CLINICAL REVIEW

Treatment strategies for recurrent oral aphthous ulcers

ROBERT W. BARRONS

Abstract: The clinical features, etiology, and treatment of recurrent aphthous ulcers (RAU) are discussed.

Aphthous ulcers are among the most common oral lesions in the general population, with a frequency of up to 25% and three-month recurrence rates as high as 50%. The ulcers, which usually occur on the nonkeratinized oral mucosa, can cause considerable pain and may interfere with eating, speaking, and swallowing. RAU is classified as minor, major, and herpetiform on the basis of ulcer size and number. The cause of RAU is idiopathic in most patients. The most likely precipitating factors are local trauma and stress. Other associated factors include systemic diseases and nutritional deficiencies, food allergies, genetic predisposition, immune disorders, the use of certain medications, and HIV infection. The primary goals of therapy for RAU are relief of pain, reduction of ulcer duration, and restoration of normal oral function. Secondary goals include reduction in the frequency and severity of recurrences and maintenance of remission. Topical medications, such as antimicrobial mouthwashes and topical corticosteroids, can achieve the primary goals but have not been shown to alter recurrence or remission rates. Systemic medications can be tried if topical therapy is ineffective. Levamisole has shown variable efficacy in reducing ulcer frequency and duration in patients with minor RAU. Oral corticosteroids should be reserved for severe cases of major RAU that do not respond to topical agents. Thalidomide is effective but, because of its toxicity and cost, should be used only as an alternative to oral corticosteroids.

RAU can be effectively managed with a variety of topical and systemic medications.

Index terms: Amlexanox; Analgesics and antipyretics; Angiotensin-converting-enzyme inhibitors; Anti-infective agents; Antineoplastic agents; Aspirin; Drugs; HIV infections; Immunomodulating agents; Levamisole; Mouthwashes; Pancreatic enzymes; Potassium chloride; Skin and mucous membrane preparations; Steroids, cortico-; Stomatitis; Thalidomide

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Aphthous ulcers are among the most common oral lesions in the general population, with a frequency of 5–25% and three-month recurrence rates as high as 50%.[1] Aphthous ulcers have been reported in 2–4% of HIV-seropositive patients, although these patients suffer from larger and more frequent aphthae in advanced stages of their disease.[2] Aphthous ulcers are often quite painful; may lead to difficulty in speaking, eating, and swallowing; and may negatively affect patients' quality of life.[2,3] In patients with advanced HIV disease, aphthous ulcers may exacerbate weight loss. While most aphthae are small and heal within 7–10 days, larger ulcers can persist for weeks or months. Consequently, therapy for the disease of recurrent aphthous ulcers (RAU) should address both healing and the prevention of new ulcers.

This article reviews the clinical features and etiology of RAU in HIV-seropositive and HIV-seronegative persons; the mechanisms of action, efficacy, and safety of medications used to treat RAU; and the recommended therapeutic strategies. The studies that provided the basis for these recommendations were identified by a MEDLINE search (1966 to present) of the English-language literature pertaining to aphthous ulcers and aphthous stomatitis.

Clinical features

"Aphthous" comes from the Greek word "aphtha," which means ulcer. Despite the redundancy, the medical literature continues to refer

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to these oral lesions as aphthous ulcers.[4] "Aphthous stomatitis" has been used interchangeably with "aphthous ulcers" and may be more accurate terminology.[4,5] Aphthous ulcers are round or oval, with a grayish yellow, crateriform base surrounded by an erythematous halo of inflamed mucosa.[6] For 24–48 hours preceding the appearance of an ulcer, most patients have a pricking or burning sensation in the affected area. The ulcer usually occurs on the nonkeratinized oral mucosa, including the lips, the buccal mucosa, the floor of the mouth, the soft palate, and the ventral surface of the tongue. Regions of keratinized oral mucosa, such as the hard palate, the gums, and the dorsal surface of the tongue, are uncommon locations.

Classification

RAU is classified as minor, major, and herpetiform.[5,6] Seventy to 87% of all RAU cases are minor. Minor RAU involves the presence of one to five ulcers at a time, with each ulcer less than 1 cm in diameter. These ulcers are self-limiting and resolve in 7–10 days without scarring. Major RAU occurs in 7–20% of affected patients. There are 1–10 ulcers at a time, the ulcers exceed 1 cm in diameter, and they persist for up to six weeks. Major aphthae are a cause of significant dysphagia and often result in extensive scarring. Herpetiform aphthae account for 7–10% of RAU cases. In herpetiform RAU there are 10–100 ulcers at a time, ulcer size is usually 1–3 cm, and the ulcers form clusters that coalesce into widespread areas of ulceration lasting 7–10 days. These ulcers are only herpes-like in appearance; herpes simplex virus has not been cultured from them.

Etiology

Trauma and stress. The most likely factors precipitating aphthous ulcers are local trauma and stress. Injury to the oral mucosa may result from accidental self-biting, dental procedures, toothbrush bristles, and sharp-edged foods (e.g., potato chips). In a trial involving 128 patients, 16% claimed that a traumatic incident was associated with their RAU.[5] Emotional and environmental stress may precede 60% of first-time aphthous ulcer cases and involve 21% of recurrent episodes.[5] A frequency of RAU of 31–66% has been reported among medical and dental students, compared with 10–20% in the general population.[5]

Systemic diseases and nutritional deficiencies. Systemic diseases involving immune and nutritional deficiencies have been associated with aphthous ulcers.[5] Oral ulcers have been reported in patients with cyclic neutropenia and agranulocytosis and are common in patients with HIV disease. Nutritional deficiencies involving iron, folic acid, zinc, and vitamins B_1, B_2, B_6, and B_{12} are twice as common in patients with RAU as in healthy persons, occurring in up to 20% of patients. RAU has been associated with gastrointestinal problems, including Crohn's disease, ulcerative colitis, and celiac disease; whether the link is related to immunologic mechanisms or nutritional deficiencies resulting from malabsorption is unknown.

