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# Recurrent Aphthous Stomatitis: Diagnosis and Management in Primary Care

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## Abstract

Recurrent aphthous stomatitis (canker sores) is a very common oral condition that remains incompletely understood. Presentation has been well-classified into minor, major or herpetiform subcategories based on clinical features, but exact etiology is unknown. Because etiology is unclear, treatments are primarily empiric and aimed at symptom reduction rather than prevention or cure. However, there are several methods, both topical and systemic, that can be easily and affordably utilized in the primary care setting. (*J Patient-Centered Res Rev.* 2014;1:197-200.)

## Keywords

recurrent aphthous stomatitis, aphthous ulcer, treatment, management

## Introduction

Recurrent aphthous stomatitis (RAS) is a painful disease of the oral mucosa that affects 20% of the general population worldwide and possibly more in the North American population. It is one of the most common oral complaints seen in the primary care setting. Despite its prevalence, its causes remain largely unknown.<sup>1</sup> Because of this, finding a definitive treatment has thus far been elusive, and treatments are largely empiric and focused on short-term symptom management. It is the goal of this paper to discuss various treatment options, both symptomatic and preventive, currently being used or proposed that could be relevant for use in primary care.

## Clinical Features

There appears to be no consistent definition for what qualifies as *recurrent* aphthous stomatitis; however, one group has proposed at least three attacks of oral ulcers, not in the same focal site, over a 3-year period.<sup>2</sup> Aphthous ulcers have been categorized into three groups: minor, major and

herpetiform. Table 1 lists the categories of aphthous ulcers and their respective features. Minor aphthae are by far the most common presentation of RAS, representing 80-85% of cases.<sup>1-4</sup> Ulcers are up to 1 cm in size, shallow and generally last 10-14 days. They occur on the labial or buccal mucosa, soft palate, tongue or floor of the mouth.<sup>1-4</sup> There may be a prodromal burning or stinging sensation prior to appearance of the lesions. Scar formation does not occur with healing of minor aphthae.<sup>1-4</sup>

**Table 1.** Categories of aphthous ulcers

	Features at presentation			
	Size (mm)	No. of ulcers in an outbreak	Duration (days)	Scarring
Minor ulcers	5-10	Few	10-14	No
Major ulcers	>10	Few	14+	Yes
Herpetiform ulcers	<5	Many (5-100)	10-14	No

Major aphthae are rare, representing approximately 10-15% of RAS cases. They are defined by ulcers larger than 1 cm, are generally deeper and have a longer duration than minor aphthae. Major aphthae may form a scar with healing.<sup>1-4</sup> Major aphthae can be seen with human immunodeficiency virus (HIV) infection, and HIV testing should be considered when major aphthae are present.<sup>3</sup>

The herpetiform presentation is also rare, representing 10% or less of all RAS cases, and is defined by outbreaks of numerous, small, vesicular lesions. Vesicles may coalesce into larger ulcers. Duration of outbreaks is similar to minor aphthae, and generally no scar is formed.<sup>1,3,4</sup>

Benign RAS should not be associated with systemic symptoms such as fever, lymphadenopathy, gastrointestinal symptoms, or mucosal or skin lesions beyond the nonkeratinized oral mucosa. If other symptoms are present, evaluation for systemic disease such as Behçet's disease, inflammatory bowel disease, celiac disease, HIV, or other autoimmune or immunodeficiency disorders should be considered.<sup>3,4</sup>

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## Etiology/Pathogenesis

While there are clear clinical characteristics to aphthae, the exact etiology remains unknown.<sup>1,3</sup> It may be that RAS is a manifestation of a group of separate disorders rather than a single disease, which could explain the difficulty in definitively determining the cause. Aphthous stomatitis has a clear genetic predisposition. More than 42% of patients with RAS will have at least one first-degree relative who is also affected, and there is a 90% chance of developing RAS if both parents are affected.<sup>3</sup> Ulcers appear to be a cell-mediated immune response in which T-cells and tumor necrosis factor (TNF)- $\alpha$  are involved. TNF- $\alpha$  is a proinflammatory cytokine that recruits T-cells and other leukocytes to the lesion, creating a painful papule that then ulcerates before healing.<sup>5</sup> Predisposing factors include local trauma, stress, certain foods, hormonal fluctuations related to the menstrual cycle, and tobacco smoking.<sup>1-5</sup> Sodium lauryl sulfate-containing toothpaste also may trigger aphthae in certain individuals.<sup>6</sup> In addition, deficiencies in iron, folic acid or vitamin B<sub>12</sub> have been correlated with aphthous ulcer outbreaks.<sup>6</sup>

