APHTHOUS STOMATITIS

This condition, also called recurrent aphthous stomatitis (RAS), recurrent oral ulcers, canker sores, or ulcerative stomatitis, is thought to affect 20% of the population.¹

Recurrent aphthous stomatitis usually appears as a single, or clusters of, painful oral ulcers. Lesions heal in 1 to 2 weeks but may recur monthly or several times a year.

Although in a minority of cases RAS may indicate underlying systemic disease (see later discussion), in most patients no cause can be identified and the diagnosis remains a clinical one. In the minority of patients in whom underlying disease is thought to be causative, the identifiable etiologic factor should be considered:

- microbial disease (eg, hand, foot, and mouth disease, infectious mononucleosis, human immunodeficiency virus [HIV], syphilis);
- malignancy or blood disorders (eg, oral cancers, leukemia, anemia, cyclic neutropenia);
- gastrointestinal disease (eg, celiac disease [gluten-sensitive enteropathy], Crohn disease, ulcerative colitis);
- rheumatoid diseases (eg, lupus, Reiter disease, Behcet syndrome);
- cutaneous disease (eg, lichen planus, pemphigus, erythema multiforme, and others); or
- drugs.²

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Although any patient presenting with recurrent oral ulcers should be evaluated for these medical conditions, as already stated most patients with aphthous stomatitis are otherwise healthy. Three major types of aphthous stomatitis are:

- Minor aphthous ulcers (80% of cases) are less than 5 mm in diameter and heal in 7 to 14 days.
- Major aphthous ulcers are larger ulcers that heal slowly over weeks or months with scarring.
- Herpetiform ulcers are multiple pinpoint ulcers that heal within about a month.

The primary differential diagnosis is oral herpes simplex.

**Conventional Therapy**

Topical corticosteroids (0.1% triamcinalone/kenalog in orobase, 2 or 4 times daily) are the mainstay of conventional therapy. However, antibiotics (tetracycline swish and swallow 4 times daily), immune modulators (thalidomide in HIV patients), and sucral-fate solution have also been found to shorten the duration of symptoms. Pain reduction has been noted with the application of silver nitrate. Some clinicians are using a topical mixture of viscous lidocaine, Mylanta, and Benadryl mixed 1:1:1 for symptomatic relief.

**Helicobacter pylori Eradication**

*Helicobacter pylori* has been postulated to be a possible causative or contributing factor in RAS. The bacterium is thought to cause oral inflammation, subsequent release of proteolytic enzymes from neutrophils, and resultant ulcer formation. In general, studies examining the correlation between *H pylori* and RAS are conflicting; however, the latest trial seems to support the theory. In this trial, 23 patients underwent endoscopy, biopsy, and subsequent *H pylori* eradication. In patients who underwent eradication, the average annual number of recurrences dropped from 5.6 to 2.7, indicating a possible correlation. These patients also were noted to have fewer lesions (4 vs 14) and quicker resolution of symptoms (3 days vs 9 days).

**Dietary Intervention**

Roughly 5% of outpatients who present with RAS are thought to have gluten-sensitive enteropathy (celiac disease); however, in clinical practice the withdrawal of gluten rarely results in significant benefit. A literature search could find no efficacious dietary modifications.

**Vitamin B12**

A 2009 trial randomized 58 patients with normal serum B12 levels to receive either 1000 mg of B12 sublingually per day or placebo. At the end of the 6-month trial period, 74% of those in the treatment arm had complete resolution of episodic ulcers while only 32% of the placebo group experienced similar relief. The investigators postulate that a “functional B12 deficiency” may exist at the cellular level and play a role in the etiology, and propose that future studies take this into consideration in their study design.

**Bee propolis**

Bee propolis is an over-the-counter natural supplement collected by bees from plant sources. The resinous substance is used as a sealant in the construction of beehives and contains flavonoids with antimicrobial activity, antioxidant activity, and immune-
modulating activity.\textsuperscript{11} The use of propolis in the treatment of aphthous ulcers is a traditional therapy used in the Middle East.

In a randomized trial of 17 patients receiving either 500 mg of oral propolis or placebo, 60\% of patients in the treatment arm experienced a 50\% reduction in the frequency of attacks, whereas only 11\% of those in the placebo group experienced similar results. Larger studies need to be performed to confirm these results.\textsuperscript{12}

\textbf{Biologic-Based Therapies}

Although there are reports of lysine, vitamin C, sage, chamomile, echinacea, carrot juice, celery juice, and cantaloupe juice being used to treat aphthous stomatitis, no clinical trials evaluating these products could be found in the literature.