Food allergies. Antibodies to cow's milk and wheat protein (celiac disease) have been demonstrated in patients with RAU.[6] Strict elimination diets involving cow's milk or glutens (wheat, barley, and oats) have resulted in resolution of or improvement in persistent aphthae in greater than 25% of patients.[6,7] However, many foods that are commonly allergenic (e.g., strawberries, tomatoes, and nuts) have not been causally associated with RAU.[6]

Infection. A bacterial or viral cause of RAU has been suggested, but bacterial antibody titer association with RAU has been inconclusive. Antibodies to herpes simplex virus and cytomegalovirus have not been consistently demonstrated in the serum or lesional tissue of patients with RAU. The precipitation of RAU after viral infections may result from the systemic and local immunosuppression associated with viral reactivation rather than from the virus itself.[5,6]

Genetic predisposition. Some people have a well-established familial basis for RAU. However, evidence for a genetic predisposition is not strong.[1] Patients with a family history of RAU may develop the disease earlier and more severely than those with no family history.[5] Forty to fifty percent of first-degree relatives of patients with RAU may have the condition.[5,6] RAU has been found more commonly in identical twins than in nonidentical twins. Elevations in human leukocyte antigen markers have been observed in Israelis with RAU and in patients with Behçet's syndrome.[5] However, what appears to be a familial association may reflect the effects of personality and stressors in the domestic and work environments that collectively activate RAU.[1]

Immune disorders. RAU may be more common and more severe in patients with immune disorders, including cyclic neutropenia, inflammatory bowel disease, Behçet's disease, and HIV disease.[8] Patients with RAU have evidence of antibody-dependent cytotoxicity and elevated serum immunoglobulins.[1] Immunopathogenesis of RAU may involve an imbalance in T-helper/inducer cells and T-suppressor/inducer cells.[8] Patients with severe RAU have increased numbers of T-helper/inducer cells and fewer T-suppressor/inducer cells.[9] The presence of activated T lymphocytes in the periphery of ulcers indicates that RAU may result from an activated cell-mediated response.[10] Similarities in immunohistologic findings in HIV-seronegative and HIV-seropositive individuals with RAU further confirm the hypothesis of a cell-mediated immunologic dysfunction involving primarily T lymphocytes.[1,11] The antigen precipitating this reaction is unknown but may include many of the factors discussed previously, including trauma, microorganisms, and food allergies.[10]

Drug induction. Antineoplastic

medications cause ulcerative stomatitis in up to 37% of patients receiving therapy for acute or chronic leukemia.[12] The likely mechanism is accelerated detachment of oral epithelial cells. Antineoplastic drugs associated with stomatitis include methotrexate, daunorubicin, doxorubicin, and hydroxyurea. Predicting which patients are most likely to manifest stomatitis is not possible. However, patients sensitive to one stomatotoxic drug are often sensitive to others.[12] Burning and reddening of the oral mucosa occur within hours of drug administration. The painful erosions and ulcerations involve both keratinized and nonkeratinized epithelium. Chemotherapy-induced stomatitis should alert the clinician to the possibility of gastroenterocolitis, which often follows a parallel course.[12] Precautionary oral hygiene measures may avoid superimposed infections.

Contact stomatitis with ulceration may occur after prolonged exposure to uncoated potassium chloride, aspirin, and pancreatic enzyme preparations. Cases of "scalded mouth" have been reported with angiotensin-converting-enzyme inhibitors, especially captopril.[13] Patients should be instructed to swallow the tablets as quickly as possible. Stomatitis associated with systemic effects of medications is rare, and objective methods for associating a drug with an event are lacking.

Other medications observed to cause stomatitis include antimicrobials, auranofin, barbiturates, didanosine, foscarnet, griseofulvin, nonsteroidal anti-inflammatory drugs, penicillamine, quinidine, and sulfonamides.[13]

HIV disease. The frequency of aphthous ulcers is similar in persons seronegative and persons seropositive for HIV. However, HIV-seropositive patients with CD4+ lymphocyte counts below 100 cells/mm^3 are more likely to have major recurrent aphthae, which may lead to difficulty eating.[2] Therefore, early diagnosis and treatment are important. The same causes of RAU in HIV-seronegative patients must be considered in HIV-seropositive patients.[14] However, the presence of HIV infection may suggest other causes of oral ulcers—neoplasms, infections, and medications—that should be excluded before the lesions are diagnosed as aphthous ulcers.[15]

Kaposi's sarcoma is the most common cause of oral tumors in AIDS patients, while tumors in non-Hodgkin's lymphoma may be primarily located in the oral cavity. Herpes simplex virus reactivation and associated lesions are frequent in HIV-infected individuals at any level of immunocompetence.[15] Oral ulcers attributable to *Histoplasma capsulatum* and *Crytococcus neoformans* are uncommon but may occur in the setting of disseminated disease. *Candida albicans* may cause oral ulcers in advanced stages of AIDS.[15] Oral and esophageal ulcers are found in acute HIV infection, together with malaise, fever, myalgia, rash, acute myelitis, and encephalitis.[15]