## Management Options

As previously stated, because the exact etiology is unknown, finding a definitive treatment has been difficult. Avoidance of triggers should be recommended to limit recurrence. Most treatments currently used are palliative, with several systemic and preventive treatments recently proposed. There is currently no curative treatment known. Table 2<sup>7-14</sup> summarizes treatments discussed in this article.

### *Topical Treatments*

**Amlexanox paste:** Amlexanox is an anti-inflammatory agent that is approved by the U.S. Food and Drug Administration for the treatment of aphthous ulcers. Four randomized, placebo-controlled, double-blind, multicenter trials studied a total of 1,335 subjects and found amlexanox both safe and effective.<sup>7</sup> Participants applied a small amount of 5% amlexanox paste to their ulcers 4 times a day until their ulcers healed or the study ended. Patients had reduced pain (by day 2-3) and increased healing (starting from day 3-4 of treatment) compared to no treatment or placebo. Amlexanox also may help prevent ulcer formation if applied during the prodromal symptom phase; 35% of patients who applied amlexanox paste to the area of symptoms developed an ulcer after 3 days versus 97% of patients who received no treatment. In regards to adverse events, rates were similar for amlexanox (2.1%) versus placebo (2.5%). The most common complaint was transient burning or stinging at the application site, which occurred in equal rates in both groups; likely this sensation

was due to the alcohol in the paste or the coarse texture rather than the amlexanox itself.

**Topical steroids:** Topical steroids are frequently used to treat aphthous ulcers. A recent multicenter, double-blind, placebo-controlled trial tested a total of 240 patients for the safety and efficacy of dexamethasone ointment.<sup>8</sup> In the study, patients either applied a 1 mg/g dexamethasone ointment or placebo ointment to their lesion 3 times daily after meals for 5 days. Size and pain level of ulcers before and after treatment were evaluated. In addition, serum levels of dexamethasone were tested in 89 randomly selected subjects. They found significant reduction in ulcer size of the treatment group compared to the control group at the end of treatment, with a healing ratio of 83.3% in treatment group vs. 54.7% for placebo. Pain levels also were significantly improved with steroid treatment compared to placebo. Serum dexamethasone measurements found no detectable level of dexamethasone in either group, meaning a serum concentration level less than 0.502 ng/mL.

**Silver nitrate cautery:** Silver nitrate cautery has been used for many years to relieve pain related to aphthous ulcers. There has been concern related to the painfulness of the procedure and possible impedance of ulcer healing with this technique. Two recent studies with 97 and 65 patients, respectively, showed significant pain relief and increased rate of healing compared to placebo.<sup>9,10</sup> In each study the lesions were first anesthetized with topical lidocaine prior to the procedure. Treatment groups were treated with one application of a silver nitrate stick gently touched to the base of ulcer until the ulcer became white. Patient mouths were rinsed with copious amounts of water for 5 minutes after the procedure. Placebo groups used the same method but with a placebo treatment stick. Both studies found improved pain levels and decreased healing time compared to placebo. No significant adverse events were documented.

### *Systemic Treatments*

Therapies such as thalidomide, dapsone, levamisole, pentoxifylline or colchicine have proved effective in treating RAS, but significant side effects limit their use, particularly in the primary care setting.<sup>2,5,6</sup> Other treatments have recently shown some hope in providing successful treatment while limiting side effects and cost, although the studies have been small. The following sections will review these recently studied treatments.

**Montelukast:** In a small, randomized, double-blind, placebo-controlled study, the efficacy of systemic prednisone

and montelukast were compared.<sup>11</sup> With 20 patients in each arm, patients were treated with either a prednisone taper, montelukast or placebo for a course of 2 months and followed for a further 2 months following the end of treatment. Prednisone provided faster resolution and greater pain relief (by day 2-3) than montelukast, but montelukast did provide more benefit than placebo (day 3-4 vs. day 4-5). Overall, the number of ulcers during treatment was reduced by 76% while on prednisone, 71% while on montelukast and only 5% for the placebo group. Prednisone had a greater rate of adverse events (30%) versus montelukast (10%) or placebo (10%). This study was designed as a pilot study, and a larger study would be needed to confirm efficacy of montelukast as a long-term treatment.

