

Selecting Topical and Systemic Agents for Recurrent Aphthous Stomatitis

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GOAL

To discuss topical and systemic medications used for palliation of recurrent aphthous stomatitis (RAS).

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Contrast the characteristics of recurrent aphthous stomatitis and intraoral herpes simplex virus infection.
2. Discuss topical treatments and their efficacy for RAS.
3. Summarize systemic treatments for RAS.

CME Test on page 214.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: August 2001.

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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, pre-

scribed 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.

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Recurrent aphthous stomatitis (RAS), or canker sore, is the most common form of oral ulcerations in both children and adults.¹ The clinical characteristics of RAS and differentiation

Table 1.

Clinical Characteristics of Recurrent Aphthous Stomatitis and Intraoral Herpes Simplex Virus Infection*

	Minor RAS	Major RAS	Herpetiform RAS	HSV Infection
Incidence	Common	Uncommon	Rare	Uncommon
Location	Buccal mucosa	Labial mucosa	All oral mucosa	Hard palate
	Labial mucosa	Soft palate		Attached gingiva
	Lateral tongue	Oropharynx		
	Floor of mouth			
Number	1–10	1–5	5–100	1–10
Size, cm	<1.0	>1.0	<0.3	0.1–1.0
Pain	None to moderate	Severe	Mild to moderate	None to moderate
Duration, d	7–14	15–60	7–14	7–14
Scarring	Rare	Common	None	None
Comments	Multiple contributing etiologic factors	History of HIV and GI disease	No viral etiology	History of HSV

*RAS indicates recurrent aphthous stomatitis; HSV, herpes simplex virus; HIV, human immunodeficiency virus; GI, gastrointestinal.

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.² 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.³ 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.⁴ 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.



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.

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

Table 2.

Topical and Systemic Agents for Recurrent Aphthous Stomatitis*

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

*FDA indicates US Food and Drug Administration; RAS, recurrent aphthous stomatitis; OTC, over-the-counter medications; GI, gastrointestinal.

severity of RAS and to possibly reduce the occurrence of ulcerations in susceptible patients.¹⁰ 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.¹¹

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.¹² It also has been used

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.^{13,14} Several small uncontrolled trials utilizing pentoxifylline, 400 mg 3 times daily, have reported excellent results, some with long-term benefits.^{15,16} 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.^{17,18} 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.¹⁹ The safety of the drug was highlighted in a study involving 350 children (younger than 16 years) with familial Mediterranean fever²⁰ who were maintained with 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.^{21,22} 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 rare²³; 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.^{24,25} Thalidomide also has been used to treat aphthous ulcerations in immunocompetent patients with Behçet's disease and Crohn's disease.²⁶ 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.²⁷ 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

- Porter SR, Scully C, Pedersen A. Recurrent aphthous stomatitis. *Crit Rev Oral Biol Med*. 1998;9:306-321.
- Rogers RS III. Recurrent aphthous stomatitis: clinical characteristics and associated systemic disorders. *Semin Cutan Med Surg*. 1997;16:278-283.
- Khandwala A, Van Inwegen RG, Alfano MC. 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers, I: clinical demonstration of acceleration of healing and resolution of pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997;83:222-230.
- Binnie WH, Curro FA, Khandwala A, et al. Amlexanox oral paste: a novel treatment that accelerates the healing of aphthous ulcers. *Compend Contin Educ Dent*. 1997;18:1116-1118,1120-1122,1124.
- Pimlott SJ, Walker DM. A controlled clinical trial of the efficacy of topically applied fluocinonide in the treatment of recurrent aphthous ulceration. *Br Dent J*. 1983;154:174-177.
- MacPhail L. Topical and systemic therapy for recurrent aphthous stomatitis. *Semin Cutan Med Surg*. 1997;16:301-307.
- Lozada-Nur F, Huang MZ, Zhou GA. Open preliminary clinical trial of clobetasol propionate ointment in adhesive paste for treatment of chronic oral vesiculoerosive diseases. *Oral Surg Oral Med Oral Pathol*. 1991;71:283-287.
- Voute AB, Schulten EA, Langendijk PN, et al. Fluocinonide in an adhesive base for treatment of oral lichen planus: a double-blind, placebo-controlled clinical study. *Oral Surg Oral Med Oral Pathol*. 1993;75:181-185.
- Brice S, Jester J, Huff J. Recurrent aphthous stomatitis. *Curr Probl Dermatol*. 1991;3:109-127.
- Meiller TF, Kutcher MJ, Overholser CD, et al. Effect of an antimicrobial mouthrinse on recurrent aphthous ulcerations. *Oral Surg Oral Med Oral Pathol*. 1991;72:425-429.
- Scully C, Porter S. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. *J Oral Pathol Med*. 1989;18:21-27.
- Aviado DM, Porter JM. Pentoxifylline: a new drug for the treatment of intermittent claudication: mechanism of action, pharmacokinetics, clinical efficacy and adverse effects. *Pharmacotherapy*. 1984;4:297-307.
- Bruynzeel I, Stoof TJ, Willemze R. Pentoxifylline and skin inflammation. *Clin Exp Dermatol*. 1998;23:168-172.
- Doherty GM, Jensen JC, Alexander HR, et al. Pentoxifylline suppression of tumor necrosis factor gene transcription. *Surgery*. 1991;110:192-198.
- Chandrasekhar J, Liem AA, Cox NH, et al. Oxyptentifylline in the management of recurrent aphthous oral ulcers: an open clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1999;87:564-567.
- Wahba-Yahav AV. Pentoxifylline in intractable recurrent aphthous stomatitis: an open trial. *J Am Acad Dermatol*. 1995;33:680-682.
- Izquierdo C, Isanta C, Guillen A, et al. Recurrent oral aphthosis. its treatment with colchicine [letter]. *Aten Primaria*. 1989;6:358-359.
- Gatot A, Tovi F. Colchicine therapy in recurrent oral ulcers [letter]. *Arch Dermatol*. 1984;120:994.
- Harris R, Marx G, Gillett M, et al. Colchicine-induced bone marrow suppression: treatment with granulocyte colony-stimulating factor. *J Emerg Med*. 2000;18:435-440.
- Zemer D, Livneh A, Danon YL, et al. Long-term colchicine treatment in children with familial Mediterranean fever. *Arthritis Rheum*. 1991;34:973-977.
- Mangelsdorf HC, White WL, Jorizzo JL. Behçet's disease: report of twenty-five patients from the United States with prominent mucocutaneous involvement. *J Am Acad Dermatol*. 1996;34:745-750.
- Ghate JV, Jorizzo JL. Behçet's disease and complex aphthosis. *J Am Acad Dermatol*. 1999;40:1-18.
- Prussick R, Shear NH. Dapsone hypersensitivity syndrome. *J Am Acad Dermatol*. 1996;35:346-349.
- Ghigliotti G, Repetto T, Farris A, et al. Thalidomide: treatment of choice for aphthous ulcers in patients seropositive for human immunodeficiency virus. *J Am Acad Dermatol*. 1993;28:271-272.
- Jacobson JM, Greenspan JS, Spritzler J, et al, for the National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. *N Engl J Med*. 1997;336:1487-1493.
- Calabrese L, Fleischer AB. Thalidomide: current and potential clinical applications. *Am J Med*. 2000;108:487-495.
- Tseng S, Pak G, Washenik K, et al. Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. *J Am Acad Dermatol*. 1996;35:969-979.

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