\textit{Zinc}

It was observed in one study that 42\% of patients with RAS were found to have below normal levels of serum zinc. With this in mind, Orbak and colleagues\textsuperscript{13} randomized 40 patients with RAS to receive either 220 mg of zinc sulfate or placebo for 1 month, then observed both groups for an additional 3 months. Although the investigators concluded that zinc supplementation could be beneficial to patients with RAS, their results did not substantiate this conclusion. Their article is so poorly written that no clinically useful conclusions could be obtained. Zinc therapy remains unproven as an efficacious therapy.

\textbf{Alternative Systems}

\textit{Homeopathic remedies}

Numerous homeopathic remedies for RAS are available including propolis MT, myrrh MT, mercury, and at least a dozen others, but none has been shown to have any effect over placebo in controlled double-blind trials.

The mainstay of therapy for aphthous stomatitis remains conventional.

\textbf{ACNE VULGARIS}

Acne is thought to be caused by an interaction between testosterone, sebum production, bacteria, and hyperkeratinization. Normal skin bacteria (\textit{Propionibacterium acnes} and \textit{Staphylococcus albus}) have been implicated as causative agents, as have the enzymes that hydrolyze sebum into free fatty acids, which promote the inflammatory cascade. An increase in bacterial resistance recently has been noted with the use of oral and topical antibiotics, which may account for a decreased efficacy of antibacterials; this may also be partly responsible for the current interest in the use of alternative therapies in acne.

\textit{Biologic-Based Therapies}

\textit{Witch hazel}

Witch hazel bark (\textit{Hamamelis virginiana}) has been used on acne because of its naturally astringent properties. A decoction (boiled down extract) of 5 to 10 g of herb in one cup of water is recommended. Commercially available products are not recommended because the active tannins may be lost in the distillation process.\textsuperscript{14} Although often in the acne armamentarium, the authors could find no randomized trials to substantiate its use.

\textit{Oral zinc}

The mechanism of action of oral supplementation with zinc is uncertain, but it is thought to play a role in the metabolism of retinol-binding proteins and maintaining blood levels of vitamin A.
Some trials show improvement in acne with oral zinc. A 1977 randomized, double-blind, placebo-controlled trial of 91 patients found that oral zinc sulfate (400 mg/d) was significantly better than placebo at 12 weeks, with 36 of 48 patients noting improvement in the zinc group while only 22 of 43 patients in the placebo arm noted benefit. In another 1977 trial of 37 patients with moderate to severe acne, patients were randomized to receive 200 mg of zinc sulfate or 250 mg of tetracycline 3 times per day. At the end of 12 weeks both groups noted a 70% improvement, with no significance noted between groups. However, a study 2 years later comparing oral zinc to tetracycline (250 mg twice daily) found tetracycline to be far superior to zinc sulfate in the treatment of acne.

Two additional supporting studies were conducted in the 1980s. The first, a randomized trial of 56 patients, found that in 15 of 27 patients treated with 600 mg of oral zinc noted improvement, whereas none of the 27 patients receiving placebo showed any benefit. The second study, a 1989 trial, found that zinc gluconate taken for 2 months was effective in improving acne. The investigators rated 24 of 32 patients in the zinc group as responders and only 8 of 34 in the placebo group as responders. Inflammatory scores dropped from 58 to 47 in the placebo group and from 49 to 27 in the zinc group.

However, 2 randomized trials have shown oral zinc sulfate (600 mg/d and 411 mg/d) to be no more efficacious than placebo. A third has found it to be minimally effective. In summary, no clear evidence exists for the use of oral zinc in the treatment of acne.

**Topical zinc**

Although early studies seemed to indicate that topical zinc, when combined with topical erythromycin, was more effective than erythromycin alone, later more standardized studies proved that the addition of zinc to topical erythromycin offered no added benefit over topical erythromycin alone. A 1997 study that compared erythromycin/benzoyl peroxide combinations to erythromycin/zinc combination found the former to be significantly more effective than the erythromycin/zinc combination.

**Oral zinc/nicotinamide**

A recent open-label trial of 198 patients with moderate acne or rosacea found that 79% of patients over an 8-week trial had at least moderate improvement in acne when taking nicotinamide (one of the B-complex vitamins) 750 mg, zinc 25 mg, copper 1.5 mg, and folic acid 500 μg. Of note, when an antibiotic was added to this regime no greater improvement was noted.