Accurate diagnosis of oral lesions in HIV-seropositive patients may require biopsy in combination with a clinical examination and patient history. Lesions located on keratinized mucosa are probably not aphthous ulcers. Any ulcer located on keratinized oral mucosa, major aphthous ulcer, or ulcer not responding to topical corticosteroid treatment should be biopsied. Diagnostic protocols addressing the role of cultures, biopsies, and cytology studies have been developed to help the clinician.[14,15]

Antimicrobial mouthwashes

Antimicrobial mouthwash use in RAU is intended to control microbial contamination and secondary infection. Both antibiotic (e.g., tetracycline) and antiseptic (e.g., chlorhexidine) mouthwashes have been studied. The time required for healing of aphthous ulcers has been correlated with the ability of antimicrobial mouthwashes to reduce the population of oral mucosal flora.[16] Double-blind, placebo-controlled trials of antiseptic and antibiotic mouthwashes are summarized in Table 1.

Four double-blind, placebo-controlled trials of antiseptic mouthwashes were identified. In these studies, 197 patients were treated for at least five weeks.[16-19] In three of the studies, the patients had a history of minor RAU, with maximum ulcer-free periods of three to four weeks.[16,18,19] Concurrent therapy for RAU was prohibited in these three trials. Patients whose immune function might be compromised because of drugs or diseases were excluded from two of the trials.[16,19]

In three of the four studies, no significant differences in ulcer duration or pain severity were evident between patients treated with antiseptic mouthwash and patients given placebo.[16,18,19] In two studies, the total number of ulcers was significantly lower with antiseptic mouthwash than with placebo.[17,19] Three trials demonstrated significant benefits in both the active therapy and the placebo groups throughout the treatment course.[16,18,19] While placebo therapy with quinine sulfate may have some antimicrobial properties,[17,19] the remaining vehicles were without known activity.[16,18] Enhanced patient awareness and improved oral hygiene from study involvement may have contributed to these findings. Adverse drug reactions were reported for only two trials.[18,19] These events included nausea in one patient, inflammation of the gums in one patient, and discoloration of the teeth and gums in an unspecified number of patients. Chlorhexidine caused brown staining of the teeth and tongue after two weeks of therapy. Although frequency and severity were not addressed, the potential for staining during prolonged treatment may limit the use of chlorhexidine.

In three studies involving 81 patients, tetracycline or chlortetracycline mouthwash significantly reduced the duration and pain of RAU

Table 1.
Summary of Double-Blind, Placebo-Controlled Trials of Topical Antibiotics, Antiseptics, and Corticosteroids for Treatment of Aphthous Ulcers[a]

Reference	No. Patients	Dosage Regimen	Duration of Ulcers (Days)	Frequency of New Ulcers[b]	No. Ulcers	Subjective Improvement (Score or %[c])
Antiseptics						
17	20	1% chlorhexidine gel t.i.d. after meals × 35 days	Mean: T = 4.8, PC = 7.7 ($p < 0.05$)	NA	T = 104, PC = 140[d] (NS[e])	Score: T = 0.93, PC = 1.21 ($p < 0.05$)
18	40	0.1% hexetidine mouth rinse 15 mL for 1 min t.i.d. after meals × 6 wk	NA ($p > 0.05$[f])	NA	NA ($p > 0.05$[f])	NA ($p > 0.05$[f])
19	41	0.2% chlorhexidine mouthwash 10 mL for 1 min t.i.d. × 6 wk	Mean: T = 5.02, PC = 5.78 ($p > 0.05$)	NA	Mean: T = 7.54, PC = 8.32[g]	NA (NS[f])
16	96	Listerine mouth rinse (unspecified volume) for 30 sec b.i.d. × 6 mo	NA (NS[f])	NA	NA (NS[f])	NA (NS[f])
Antibiotics						
20	7	0.5% chlortetracycline 50 mL held in mouth 1 min q.i.d.	NA ($p < 0.01$[h])	NA	NA	T = 58%, PC = 62% (NS[e])
21	49	2.5% chlortetracycline 10 mL held in mouth 1 min q.i.d.	NA ($p < 0.01$[h])	NA	NA	NA ($p < 0.01$[h])
22	25	5% tetracycline 1 tsp held in mouth 1 min q.i.d.	Mean: T = 5.46, PC = 8.21 ($p < 0.05$)	T = 1.07, PC = 0.20[i] (NS[e])	NA	Score: T = 1.11, PC = 1.78 ($p < 0.05$)
Corticosteroids						
23	57	0.025% betamethasone benzoate gel 1 drop over lesion t.i.d. and h.s.	T < 6, PC > 6 ($p < 0.05$)	NA	NA	T = 88%, PC = 60% ($p < 0.05$)
24	15	Beclomethasone dipropionate spray 2 puffs (800 μg) directly to ulcer q.i.d.	NA ($p < 0.001$[h])	NA	NA	NA ($p < 0.05$[h])

