Recurrent aphthous stomatitis

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INTRODUCTION

Recurrent aphthous stomatitis (RAS), also known as "canker sores," is a common disease of the oral and, occasionally, genital mucosa characterized by the repeated development of one to many discrete, painful ulcers that usually heal within 7 to 14 days [1-6]. The lesions are typically 3 to 5 mm, round to oval ulcers with a peripheral rim of erythema and a yellowish adherent exudate centrally. The process may range in severity, with some patients noting only an occasional lesion and others experiencing such frequent episodes that they have almost continuous ulcer activity [1-6].

This topic will discuss the pathogenesis, clinical manifestations, and management of RAS. Other causes of oral and genital ulceration are discussed separately.

- (See "Oral lesions".)
- (See "Clinical manifestations and diagnosis of Behçet syndrome".)
- (See "Approach to the patient with genital ulcers".)
- (See "Acute genital ulceration (Lipschütz ulcer)".)

EPIDEMIOLOGY

RAS is seen throughout the world, with the greatest prevalence in the Middle East, Mediterranean region, and South Asia [6,7]. In North America, it occurs approximately in one out of five individuals and is the most common cause of acute recurrent oral ulcers. Most individuals first develop RAS during adolescence, although it is not uncommonly seen in children. The disease may continue into adulthood but typically wanes with increasing age. It is unusual for patients over the age of 40 to develop new-onset RAS.

CLASSIFICATION

Simple aphthosis — RAS is referred to as simple aphthosis (also called Mikulicz ulcers) when the individual experiences several episodes per year involving one to several ulcers lasting up to 14 days and limited to the oral mucosa. This is the most common form of the disease.

Complex aphthosis — In "complex aphthosis," the patient may have involvement of both the oral and genital mucosa, although oral lesions are more common. The lesions are more numerous, more painful, and larger (>1 cm in diameter), often taking up to four to six weeks to resolve. Some patients with complex aphthosis will have such frequent episodes that they are almost never without at least one active ulcer. In patients with complex aphthosis, the diagnosis of Behçet syndrome must be excluded [8,9]. (See "Clinical manifestations and diagnosis of Behçet syndrome".)

Ulcer morphology — Three morphologic types of ulcers are recognized in patients with RAS [10]; they can be seen both in patients with simple and complex RAS:

- Minor ulcers, <1 cm in diameter, usually 3 to 5 mm
- Major ulcers, >1 cm in diameter
- Herpetiform ulcers, 1 to 2 mm in diameter, typically present in clusters, sometimes coalescing in larger ulcers

PATHOGENESIS

The pathogenesis of RAS is unknown and is likely multifactorial [1-6]. Most investigations have supported the concept of immune dysregulation involving the oral mucosa leading to an exaggerated proinflammatory process or a relatively weak anti-inflammatory response [11-17]. There appears to be a genetic predisposition to developing RAS, as it is common for patients to have a family history of RAS.

Although certain foods may exacerbate RAS, there is no evidence to suggest an etiologic role for food allergy. Vitamin and mineral deficiencies have also been implicated in the pathogenesis of RAS, particularly deficiency of vitamin B12, although the role of vitamin supplementation in the treatment of RAS remains uncertain [18].

Infectious etiologies have been explored, but not documented, to be a direct cause of disease. Many patients with RAS observe pathergy, so that any trauma to the lining of the mouth may result in the development of an ulcer in that location [13,19]. Emotional stress will frequently lead to an exacerbation of disease [20]. Certain drugs have been documented to induce oral ulcers similar to aphthous ulcers. The ulcers typically resolve when the drug is discontinued. Although a few

observational studies reported a temporary increase of RAS in the first few weeks after smoking cessation, other studies have not found an association between RAS and smoking [7,21-23].

CLINICAL MANIFESTATIONS

Lesions of RAS have a very characteristic appearance [1-6]. The ulcers are discrete, round to oval with an erythematous rim and adherent yellowish exudate centrally. Patients with simple aphthosis typically have one to five discrete ulcers limited to the oral mucosa that are <1 cm in diameter (picture 1A-C) [4]. In some patients with simple RAS, however, ulcers may be larger than 1 cm or, infrequently, 1 to 3 mm in diameter and occurring in clusters (herpetiform ulcers). Patients with complex aphthosis often present with large ulcers (>1 cm in diameter) but will typically also have smaller lesions similar to those seen in simple aphthosis. The episodes of ulcers are frequent and the duration more prolonged. Lesions may involve both the oral and genital areas.

