Lambert Consumer Healthcare, Morris Plains, NJ), whose active ingredients include a mixture of essential oils, can be used to decrease the duration and

Minor aphthous ulcers (A) are small (less than 1 cm in diameter) shallow ulcers covered by a pseudomembrane and surrounded by erythema. Major aphthous ulcers (B) are larger, deeper, and heal with scar formation.
severity of RAS and to possibly reduce the occurrence of ulcerations in susceptible patients. Chlorhexidine gluconate, a widely prescribed oral rinse used to reduce plaque and gingivitis, increases ulcer healing and intervals between episodes of RAS but not the recurrence rate of oral ulcerations.

Systemic Treatments
The use of systemic agents should be reserved for patients with frequent episodes of painful and multiple ulcerations. An exception is the use of systemic corticosteroids as an acute treatment for patients with ulcerations that are either unresponsive to topical therapy or that develop in the oropharynx, a location resistant to topical treatment. Prednisone, at doses of 40 to 60 mg administered daily for 3 to 4 days, usually relieves inflammation and pain. Severe ulcerations may require 2 full weeks of treatment with tapering doses. The toxicity of systemic corticosteroids limits their chronic use, and even frequent short courses should be minimized. The need for repeated treatment with prednisone is an indication for suppressive therapy with a corticosteroid-sparing immunomodulatory agent.

Pentoxifylline is an anti-inflammatory, immunomodulatory, methylxanthine derivative that blocks neutrophil adherence and is indicated for peripheral vascular disease. It also has been used

---

Table 2.
Topical and Systemic Agents for Recurrent Aphthous Stomatitis*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td></td>
</tr>
<tr>
<td>Amlexanox</td>
<td>Only FDA-approved drug for RAS</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>May be used as a rinse for patients with multiple ulcers</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Effectiveness is unpredictable</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Superpotent strength formulations are more effective than potent or midpotent agents</td>
</tr>
<tr>
<td>OTC preparations</td>
<td>May reduce the pain and shorten the duration of minor ulcers</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
</tr>
<tr>
<td>Colchicine</td>
<td>Suppressive therapy</td>
</tr>
<tr>
<td></td>
<td>Limited by GI toxicity</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Suppressive therapy</td>
</tr>
<tr>
<td></td>
<td>Requires careful laboratory testing</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Least toxic suppressive therapy</td>
</tr>
<tr>
<td></td>
<td>Controlled efficacy studies are needed</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Acute treatment for patients with ulcerations unresponsive to topical therapy or those in the oropharynx</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Most effective suppressive therapy. Pharmacies and doctors must follow the System for Thalidomide Education and Prescribing Safety Program for careful monitoring of adverse effects</td>
</tr>
</tbody>
</table>

*FDA indicates US Food and Drug Administration; RAS, recurrent aphthous stomatitis; OTC, over-the-counter medications; GI, gastrointestinal.
to treat infectious diseases, immunodeficiency, hypercoagulable states, a diverse group of cutaneous diseases, and RAS. The mode of action for pentoxifylline appears to be due to the inhibition of tumor necrosis factor α and other inflammatory cytokines. Several small uncontrolled trials utilizing pentoxifylline, 400 mg 3 times daily, have reported excellent results, some with long-term benefits. We have treated a significant number of patients who do not respond to this drug and require alternative agents. Controlled double-blind studies are needed to confirm the efficacy of pentoxifylline before it can be used as a treatment for RAS. Minor adverse reactions to pentoxifylline include nausea and vomiting, which resolve when the drug is discontinued.