**Tea tree oil**

An essential oil distilled from the *Melaleuca alternifolia* tree native to Australia, tea tree oil has been shown to have antibacterial and antifungal properties. Tea tree oil contains more than 100 chemical compounds, mainly terpenes and alcohols.

In a randomized blinded trial, application of topical (5%) tea tree oil was found to offer a significant reduction in mild to moderate acne, but was less effective and had a slower onset of action when compared with benzoyl peroxide (5%). After 3 months of treatment, significantly fewer side effects were reported with the use of tea tree oil (44% vs 79%). The investigators postulate that better results may have been obtained if a higher concentration of tea tree oil was used.

**Azelaic acid**

A naturally occurring 9-carbon acid found in whole grain cereals and animal products, this acid has been noted to normalize keratinization and decrease proliferation of
bacteria that contribute to acne. Azelaic acid is approved by the Food and Drug Administration (FDA) as a topical preparation to treat acne vulgaris, and has become standard treatment in some circles. It is mentioned here because it is a naturally occurring compound that may be an alternative choice for those physicians treating patients who have an aversion to conventional medicines.

In the literature, some studies have found azelaic acid (20%) cream to be equally as efficacious as topical benzoyl peroxide (5%),28 tretinoin (5%), erythromycin ointment (2%),29 and 500 to 1000 mg of oral tetracycline per day in the treatment of acne. Azelaic acid exhibited a lower incidence of local side effects (irritation, scaling erythema) with no bacterial resistance noted.30 Twice daily treatment is recommended, and effects can be expected at 4 weeks. Use must be continued for 6 months to maintain the effect.

**Nicotinamide gel (4%)**

A physiologically active form of niacin has been shown to have anti-inflammatory properties. Nicotinamide gel was found to be as effective in moderate inflammatory acne (30%–50% improvement) as 1% clindamycin in a randomized, double-blind, placebo-controlled study involving 76 patients.31 The only side effect was mild, local burning without any emergence of antibiotic resistance. The investigators conclude that nicotinamide gel may be an option in patients with mild to moderate acne who are at risk for developing antibiotic resistance.

**Gugulipid**

This standardized oral extract of an Indian medicinal plant was found in one randomized (nonblinded) trial of 20 patients to be effective in the treatment of nodulocystic acne and to be equally as efficacious as oral tetracycline over the 3-month study period (gugulosterone, 25 mg twice daily vs tetracycline, 500 mg twice daily). Both treatments afforded 65% to 68% improvement. Although the study was not blinded and made no mention of patient satisfaction, this initial work should lead to further, more exacting investigations.32

**Phototherapy**

Before leaving the topic of alternative treatments for acne, the ongoing research in phototherapy must be mentioned. Phototherapy has been shown to have bactericidal effects as well as downmodulating sebum production. Several early studies33–35 have shown this modality to have promise. One would expect to hear more about this form of treatment as wavelengths and exposure durations are standardized.

**ECZEMA/ATOPIC DERMATITIS**

Atopic dermatitis occurs in 2% to 7% of the population. Although its exact pathophysiology remains unknown, it has been postulated to be due to a minor inherited abnormality of essential fatty acid metabolism (reduced conversion of linoleic acid to \(\gamma\)-linolenic acid) and a resultant reduced incorporation of essential fatty acids into cell membrane phospholipids. There is also a postulated role for immediate hypersensitivity reactions and possibly to certain immune/leukocyte defects.36

**Biologic-Based Therapies**

**Evening primrose oil**

Because decreased conversion of linoleic to \(\gamma\)-linolenic acid has been postulated to play a role in atopic dermatitis, replacement of \(\gamma\)-linolenic acid (primrose oil or borage oil) was hypothesized to benefit these patients. Two early meta-analyses (1989 and
1991)\(^{37}\) found the use of evening primrose oil to be significantly better than placebo in the treatment of atopic dermatitis. However, both meta-analyses have been criticized for methodological flaws, and a more recent study showed primrose oil capsules to have no benefit over placebo.\(^{38}\)