**Vitamin B<sub>12</sub> supplementation:** One recent study tested the efficacy of vitamin B<sub>12</sub> supplement in reduction of aphthous ulcer outbreaks. In a randomized, double-blind, placebo-controlled test, a total of 58 patients were studied to determine the effect of 1,000 mcg of sublingual vitamin B<sub>12</sub> on aphthous ulcer outbreaks.<sup>12</sup> The authors found that “the duration of outbreaks, the number of ulcers, and the level of pain were reduced significantly (P>0.05) at 5 and 6 months of treatment.” In addition, they found that 74% of the treatment group reached had no ulcers by the end of their 6-month observation period vs. 32% in the control group. The primary limitation of the study was sample size, with only 31 patients in the treatment group and 27 in the

control group. However, vitamin B<sub>12</sub> is relatively safe and inexpensive, making it a reasonable option to trial in patients suffering from RAS.

**Omega-3 fatty acids:** A recently published study assessed the efficacy of dietary omega-3 fatty acid supplementation in reducing symptoms of RAS and improving quality of life.<sup>13</sup> Fifty patients were divided evenly into a treatment group receiving 1,000 mg of omega-3 supplementation daily versus a placebo group and were followed monthly for 6 months. Each omega-3 capsule provided 200 mg of docosahexaenoic acid and 300 mg of eicosapentaenoic acid. By 3 months of treatment, level of pain, number of ulcers and length of outbreaks were reduced with omega-3 supplementation versus placebo, and this effect lasted for the remainder of the observation period of 6 months. No adverse events were reported during the duration of the study.

**Multivitamin supplementation of no benefit:** Although certain vitamin deficiencies have been proposed as playing a role in RAS, a large study that followed 160 patients for 1 year showed no benefit in the use of a daily multivitamin (containing 100% of the recommended daily intake of essential vitamins) to reduce number of ulcers or frequency of outbreaks when compared to placebo.<sup>14</sup> Multivitamin use should not be recommended to reduce ulcer outbreaks.

**Table 2.** Summary of treatments for recurrent aphthous stomatitis

Treatment	Dosage	No. of patients studied	Outcomes
Amlexanox 5% paste <sup>7</sup>	Apply to ulcer 4 times daily	1,335	Pain resolved by day 3 Ulcer healed by day 3 Ulcer prevention if started during prodromal stage
Dexamethasone 0.1% ointment <sup>8</sup>	Apply to ulcer 3 times daily after meals	89	Pain reduction
Silver nitrate cautery <sup>9,10</sup>	One application to ulcer until ulcer blanches	162	Pain reduction by day 1
Montelukast <sup>11</sup>	10 mg orally daily	40	Resolution of pain in 3-4 days Decreased number of ulcers during treatment
Vitamin B <sub>12</sub> <sup>12</sup>	1,000 mcg sublingually daily	58	No ulcers after 6 months of treatment
Omega-3 fatty acids <sup>13</sup>	200 mg DHA/300 mg EPA daily	50	Decreased number of ulcers, decreased pain, and outbreak duration shortened by 3 months
Multivitamin <sup>14</sup>	100% RDI daily	160	No benefit

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; RDI, recommended daily intake.

## Conclusions

Recurrent aphthous stomatitis remains a poorly understood entity, despite having clear clinical features. However, it is a common oral complaint and causes significant pain and impact on quality of life. Much research has been done to find treatments to reduce pain related to, duration of and frequency of ulcer outbreaks. There are several treatment options, both local and systemic, that could be helpful for management of aphthae in the primary care setting. More research needs to be done regarding recent systemic treatments such as montelukast, vitamin B<sub>12</sub> or omega-3 fatty acid supplementation to prove efficacy, but safety and relatively low cost make these reasonable options to trial if there is a possibility the treatment will improve symptoms in patients with frequent recurrence.

## Conflicts of Interest

None.

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