The oral lesions in RAS most commonly develop on the buccal and labial mucosae. The gingival sulci, lateral and ventral tongue, soft palate, and anterior pharynx may also be involved. Although ulcers are predominantly found on the nonmasticatory mucosal surfaces, they may also be seen on the hard palate and attached gingivae.

A lesion typically progresses from a painful, pinpoint papule into an ulcer over a period of one to two days; the ulcer gradually expands to its final size over the next three to four days and then stabilizes before beginning to heal. In some patients, lesions may come and go within four to five days, but in most individuals, they resolve in 10 to 14 days. Patients who experience frequent episodes are often able to identify lesions in the early phase, which can be useful in terms of initiating therapy [2].

Many patients with RAS experience an exacerbation of their disease following trauma to the oral mucosa, such as biting the inside of the cheek or undergoing a dental procedure. In these patients, one or more ulcers will predictably develop in the area of trauma over the next couple of days [13,19].

Most patients with RAS first experience oral ulcers during the second and third decades of life. They may continue to develop lesions through middle age, but the frequency typically diminishes.

Although patients may be very uncomfortable, few experience systemic symptoms or signs associated with outbreaks of their aphthous ulcers. The routine presence of fever, malaise, or other systemic manifestations should raise the suspicion of an autoinflammatory disease, such as PFAPA (**p**eriodic **f**ever, **a**phthous stomatitis, **p**haryngitis, and **a**denopathy) syndrome, cyclic neutropenia, or hyperimmunoglobulin D (hyper IgD) syndrome. (See 'Differential diagnosis' below.)

PATHOLOGY

Lesions of RAS are not usually biopsied. However, typical findings of an active ulcer would be epithelial necrosis and a neutrophilic infiltrate centrally. At the periphery, the infiltrate is predominantly lymphocytic with some exocytosis and epithelial degeneration [24].

Direct immunofluorescence is nonspecific, with possible deposition of C3 or immunoglobulin M in blood vessels.

DIAGNOSIS

Diagnostic criteria — The diagnosis of RAS is typically made clinically, based on patient history and physical examination. A history of recurrent, self-limited ulcers of the oral mucosa that demonstrate the characteristic appearance of discrete, round to oval ulcers with an erythematous rim and yellowish exudate is generally sufficient to make the diagnosis of simple aphthosis [1-6].

Patient history — Patients often begin experiencing ulcers during adolescence and early adulthood. They may develop one to several lesions at a time that are self-limited in nature. A history of lesions persisting for several days up to several weeks and then resolving is characteristic of RAS. The ulcers may be very painful and, in some cases, may interfere with the ability to eat, drink, and talk. Although some patients may report such frequent episodes that they almost always have at least one ulcer present, the individual lesions heal completely. Most patients will go for weeks to months between episodes. The history of developing an ulcer at a site of trauma is very common in patients with RAS.

Below is a list of suggested questions for patients with oral ulcers:

- What is the natural history of the lesions? Do they come and go? Come and persist?
- Does trauma tend to precipitate a new lesion?
- Are the lesions symptomatic?
- Is there a history of skin disease involving other body sites? Specifically ask about the anogenital region.
- Does the patient have any symptoms suggestive of other sites of mucosal involvement (eg, dysphagia, hoarseness, stridor, ocular irritation, dysuria, dyspareunia, hematuria)?
- Does the patient have other medical conditions, including immunosuppression?
- Does the review of systems suggest any underlying disease?
- Is the patient currently taking any suspect medications?

Physical examination — Aphthous ulcers have a very characteristic appearance. The ulcers are discrete and usually 3 to 5 mm in diameter (picture 1A-C). They have an erythematous halo at the margin and a yellowish exudate centrally. They may be found throughout the oral mucosa but are especially common on the buccal and labial mucosae and the lateral and ventral tongue. Lesions in the genital area are similar in appearance but may develop on both the mucosal and cutaneous areas of the vulva, distal vagina, scrotum, and penis. When evaluating the patient with oral ulcers, it is recommended that a physical examination of all mucocutaneous surfaces, including the scalp, nails, and anogenital region, be performed to exclude other underlying skin disease.