**Dietary \(\omega-3\) fatty acids**

The ratio of \(\omega-3\) fatty acids to \(\omega-6\) fatty acids was observed to be lower in patients with atopic dermatitis,\(^{39}\) and early studies seemed to point to an improvement with \(n-3\) fatty acid supplementation.\(^{39,40}\) However, 2 later trials contradicted these pilot studies. In the first, a 1994 multicenter randomized trial, 145 patients with moderate to severe atopic dermatitis were randomly assigned to receive either 6 g daily of concentrated \(n-3\) fatty acids, or an equivalent amount of corn oil. At the end of the 4-month trial period, no significant difference was found between the 2 groups.\(^{41}\)

In the latest trial,\(^{42}\) 20 patients hospitalized for severe atopic dermatitis were randomized to receive an intravenous solution of either \(n-3\) fatty acids (fish oil) or \(n-6\) fatty acids (soybean oil). Although both groups showed significant improvement, there were significantly better results in the \(n-3\) fatty acid group at days 6, 7, 8, and 10. However, the clinical usefulness of this intravenous infusion remains uncertain.

**Trans fatty acids**

Trans fatty acids occur in dairy products, animal fat, and industrially hydrogenated vegetable fats such as margarine. Trans fatty acids have been postulated to play a role in the exacerbation of atopic dermatitis. In a recently published article in the *Lancet*, dietary surveys were conducted in 55 study centers in 10 European countries, and a positive association was found between an increased intake of trans fatty acids and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema.\(^{43}\) However, as yet no clinical trials have been conducted to verify these dietary surveys.

**Zinc**

Responsible for playing a role in the conversion of linoleic acid to \(n-3\) fatty acids, zinc supplementation was also theorized to have a beneficial effect on atopic dermatitis. Indeed, early studies\(^{44}\) found low serum zinc levels in patients with atopic dermatitis. However, later larger studies have disproved this,\(^{45}\) and the authors could find no clinical trials of the use of zinc supplementation in atopic dermatitis.

**Chinese herbal tea (10 herbs)**

In a 1992 randomized trial, 37 children who had failed “western treatments” were treated with a 10-herb Chinese tea. The treatment group showed a 51% decrease in erythema and a 63% decrease in body surface involvement over the 8-week study period, as opposed to a 6.1% decrease in erythema and a 6.2% decrease in body surface involvement in the placebo group.\(^{46}\) All 37 patients elected to continue treatment for an additional year, and at the end of the study period 18 of the 37 patients had a 90% reduction in eczema scores, 5 had a lesser degree of improvement, and 10 showed no improvement. Four dropped out of the study because of the difficulty of tea preparation or disagreeable taste. The investigators concluded that “Chinese medicinal herbs provide a therapeutic option for children with extensive atopic eczema which has failed to respond to other treatments.”\(^{47}\)

The second randomized trial involved 31 adults who had also failed standard therapy, and found a similar improvement after 8 weeks of taking 10-herb tea.\(^{48}\) A follow-up study, following patients for 1 year, revealed that 12 of 17 patients who elected to continue treatment had greater than 90% reduction in eczema. The 5 remaining patients had greater than 60% reduction in clinical scores compared with baseline
values. The 11 patients who elected not to continue taking the tea experienced a deterioration in symptoms by the end of the year. The difference between groups was highly significant.

In contrast, the subsequent double-blind, randomized, crossover trial involving 40 patients found that a proprietary 10-herb formula (Zemaphyte) was not significantly different to placebo after 8 weeks of treatment.49

The latest randomized, placebo-controlled study of 85 children with moderate atopic dermatitis (using a 5 herb formula) seems to speak in favor of the use of traditional Chinese medicine. This study found that, although objective improvement was not significantly different between groups, patient-rated quality of life was improved in the treatment group and, significantly, the treatment group was able to cut their steroid use by one-third.50

Probiotics
Probiotics, or the ingestion of potentially beneficial bacteria, may play a role in the prevention of atopic dermatitis. In a prospective randomized trial, 159 mothers with a first-degree relative with atopic dermatitis were randomized to receive either 2 capsules of lactobacillus per day or 2 placebo for 4 weeks prior to delivery.51

In addition, the infants were continued on their respective treatments for an additional 6 months after birth. During the 2-year observational period, atopic dermatitis was diagnosed in 15 of 64 children in the probiotic group and in 31 of 68 children in the placebo group.

In conclusion, atopic dermatitis is a difficult to treat condition. The condition may be prevented by the timely administration of probiotics and may be helped by a trial of elimination diet, n-3 fatty acid supplementation, and Chinese 10-herb tea.