[a]T = active treatment, PC = placebo, NA = not available, NS = no significant changes. All *p* values apply to comparisons between active treatment and placebo unless otherwise indicated.
[b]Mean number of new ulcers, compared with baseline.
[c]Mean score on a scale from 0 to 3 (0 = no pain, 1= mild pain, 2 = moderate pain, 3 = severe pain) or percentage of patients with symptomatic relief.
[d]Cumulative number of ulcers in all patients.
[e]Details of statistical analysis not reported.
[f]Reported as no significant difference between treatment and placebo groups in change in duration, number, or severity of ulcers.
[g]Daily number of ulcers per patient. Statistical analysis not reported.
[h]Reported as a significant difference between treatment and placebo groups in days with ulcers or ulcer pain.
[i]Mean number of new ulcers per week, compared with baseline.

compared with placebo; however, the frequency of ulceration was unchanged.[20-22] RAU classification and criteria for recurrence were well-defined in only one trial.[20] The patients received 250-mg doses of antibiotic mouthwash four times daily and were instructed to hold the solution in the mouth for one to two minutes.[20-22] Aphthous ulcers were treated for 4 days to 2 weeks, and follow-up lasted 2.5–8 weeks. Adverse effects were reported only in patients using the mouthwash in excess of five days and included dysgeusia, skin reactions, thrush, angular cheilosis, and burning and soreness of the throat.[20]

Corticosteroids

Topical corticosteroid use in patients with RAU is intended to limit the inflammatory process associated with the formation of aphthae. Corticosteroids may act directly on T lymphocytes or alter the response of effector cells to precipitants of immunopathogenesis (e.g., food allergies, trauma, microorganisms).[25] Only two double-blind, placebo-controlled trials have evaluated the efficacy of topical corticosteroids for RAU.[23,24] The patients enrolled in one trial had minor RAU.[24] Classification of ulcers was not available for the other trial. Both trials assessed patients for immunocompetence

through laboratory studies. One trial excluded other medications used in RAU.[24] In both trials there were significant reductions, compared with placebo, in ulcer duration and pain severity and no changes in the frequency of RAU in patients who applied betamethasone gel or beclomethasone aerosol spray to ulcers four times daily for six days to four weeks.[24,25]

Two non-placebo controlled trials found no significant differences between triamcinolone ointment or betamethasone tablets and adhesive vehicles (Biobase [no longer available] and Orabase [Colgate-Hoyt]) in the frequency and duration of severe RAU.[26,27] Subjective improvement tended to be greater with corticosteroids than with adhesive vehicle (Orabase), although the difference was not statistically significant.[27] A single-blind, placebo-controlled trial involving fluocinonide ointment was performed in patients with minor and major RAU.[28] Fluocinonide ointment significantly reduced ulcer duration, but ulcer frequency and subjective improvement were the same as for adhesive vehicle (Orabase). In the latter three trials, study design, ulcer severity, and vehicle activity may have contributed to findings inconsistent with those in the double-blind, placebo-controlled studies.

Amlexanox

A tablet formulation of amlexanox has been marketed in Japan since 1987 for the long-term treatment of asthma.[29,30] In the United States, amlexanox is available only as a 5% topical paste (Aphthasol, Block) for use in the treatment of RAU. Amlexanox is a potent inhibitor of the formation and release of inflammatory mediators from mast cells, neutrophils, and mononuclear cells. Given topically, amlexanox could be expected to facilitate the healing of aphthous ulcers but not to reduce the frequency of RAU episodes.[30]

Four vehicle-controlled, randomized, double-blind, multicenter trials assessed the efficacy of amlexanox with respect to ulcer healing and pain resolution in 1335 patients with minor RAU.[31] All the trials excluded patients using concurrent medications to treat RAU, patients with medical conditions posing a risk for study involvement and patients with alternative causes of RAU, including irritable-bowel disease, Behçet's syndrome, and anemia. The patients applied small dabs of amlexanox oral paste four times daily directly to the ulcers for 4–10 days. The first trial established the efficacy of 5% amlexanox paste relative to either 1% amlexanox paste or the paste vehicle. The 5% amlexanox paste produced significantly greater reductions in ulcer size than the vehicle and greater improvement in the rate of healing and erythema than either the vehicle or 1% amlexanox paste. The results of the remaining three trials comparing 5% amlexanox paste with the paste vehicle were presented as a meta-analysis examining rates of complete healing of ulcers and resolution of pain. After six days of therapy, 74% of the patients receiving amlexanox paste had complete healing of ulcers, versus 54% of those using the vehicle ($p < 0.001$). Similarly, 83% of the patients treated with amlexanox paste had complete resolution of pain, compared with 73% of those receiving the vehicle ($p < 0.001$). The self-limiting nature of aphthous ulcers, combined with the protective effects of the paste vehicle, produced high rates of healing and pain resolution independent of amlexanox. Patients may benefit from earlier application of amlexanox during the prodromal stage of an RAU episode.

In a review of clinical trials and premarketing studies involving 991 subjects, only 2.1% of those using 5% amlexanox paste reported adverse events.[29] Almost 70% of these events were associated with the topical application of amlexanox and included stinging, dryness, bumps on the lips, and mucositis. All of the adverse events were transient, and none resulted in early discontinuation of amlexanox therapy.

Levamisole

An increase in T-helper cells (CD4+ cells) and a decrease in T-suppressor cells (CD8+ cells) may accompany RAU during periods of disease exacerbation and normalize during remission.[32] Levamisole is an immunopotentiating agent that has demonstrated the ability to normalize the CD4+ cell/CD8+ cell ratio and improve symptoms in RAU patients.[32] Correction of T-suppressor-cell deficiency may reduce the inflammatory response resulting from cellular immunity and promote resolution of aphthae.