Biopsy — The diagnosis of RAS is typically made clinically. However, in more severe or atypical presentations, a biopsy may be useful to rule out an alternate mucosal process. A shave biopsy at the periphery of an early ulcerative lesion is the most useful. However, a biopsy does not help distinguish RAS from Behçet syndrome [8,9]. If the disease is extensive enough to mimic an autoimmune bullous disease such as pemphigus vulgaris or cicatricial pemphigoid, performing a biopsy for direct immunofluorescence examination may be helpful. (See "Skin biopsy techniques" and "Pathogenesis, clinical manifestations, and diagnosis of pemphigus", section on 'Diagnosis'.)

Other laboratory tests — For most patients with simple aphthosis, no additional laboratory assessment is needed. For patients with more severe disease or those who develop the process later in life, it is reasonable to search for an underlying cause [25]. A complete blood count, erythrocyte sedimentation rate, and assessment of nutritional deficiencies (eg, vitamin B12, folate, iron) may reveal a disorder that, when corrected, could potentially lead to resolution or improvement of the ulcers [10,26]. Additional laboratory assessment may be considered in those individuals with signs or symptoms suggesting an underlying or associated systemic disease.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of RAS includes a wide range of conditions, including:

- **Behçet syndrome** – Behçet syndrome is a rare disease characterized by recurrent oral aphthae and any of several systemic manifestations, including genital aphthae, ocular disease, skin lesions, gastrointestinal disease, neurologic disease, vascular disease, and arthritis [9]. The diagnosis is based upon the presence of recurrent oral ulcerations plus at least two additional findings, including recurrent genital ulcerations, eye lesions, skin lesions, and positive pathergy test (table 1). Care should be used in making the diagnosis of Behçet syndrome in patients with complex aphthosis, especially in patients who are not from areas where this disease is more prevalent (eg, Middle East and Asia). In a United States study of 64 patients with complex aphthosis, only 10 (16 percent) met the diagnostic criteria for Behçet syndrome [8]. (See "Clinical manifestations and diagnosis of Behçet syndrome".)

- **MAGIC syndrome** – MAGIC (**m**outh **a**nd **g**enital ulcers with **i**nflamed **c**artilage) syndrome represents an overlap syndrome of relapsing polychondritis and Behçet syndrome [27]. Associated findings may include aortitis and thoracic aortic aneurysm [28-30]. (See "Clinical manifestations of relapsing polychondritis".)

- **Systemic lupus erythematosus** – Oral or nasopharyngeal ulcers satisfy one criterion for the diagnosis of systemic lupus erythematosus (SLE) (picture 2). Biopsy shows a lichenoid pattern of inflammation, which differs from typical RAS [31]. In addition, photosensitivity, malar rash, arthritis, and other systemic involvement would be anticipated in patients with SLE. (See "Overview of cutaneous lupus erythematosus", section on 'Mucosal manifestations'.)

- **Gluten-sensitive enteropathy** – There is evidence of an association between gluten-sensitive enteropathy (celiac disease) and aphthous stomatitis [32-34]. In the patient presenting with RAS, it is reasonable to inquire about a history of gastrointestinal complaints or a known gluten intolerance. (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in children" and "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults".)

- **Inflammatory bowel disease** – An association between inflammatory bowel disease and oral ulcers has been reported [35]. In Crohn's disease, the ulcerations may have a characteristic linear shape (picture 3). In the patient presenting with RAS, it is reasonable to inquire about a history of gastrointestinal complaints [36]. (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults" and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults" and "Clinical manifestations and complications of inflammatory bowel disease in children and adolescents".)

- **HIV infection** – RAS, especially complex aphthosis, can be a significant problem in patients with HIV infection. A diagnosis of RAS in these patients must be made with greater caution because of the possibility of concomitant underlying infections that may present in atypical ways. In general, complex aphthosis has become less common in HIV-positive patients since the advent of successful antiretroviral therapy [37-39]. (See "The natural history and clinical features of HIV infection in adults and adolescents".)

- **Herpes simplex virus** – Primary herpetic gingivostomatitis may present with extensive oral ulcerations. Recurrent herpes simplex virus (HSV) often involves the cutaneous lip; it is unusual for these lesions to develop within the oral cavity. When this does occur, it is typically on the masticatory mucosa of the gingivae or hard palate. Recurrent intraoral HSV may also raise suspicion for underlying immunosuppression [40]. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Oral infections'.)