Colchicine, indicated for the treatment of acute gouty arthritis, interferes with microtubule growth and affects mitosis and other microtubule-dependent functions. Its wide spectrum of anti-inflammatory actions for disorders characterized by the accumulation of polymorphonuclear leukocytes may explain the benefits obtained in several open studies utilizing continuous colchicine therapy in the prevention of RAS. Doses of 0.6 mg, administered 3 times daily, appear to not only decrease the severity of RAS but also increase the intervals between episodes. At least 50% of patients appear to respond to treatment, and responders may be maintained on therapy chronically. Colchicine can cause gastrointestinal side effects, especially diarrhea, which may limit its use. Some patients can tolerate only 1 or 2 doses daily, which may limit its use as suppressive therapy. Colchicine-induced myopathy and neuropathy require monitoring for patients on long-term therapy. Bone marrow depression also has been reported, primarily in cases of acute colchicine intoxication. The safety of the drug was highlighted in a study involving 350 children (younger than 16 years) with familial Mediterranean fever who were maintained in continuous prophylactic treatment with colchicine (1–2 mg/d) for 6 to 13 years. Side effects of colchicine were insignificant and did not require permanent discontinuation of treatment in any of the children.

The use of dapsone in the management of RAS is especially valuable for patients who require suppressive therapy. Although there are no formal studies to support this finding, the effects of dapsone on aphthous ulcerations in patients with Behçet’s disease and complex aphthosis are well documented. Furthermore, our own personal experience with dapsone as a treatment in numerous patients with RAS is favorable. Like colchicine, dapsone may exert its effects primarily through suppression of inflammatory cell migration. Daily doses of 50 to 150 mg may be used chronically to suppress ulcer formation. Dapsone should not be administered to patients with a glucose-6-phosphate dehydrogenase deficiency, and careful monitoring for hemolytic anemia is also essential. A hypersensitivity to dapsone characterized by fever, hepatitis, cholestatic jaundice, and rash is rare; and agranulocytosis, another uncommon complication of dapsone, typically develops 8 to 12 weeks after initiation of therapy. Methemoglobin levels should be obtained when clinically indicated, and periodic neurologic testing such as having patients walk on their toes and grip objects should be performed to detect peripheral motor neuropathy.

The off-label use of thalidomide for a variety of diseases including RAS has significantly increased since its introduction in 1998 as a treatment for erythema nodosum leprosum. In several trials, thalidomide has proven to be effective at doses of 100 to 200 mg per day for treating RAS in patients infected with HIV and has become the drug of choice for patients with severe disease. Thalidomide also has been used to treat aphthous ulcerations in immunocompetent patients with Behçet’s disease and Crohn’s disease. The drug can only be dispensed by registered pharmacies and healthcare professionals who are required to follow the System for Thalidomide Education and Prescribing Safety Program. This program includes mandatory informed consent, education procedures, and limitation of the quantity dispensed. Careful monitoring is necessary because of the potentially serious teratogenic and neurologic adverse effects caused by thalidomide. The development of neuropathy may be related to a cumulative dose greater than 50 g and requires electrophysiologic monitoring. Less severe adverse effects, including sedation, headache, weight gain, nausea, constipation, and rash, are reversible when the drug is discontinued.

Patients started on thalidomide therapy may require 2 to 3 months of treatment before a response is observed. A daily dose of 100 to 150 mg will usually suppress ulcer formation, although some patients may require higher doses. Once controlled, the dose may be tapered to alternate-day or every-third-day therapy.

**Comment**

Patients with RAS may be treated with a variety of agents. For those with mild disease, topical preparations or no treatment may be all that is required. Amlexanox or topical corticosteroids should be used to treat patients with ulcerations that are painful or interfere with function. Systemic agents including colchicine, dapsone, and thalidomide should be
reserved for patients with continuous and painful ulcer formation and necessitate careful monitoring. Prednisone may be used to rapidly relieve painful ulcerations, but should not be administered chronically because of its toxicity.

REFERENCES


DISCLAIMER

The opinions expressed herein are those of the authors and do not necessarily represent the views of the sponsor or its publisher. Please review complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

FACULTY DISCLOSURE

The Faculty Disclosure Policy of the College of Medicine requires that faculty participating in a CME activity disclose to the audience any relationship with a pharmaceutical or equipment company that might pose a potential, apparent, or real conflict of interest with regard to their contribution to the program. It is required by the Accreditation Council for Continuing Medical Education that each author of a CME article disclose to the participants any discussion of an unlabeled use of a commercial product or device or an investigational use not yet approved by the Food and Drug Administration. Drs. Eisen and Lynch report no conflict of interest. Dr. Fisher reports no conflict of interest.