Seven placebo-controlled clinical trials assessed the efficacy and safety of levamisole in patients with RAU (Table 2).[33-39] The RAU classification was reported for three of the seven trials.[33,34,38] More than 68% of the patients in these trials were diagnosed with minor RAU. The remaining studies did not categorize RAU but required at least one RAU episode per month. Use of concurrent drug therapies for RAU was prohibited in three trials.[34,36,39] Only two studies excluded drugs or diseases that might compromise immune function.[35,36] Levamisole was given either at the first sign of ulceration or prophylactically every one to two weeks. The trials lasted from six weeks to more than six months.

Four of the studies showed a reduction in the frequency and duration of aphthous ulcers during levamisole treatment, with ulcer recurrences decreasing by half in up to 43% of patients.[33,37-39] Efficacy did not differ whether levamisole was given routinely or started at the first sign of ulcers. In six trials, a complete absence of ulcers was found at the conclusion of the study in 16 of 144 patients receiving levamisole.[33-35,37-39] Follow-up of three of these studies[33-38] showed that 20 levamisole-treated patients were without ulcers for at least 103 days and that 4 patients were ul-

Table 2.
Summary of Double-Blind, Placebo-Controlled Trials of Levamisole and Thalidomide for Treatment of Aphthous Ulcers[a]

Reference	No. Patients	Dosage Regimen	Complete Response (%)[b]	Partial Response (%)[c]	Ulcer Duration (Days)	Subjective Improvement[d]
Levamisole						
33	71	150 mg/day × 3 days every 2 wk for 4 mo	Levamisole = 19, PC = 10 ($p < 0.05$)	NA[e]	NA[e]	Levamisole = 65, PC = 33 ($p < 0.05$)
	20	Above regimen × 2 mo, then 50 mg t.i.d. × 3 days every 2 wk if ulcers present	Levamisole = 10, PC = 0 ($p < 0.05$)	NA[e]	NA[e]	Levamisole > PC ($p < 0.001$)
35	20	150 mg/day × 3 days every 2 wk	NA	NA	Mean: levamisole = 8.43, PC = 7.40 ($p > 0.05$)	Levamisole = 90, PC = 30[f]
37	18	50 mg t.i.d. × 3 days every 2 wk if ulcers present	Levamisole = 30, PC = 0[f]	NA	Median: levamisole = 4, PC = 8 ($p < 0.05$)	Levamisole = 66, PC = 11[f]
34	48	150 mg/day × 3 days every week at first sign of ulcers	NA	NA	Median: levamisole = 7, PC = 6[f]	Levamisole = 65, PC = 28 ($p < 0.05$)
36	33	150 mg/day × 3 days every week at first sign of ulcers	NA	NA	Mean: levamisole = 8.0, PC = 5.9[f]	Levamisole = 55, PC = 38 ($p > 0.10$)
38	47	150 mg/day × 2 days every week at first sign of ulcers	Levamisole = 13, PC = NA[e]	Levamisole = 51, PC = NA[e]	NA	NA[g]
39	33	150 mg/day × 1 or 2 days/wk	NA	NA[e]	Median: levamisole = 0, PC = 8.5 ($p < 0.05$)	NA[e]
Thalidomide						
40	57	200 mg h.s. × 4 wk	Thalidomide = 55, PC = 7 ($p < 0.05$)	Thalidomide = 34, PC = 18 ($p < 0.05$)	NA	Thalidomide > PC ($p < 0.03$)
41	96	100 or 300 mg q.d. × 24 wk	Thalidomide 100 mg = 6, thalidomide 300 mg = 16, PC = 0 ($p < 0.05$[h])	NA	NA	NA
42	73	100 mg h.s. × 8 wk	Thalidomide = 48, PC = 9 ($p < 0.05$)	NA	NA	NA

[a]PC = placebo, NA = not available, NS = not significant. All *p* values apply to comparisons between active treatment and placebo.
[b]No ulcer episodes within one month of therapy.
[c]A reduction of ≥50% in the number of ulcer episodes or the total ulcer surface area.
[d]In the levamisole trials, the percentage of patients reporting moderately or markedly reduced pain. In the reference 40 trial (thalidomide), a score of 1 or 2 (on a scale from 1 to 15) on 14 of 15 quality-of-life measures.
[e]Number or duration of ulcer episodes, size of ulcers, or pain score reported as significantly improved with levamisole compared with placebo.
[f]Statistical analysis not reported.
[g]Reported as no significant difference.
[h]Thalidomide 100 mg versus placebo and thalidomide 300 mg versus placebo.

cer free for six months. In five trials, subjective improvement in a majority of patients taking levamisole was reported.[33-37] The disparity between subjective and objective responses evident in several trials was not discussed. In one trial, the subjective evaluations were performed by the investigator and may have differed from patient assessments.[36] Additionally, unidentified concurrent medications and illnesses may have altered patient perceptions of subjective improvement in the frequency and duration of ulcers.

Levamisole was well tolerated in a majority of the patients. Among 128 patients receiving levamisole, 2 withdrew as result of adverse effects (nausea and flu-like symptoms). The most frequent adverse effects were dysgeusia (21%) and nausea (16%). The other adverse effects occurred in fewer than 10% of the patients and included dysosmia, headaches, diarrhea, influenza-like symptoms, and rash. Some of these events occurred only on the days of treatment, and many may not have been attributable to levamisole.