- **Cyclic neutropenia** – Cyclic neutropenia is a rare autosomal dominant disorder of bone marrow progenitor cells characterized by the cyclic occurrence of fever, malaise, pharyngitis, and aphthous stomatitis beginning during infancy or early childhood. Neither the predictability nor the systemic symptoms are seen in typical RAS [41]. (See "Cyclic neutropenia".)

- **PFAPA syndrome** – Like cyclic neutropenia, PFAPA (**p**eriodic **f**ever with **a**phthous stomatitis, **p**haryngitis, and **a**denitis) syndrome tends to follow a pattern of recurrence approximately once a month. However, there is no associated neutropenia [42]. (See "Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA syndrome)".)

- **Hyperimmunoglobulin D syndrome** – Hyperimmunoglobulin D (hyper IgD) syndrome is a rare autosomal recessive genetic disorder characterized by recurrent febrile episodes typically associated with lymphadenopathy, abdominal pain, and an elevated serum polyclonal IgD level. Aphthous ulcers, and sometimes genital ulcers, are seen in approximately one-half of the patients with hyper IgD syndrome [43]. (See "Hyperimmunoglobulin D syndrome: Clinical manifestations and diagnosis", section on 'Mucocutaneous manifestations'.)

- **Agranulocytosis** – Agranulocytosis is defined as having a neutrophil count <500/mm^3 in the absence of anemia and thrombocytopenia. The vast majority of cases are drug induced. Agranulocytosis may be accompanied by oral ulcerations, fever, pharyngitis, dysphagia, and sepsis. (See "Drug-induced neutropenia and agranulocytosis".)

- **Autoimmune bullous disease** – The mucosal lesions of complex aphthosis can sometimes be extensive enough that this process may be confused with an autoimmune bullous dermatosis such as pemphigus vulgaris or cicatricial pemphigoid. However, even in severe complex aphthosis, there is usually an episodic nature to the disease, as opposed to the chronicity seen in pemphigus or pemphigoid. These entities may be distinguished from RAS by biopsy, including direct immunofluorescence. (See "Pathogenesis, clinical manifestations, and diagnosis of pemphigus" and "Clinical features and diagnosis of bullous pemphigoid and mucous membrane pemphigoid".)

- **Oral erosive lichen planus** – The oral lesions of complex aphthosis may heal with scarring that resembles the white, reticular network seen in oral erosive lichen planus. However, in oral lichen planus, the lesions tend to be more limited in distribution and more chronic in nature. The more characteristic, discrete, circular ulcers of RAS are not seen. (See "Oral lichen planus: Pathogenesis, clinical features, and diagnosis".)

- **Ulcus vulvae acutum** – Also known as Lipschütz ulcer, ulcus vulvae acutum typically occurs in sexually inactive adolescent females and is characterized by painful, necrotic ulcerations of the vulva or vagina [44]. There is evidence to support prior infection with Epstein-Barr

virus and ulcus vulvae acutum. Other infectious etiologies of genital ulcers, such as HSV, should be excluded. (See "Acute genital ulceration (Lipschütz ulcer)".)

- **Drug-induced mucosal ulcers** – Nicorandil, used for treating angina, has been reported to induce aphthous-like ulcers. This drug is not available in the United States. Nonsteroidal anti-inflammatory agents have also been implicated in the development of aphthous stomatitis. (See "Oral lesions", section on 'Nicorandil-induced ulceration'.)

MANAGEMENT

The goals of treatment of RAS are to provide relief from pain, hasten the healing of ulcers, and decrease the frequency and severity of episodes. However, there is no uniformly effective therapy for RAS, and many topical or systemic agents have been used with variable success.

Despite the common nature of this disorder, there is a paucity of high-quality studies evaluating treatments [45-52]. A 2011 systematic review of 43 randomized trials of topical and systemic therapies conducted in patients without systemic diseases associated with RAS found that a variety of topical (eg, topical corticosteroids, topical tetracyclines, amlexanox), systemic (systemic corticosteroids, colchicine) and destructive therapies (topical silver nitrate, laser therapy) were reported as effective in reducing pain and promoting ulcer healing [10]. However, the included studies were of low quality.