PSORIASIS
Psoriasis is a chronic, recurring skin condition characterized by rapid turnover of keratinocytes, thought to have an immunologic origin. Standard treatments for psoriasis include topicals (corticosteroids, anthrolin, coal tar, vitamin D analogues, retinoids,) phototherapy (wideband UVB [290–320 nm] is deemed more effective but narrow band [310–312 nm] is safer), and oral medications (methotrexate, cyclosporine, and retinoids). As these interventions, however, are only moderately effective, as many as 51% of patients report using alternative therapies.52

Biologic-Based Therapies
Curcumin
Curcumin is the active ingredient in the spice turmeric, and has been anecdotally touted as being beneficial in patients with psoriasis. However, the latest open-label trial of 12 patients administered 4.5 g of curcumin daily showed no significant benefit over the natural product. The investigators note that the small study size may have accounted for the lack of observed efficacy, and state that 250 patients may be needed in future studies for true conclusions to be drawn.53

Capsaicin
An extract from certain peppers, capsaicin has been traditionally used to treat arthritis and postherpetic neuralgia. Two placebo-controlled randomized trials have evaluated the use of this extract cream in the treatment of psoriasis. One (N = 197) examined the use of 0.025% capsaicin cream applied 4 times a day for 6 weeks and showed significant improvement in scaling, thickness, erythema, and pruritus over the study period.54 The other earlier study (N = 44) found that 67% of patients in the capsaicin
arm showed subject reduction of scaling and erythema, whereas only 44% of patients with placebo subjectively improved. Although inclusion in the study required that participants have psoriasis that covered at least 10% of their bodies, the investigators failed to objectively quantify improvement in body surface area involvement in their results, leading the reader to assume less than impressive results. The study failed to give practitioners clinically useful results. In addition, patients using capsaicin cream noted local burning and itching, significant enough to cause 18% of patients to drop out of the active treatment arm.

**Aloe vera**
In one well-conducted randomized trial, the use of aloe vera on psoriasis was evaluated. Sixty patients with mild to moderate chronic plaque-type psoriasis were randomized to apply aloe (5%) cream 3 times daily or placebo. At the end of the 16-week study period, 83% of the aloe vera group showed significant improvement in desquamation, erythema, and PASI score (a standard “psoriasis area and severity” score), whereas only 6.6% of the placebo group benefited. The exact degree of improvement (eg, whether lesions completely cleared or what improvement was seen in the body surface area covered by psoriasis) was not spelled out.

**Essential fatty acids**
The results of studies evaluating the therapeutic benefit of dietary fish oil have been conflicting. The latest multicenter, randomized study published in the *New England Journal of Medicine* found dietary supplementation to be of no benefit in the treatment of psoriasis (145 patients on 6 g of fish oil per day). However, one study examining the effects of intravenous ω-3 fatty acids has found them to be effective in the treatment of chronic plaque-type psoriasis. There is no good evidence for the use of topical essential fatty acid use.

**Other Alternative Therapies**

**Thermal baths**
In Argentina, thermal baths containing sulfur, minerals, and algae have been tested for beneficial effects on psoriasis. Fifty-five patients with moderate to severe psoriasis, all of whom had had no treatment for the prior 6 weeks, were evaluated after 2 different thermal baths sessions daily for 10 days. Researchers evaluating scaling, erythema, and plaque thickness found marked improvement in 11 patients, improvement in 29 patients, and mild improvement in 15 patients by day 10 of the trial. Subjectively, 20 subjects felt marked improvement, 21 felt improvement, and 14 only mild improvement.

Possibly even better results are found in the “Dead Sea” treatment of psoriasis, perhaps because the Dead Sea is below sea level and thus receives a different UVA/UVB ratio, and because of the high salinity of the water (33% in the Dead Sea vs 3% in normal ocean water) Here, twice daily bathing and twice daily sun exposure resulted in complete clearance to marked improvement in 73% to 88% of patients. In one study, the length of remission was 1 to 3 months for 55% of the patients. The best results were seen when sun exposure and Dead Sea baths were used in combination. These results compare favorably with other therapeutic regimens used in the treatment of psoriasis, with no fear of the side effects often associated with systemic medications. However, it should be mentioned that these patients have been noted to have an increased incidence of nonmelanoma skin cancer. Usual treatment consists of 2 bathing sessions of 30 minutes per day and twice daily sun exposure that need not exceed a total of 3 hours per day. Various other spas in the United States, France, Italy, Bulgaria and other locations also claim therapeutic benefits. All need a great deal more study before such claims can be validated.
REFERENCES