Thalidomide

First introduced into the European market in 1957 as a sedative, thalidomide's use was halted in 1961 after it was linked to a rare congenital

birth defect known as phocomelia.[43] Interest in thalidomide was renewed in 1980 after it was used successfully to treat erythema nodosum leprosum. This finding led to the study of thalidomide for various dermatologic disorders and exploration of thalidomide's anti-inflammatory and immunomodulatory properties.

In a study of healthy male volunteers, thalidomide demonstrated the ability to decrease the ratio of circulating helper T cells to suppressor T cells.[44] Thalidomide has also been found to inhibit the production of various cytokines as a result of its effects on T lymphocytes, monocytes, and polymorphonuclear cells. In vitro studies showed that thalidomide selectively inhibits the production of tumor necrosis factor α (TNF-α), a cytokine that plays a central role in regulating immune and inflammatory responses to infection. Patients with erythema nodosum leprosum have elevated TNF-α levels, which are highest during the lepra reactions.[43] Elevated TNF-α has also been observed both locally and systemically in patients with RAU.[45,46] However, a recent study found that thalidomide actually increased circulating TNF-α levels in HIV-seropositive patients with aphthous ulcers.[46] Whether it involves a generalized or specific cytokine regulatory pathway, thalidomide's exact mechanism of action in treating RAU remains unknown.

Three double-blind, placebo-controlled trials investigated the use of thalidomide for oral aphthous ulcers in patients with advanced HIV disease,[40] Behçet's syndrome,[41] or a history of severe RAU.[42] All the trials excluded patients taking medications that may alter immunocompetency,[40-42] and one trial excluded Behçet's syndrome and inflammatory bowel disease as alternative causes of RAU.[42]

In HIV-seropositive patients, aphthous ulcers were completely or partially resolved in 55% and 34%, respectively, of thalidomide-treated patients.[40] Complete and partial resolution rates for the placebo recipients were 7% and 18%, respectively. The thalidomide-treated patients had diminished pain, an improved ability to eat, and an average weight gain of four pounds in four weeks (compared with no weight gain in the placebo group). In patients with severe RAU, thalidomide treatment resulted in complete resolution of aphthae in 48% of patients (versus 9% of placebo recipients), significant reductions in the number of buccal aphthae, and improved function.[42] A total of 22% of patients with Behçet's syndrome who received thalidomide had complete resolution of oral ulcers, compared with none of the placebo recipients.[41] Thalidomide also reduced the number of minor oral and genital ulcers and the frequency of uveitis episodes that are commonly associated with Behçet's syndrome. Thalidomide was effective at dosages of 100 and 300 mg/day. Complete responses were seen as early as 3.5–6 weeks after the start of therapy.[40-42] The effects of thalidomide are suppressive, not disease modifying.[41,42] Once thalidomide was discontinued, the average duration of remission was 20 days.[42]

In the three trials, adverse effects of thalidomide resulted in the discontinuation or interruption of therapy in 6–26% of patients. The adverse events most frequently associated with thalidomide were neurosensory, gastrointestinal (GI), and cutaneous. Rash occurred in 24% and 32% of patients with Behçet's syndrome and HIV disease, respectively.[40,41] Constipation was the most common GI event, occurring in up to 65% of thalidomide-treated patients. Neurosensory effects included somnolence (24–87% of patients), headaches (up to 39%), and polyneuropathy (0–6%). In a recent review of thalidomide use for dermatologic conditions, the frequency of peripheral neuropathy ranged from 21% to 50%.[43] The frequency may vary with the patient population studied, ranging from less than 1% in patients with erythema nodosum leprosum to greater than 70% in patients with prurigo nodularis.[43]

Other agents

Many other agents have shown efficacy in the treatment of RAU, either in anecdotal cases or in single clinical trials. These agents include acyclovir, azelastine, azathioprine, interferon alfa, prostaglandin E_2 gel, colchicine, sucralfate, and cyclosporine.[1] Because of the number of potential therapeutic options and the unpredictable course of RAU, this review was limited to medications studied in at least two double-blind, placebo-controlled trials.

Treatment selection

Before initiating medications for RAU, clinicians should determine whether well-recognized causes are contributing to the disease. Screening tests for allergies and nutritional deficiencies should be performed, and the roles of stress and trauma should be assessed. Skin-patch tests for allergies to food additives, flavoring agents, and essential oils may be helpful. A gluten-free diet has shown success in reducing RAU episodes, both in the presence and in the absence of celiac disease.[5] Hematologic testing should be considered in patients with a history of RAU exceeding six months, since patients with nutritional deficiencies respond well to replacement therapy. Stress may play a significant role in the development and recurrence of aphthous ulcers; relaxation and imagery training has produced significant reductions in ulcer frequency.[1]

An undefinable disease cause and unpredictable disease course in most patients make patient education about the goals of therapy essential. The primary goals are to control the local pain, reduce the duration of the ulcers, and restore normal oral function. Secondary goals are to decrease the frequency and severity of recurrences and ultimately to keep the patient in remission.

Topical medications. The American Academy of Oral Medicine (AAOM) has recommended topical treatments for oral conditions.[4] Top-

ical medications include anesthetics, antihistamines, antimicrobials, and anti-inflammatory agents. However, evidence of successful use of these agents for aphthous ulcers is primarily anecdotal. Of the medications listed by AAOM, only corticosteroids have been studied in well-designed clinical trials in patients with RAU.