A subsequent systematic review of 25 randomized trials examined the efficacy of several systemic therapies, including clofazimine, colchicine, prednisone, montelukast, and pentoxifylline, for the treatment of RAS not associated with an underlying systemic disease [46]. Most of the studies were of low quality and at high risk of bias. The authors concluded that there was insufficient evidence to support a relative benefit for any of the treatments studied.

Our approach — There is no uniformly effective therapy for RAS. Our approach to the management of RAS is based upon limited evidence from low-quality randomized trials and clinical experience. General measures aimed at maintaining good oral hygiene, avoiding exacerbating factors, and reducing pain are appropriate for essentially all patients with RAS (see 'General measures' below). For patients with simple aphthosis, topical therapies in addition to general oral hygiene measures is generally all that is required (see 'Patients with simple aphthosis' below). Patients with complex RAS generally require systemic therapies for symptomatic control, in addition to topical therapies and oral hygiene measures (see 'Patients with complex aphthosis' below). In these patients, the presence of an underlying systemic disease or nutritional deficiency must be ruled out. (See 'Differential diagnosis' above.)

General measures

- **Oral hygiene** – It is important to maintain good dental hygiene while at the same time avoiding trauma. A soft toothbrush, waxed tape-style dental floss, and a soft-tipped gum stimulator to gently remove plaque are generally well tolerated. A non-alcohol-containing mouthwash is often less irritating, but still effective, in decreasing microbial overgrowth. Toothpaste containing sodium lauryl sulfate (SLS) may exacerbate RAS in some patients. A trial of using SLS-free toothpaste could be considered. Less aggressive, more frequent professional dental cleaning is advised.

- **Avoidance of exacerbating factors** – Where possible, reduce traumatic factors inside the mouth (eg, sharp/rough dental restorations, braces). Avoid habits that cause trauma (eg, biting cheeks or lips) and foods that seem to exacerbate the process.

- **Pain control** – Topical anesthetics and coating agents can provide temporary relief of discomfort if used prior to eating and performing dental hygiene:

  - **2% viscous lidocaine** – May be applied directly to surface of ulcers or used as a swish and spit
  - **Diphenhydramine liquid** – 12.5 mg/5 mL; 5 mL swish and spit
  - **Dyclonine lozenges** – Dissolve slowly in mouth
  - **Aluminum hydroxide, magnesium hydroxide, and simethicone suspension** – 5 to 10 mL swish and spit
  - **Attapulgite suspension** – 600 to 750 mg/15 mL; 5 to 10 mL swish and spit

  Our first choice is 2% viscous lidocaine. It is available by prescription and generally effective for limited pain control.

- **Control of secondary infection** – Although topical antimicrobial therapy is generally not warranted in the routine management of patients with mild to moderate RAS, it may be helpful for some patients with extensive oral ulceration, especially if they are using topical or oral immunosuppressive agents. In this setting, topical therapies that are used to control overgrowth of *Candida* or bacteria include (see "Oropharyngeal candidiasis in adults"):

  - Clotrimazole troches (10 mg) four to five times daily
  - Nystatin suspension (400,000 to 600,000 units) swish and swallow four times daily
  - Chlorhexidine 0.12% mouth rinse (15 mL) swish and spit twice daily

Patients with simple aphthosis

Topical corticosteroids — Topical corticosteroids (table 2) are the first-line treatment for patients with mild to moderate RAS. They are more effective if initiated early in the course of an episode and used frequently for at least a few days. Ideally, the patient will have medication readily available so it can be started at the first indication of an outbreak. Our first choice is almost always dexamethasone elixir (0.5 mg/5 cc). We prefer the elixir for ease of use. However, if this preparation is not available or has not been effective, medium- to high-potency topical corticosteroid preparations can be used:

- **Dexamethasone elixir 0.5 mg/5 cc** – 5 mL swish and spit three to four times daily. It is important to keep the medication in the mouth for five minutes prior to spitting it out. Do not rinse afterward and avoid eating or drinking for 30 minutes.

- **Clobetasol 0.05% gel or ointment** – Apply a small amount to the area of involvement two to three times daily. This will work better if the mucosa is dried with a piece of gauze prior to the application of the medication. Do not rinse afterward and avoid eating or drinking for 30 minutes.

- **Triamcinolone acetonide 0.1% in Orabase** – Orabase is a thick, paste-like material that may adhere better to isolated lesions but does not appeal to many patients.