Topical agents address the primary goals of RAU therapy, including reduction in ulcer pain and duration, while decreases in ulcer frequency and prolongation of remission remain elusive. In limited trials, tetracycline mouth rinse, betamethasone gel, beclomethasone spray, and amlexanox significantly reduced ulcer duration and pain. In contrast, chlorhexidine mouthwash had no significant effect on ulcer pain or duration in most studies.

Tetracycline mouthwash had no adverse effects when its use was limited to five days; however, extended use may predispose patients to oral fungal infections. After two weeks of therapy, chlorhexidine mouthwash caused brown staining of teeth and oral mucosa. This adverse effect may be especially problematic in RAU patients who repeatedly use the mouthwash for symptomatic relief.

The impact of topical betamethasone and beclomethasone on the hypothalamic–pituitary–adrenal (HPA) axis was not assessed during any of the trials. Fluocinonide gel applied to the oral mucosa in patients with erosive lichen planus had no effect on serum or urine cortisol levels over a three-week period. However, cases of HPA axis suppression have resulted from unregulated use of long-acting, highly potent topical corticosteroids.[47,48] Therefore, extended use of these products in patients with RAU requires monitoring for HPA axis suppression.

Amlexanox produced significantly higher rates of complete ulcer healing and complete resolution of pain than placebo vehicle. The ability of amlexanox to reduce ulcer frequency was not examined because the studies lasted only 4–10 days. However, in view of its antiallergic, anti-inflammatory mechanism of action, amlexanox would not be expected to affect ulcer frequency or keep patients in remission. Amlexanox is among the least expensive of the topical medications for RAU (Table 3).

Table 3.
Cost of Medications Used To Treat Recurrent Aphthous Ulcers

Agent	Formulation	Dosage	Cost/Week ($)[a]
5% amlexanox paste (Aphthasol, Block)	5-g tube	1 dab q.i.d.[b]	10.50
Tetracycline Powder, USP (Medisca)	25-g powder	250 mg q.i.d.	4.76
0.012% chlorhexidine gluconate (generic)	480 mL	10 mL t.i.d.	2.68
Beclomethasone dipropionate (generic)	17-g inhaler	2 puffs q.i.d.[b]	31.15
Levamisole hydrochloride (Ergamisol, Janssen)	50-mg tablet	50 mg t.i.d. × 3 days	55.04
Thalidomide (Thalomid, Celgene)	50-mg tablet	200 mg q h.s.	210.00

[a]Based on average wholesale price.[49]
[b]Administered directly to ulcers.

Systemic medications. Oral corticosteroids are indicated only in severe cases of major RAU,[1,14] after an inadequate response to topical corticosteroid therapy,[14] or in the presence of nonoral (i.e., esophageal and colonic) aphthae, as seen in Behçet's syndrome. Oral corticosteroid use for aphthous ulcers has not been studied in controlled clinical trials; instead, information comes from case reports.[1,14] Recommendations include giving oral prednisone 40–60 mg/day for four to seven days[14] and then tapering the dosage over two weeks.[1] Adverse reactions to systemic corticosteroid therapy in patients with HIV include cushingoid facies, thrush, reactivation of herpes simplex virus, and accelerated progression of Kaposi's sarcoma.[14] Such adverse events place oral corticosteroids among the last treatment options for RAU in HIV-seropositive patients.

Levamisole reduced the frequency and duration of aphthae in five of seven studies when administered either at the first sign of ulceration or routinely for several days every one to two weeks. Subjective improvement was found in six of the studies. However, the reductions in pain often did not parallel the reductions in frequency and duration. Most of the trials neglected to exclude concurrent medications used in managing aphthae, which may have contributed to the disparity between subjective and objective findings. Levamisole yielded remissions lasting at least six months in many patients who had complete healing of ulcers. The major adverse effects associated with levamisole were taste disturbances and nausea, although only one patient withdrew as a result of either event. Overall, levamisole was well tolerated, though plagued with a peculiar dosage schedule.

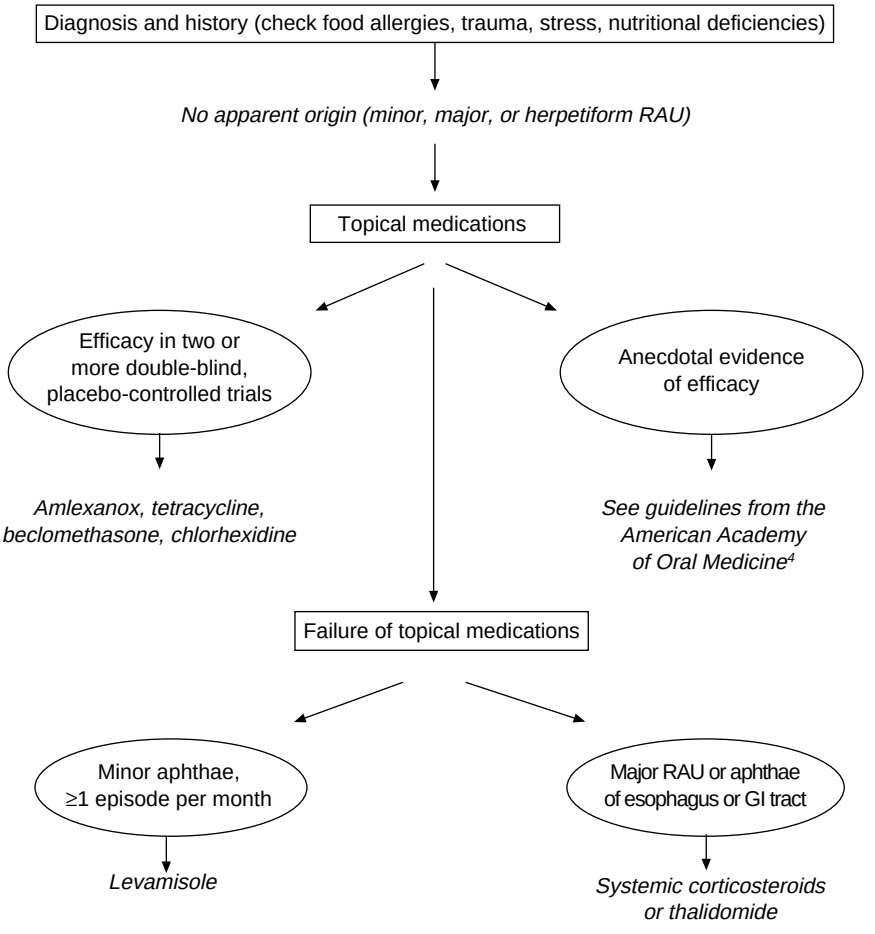
Thalidomide has pronounced efficacy in healing oral aphthae. In two trials involving difficult cases, thalidomide completely healed 48–55% of patients, compared with 7–9% of patients receiving placebo.[42] However, the effect of thalidomide was temporary, with most patients having recurrent ulcers an average of 20 days after stopping therapy. Thalidomide also significantly increased subjective improvement. Adverse effects were frequent during thalidomide therapy. Headaches, somnolence, and constipation all occurred in greater than 10% of patients, while peripheral neuropathy occurred in up to 6%.

Neuropathy associated with thalidomide is manifested by painful paresthesia of the hands and feet, often accompanied by sensory loss in the

lower limbs.[43,50] Irreversible neuropathy may result if treatment is continued too long or signs of motor dysfunction develop.[42] Neuropathy limits long-term use of thalidomide. Most reported cases occurred at dosages of 100–300 mg/day given for more than six months.[42,50] In the trials reviewed, 10 of 169 patients given thalidomide (versus 5 of 127 placebo recipients) developed evidence of peripheral neuropathy within 35 days of therapy at dosages of 100 or 300 mg/day. In one uncontrolled study, thalidomide 50 mg three times a week for 17 months was effective and did not produce evidence of polyneuropathy in 43 patients with Behçet's syndrome.[51] Further studies of low-dose thalidomide are needed to establish the minimal effective dosage.

Therapy with thalidomide requires teaching patients to identify the early signs of neuropathy and to understand the risk of teratogenicity. Prickling, tingling, numbness, or pain in the extremities suggests the need for an examination by a physician. Patients should be evaluated at baseline and monthly for the first three months, after which examinations for manifestations of neuropathy should continue periodically.[52] Sensory nerve action potential amplitude (SNAP) testing should be performed at baseline and every six months.[52] A SNAP test result more than 40% lower than the baseline result is predictive of neuropathy and requires drug discontinuation. All patients, pharmacists, and physicians must participate in the System for Thalidomide Education and Prescribing Safety (STEPS) program (1-888-4-CELGEN). Patients must meet eligibility criteria to receive the drug. Informed consent must be obtained to ensure education about contraceptive measures for men and women, the frequency of pregnancy testing, and the symptoms and evaluation of peripheral neuropathy. Pharmacist registration in the STEPS program ensures that prescriptions are filled only after physician registration in the program is verified and a signed informed-consent document is collected and filed with the initial prescription.

Figure 1. Treatment algorithm for recurrent aphthous ulcers (RAU). Chlorhexidine and levamisole were not effective in all clinical trials.



Recommendations. On the basis of efficacy, cost, and safety, topical medications remain the treatment of first choice for patients with RAU (Figure 1). Amlexanox is the most extensively studied and most cost-effective of the topical agents. Levamisole can significantly reduce ulcer duration, frequency, and pain in patients with minor RAU and may prove to be the safest and most effective systemic agent for maintaining remission in these patients. Thalidomide has shown the largest margin of efficacy in patients with severe RAU. However, long-term administration is required to maintain remission. Extended treatment has resulted in peripheral neuropathy, a potentially irreversible condition. In addition, headache and somnolence may reduce patient compliance with thalidomide therapy. Significant costs, frequent adverse effects, and extensive exclusion criteria limit thalidomide use to patients with severe RAU as an alternative to systemic cortico-steroids.

Conclusion

The primary goals of therapy for RAU are relief of pain, reduction of ulcer duration, and restoration of normal oral function. Secondary goals include reductions in the frequency and severity of recurrences and maintenance of remission. Topical medications can achieve the primary goals but have not been shown to alter recurrence or remission rates. Systemic medications can be tried if

topical therapy is ineffective. Levamisole has shown variable efficacy in reducing ulcer frequency and duration in patients with minor RAU. Oral corticosteroids should be reserved for severe cases of major RAU. Because of its toxicity, thalidomide should be used only as an alternative to oral corticosteroids.

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