The efficacy of topical corticosteroids for the treatment of RAS was evaluated in a randomized trial including 240 patients with minor RAS treated with dexamethasone ointment or placebo three times per day for five days [53]. Ulcer healing occurred in a higher proportion of patients in the dexamethasone ointment group than in the placebo group (88 versus 55 percent). Mild adverse effects occurred in 12 patients (four in the treatment group and eight in the control group) and included perioral rash, burning sensation in the larynx, and pain at the application site.

Other topical agents — Other topical agents that can be used in combination or as an alternative to topical corticosteroids include:

- **Topical tetracyclines** – Topical minocycline and doxycycline, as mouth rinses, gels, or pastes, have been reported as effective in reducing pain or healing time of RAS [54,55]. These synthetic tetracyclines have multiple anti-inflammatory effects, including inhibition of collagenases and reduction of prostaglandin release. A pooled analysis of three small clinical trials found that a single application of topical doxycycline (100 mg tablet crushed and mixed with saline and adhesive paste) was more effective than placebo in reducing the healing time (mean difference [days] -1.77, 95% CI -2.11 to -0.91) [56].

- **Sucralfate suspension** – Sucralfate is a sulfated polysaccharide complexed with aluminum hydroxide that can provide a protective barrier for mucosal ulceration. In three small, randomized trials, sucralfate suspension (eg, 1 g in 10 mL) rinses four times/day was more

effective than placebo in decreasing pain and duration of lesions in patients with RAS and in patients with oral and genital ulcers associated with Behçet syndrome [57-59].

- **Topical hyaluronic acid** – Topical hyaluronic acid (also known as hyaluronan) has been reported to provide pain relief and accelerated healing of RAS lesions. In a systematic review of nine clinical trials, the efficacy of topical hyaluronic acid in reducing pain and ulcer size was comparable with that of other interventions (topical corticosteroid, placebo, diode laser) [60]. The authors concluded that the evidence was inconclusive, based on the heterogeneity of the included studies and high risk of bias in some of the studies. Hyaluronic acid is available without prescription as a 0.2% gel or mouth rinse.

- **Amlexanox** – Amlexanox is a topical anti-inflammatory agent that has been evaluated for the treatment of RAS in a few small trials, although its precise mechanism of action is unknown. In one study including 100 patients with simple RAS, amlexanox 5% paste applied to early lesions four times daily was more effective than placebo for reducing ulcer size and pain [61]. Mild adverse effects occurred in eight patients in the amlexanox group and included stinging or cooling sensation at the application site and metallic taste.

  In another study including 96 patients with RAS, topical 5% amlexanox was as effective as 0.05% clobetasol propionate in reducing pain and ulcer size [62]. Amlexanox is no longer available in the United States.

Vitamins and dietary supplements — Patients with simple RAS in whom a nutritional deficiency is documented (eg, vitamin B12, folate, iron, zinc) may respond to the appropriate supplement (see "Treatment of vitamin B12 and folate deficiencies"). However, one small randomized trial suggests that vitamin B12 may be beneficial in all patients with RAS. In this study including 58 patients with RAS treated with sublingual vitamin B12 (1000 mcg daily) or placebo for six months, vitamin B12 was more effective than placebo in reducing the number of RAS episodes and oral pain, regardless of initial vitamin B12 levels in the blood; moreover, after six months of treatment, 74 percent of individuals in the intervention group were free of ulceration, compared with 32 percent in the control group [63]. No adverse effects were reported in both groups.

The role of multivitamin supplementation in patients without a documented deficiency remains uncertain. In one randomized trial, the efficacy of multivitamin supplementation or placebo for one year was evaluated in 160 patients with at least three episodes of idiopathic minor RAS within the previous 12 months [18]. This study did not find any significant difference in the mean number of new RAS episodes, duration of episodes, and mouth pain between patients in the multivitamin arm and those in the placebo arm during the study period.

Refractory simple aphthosis — A short course of oral corticosteroids may be beneficial in patients with severe RAS that is not controlled with topical therapies [64]. We typically use oral prednisone 20 to 40 mg per day for four to seven days.

Patients with complex aphthosis

First-line therapy — Patients with complex RAS have severe and extensive aphthosis, and topical therapies alone are usually not sufficient to control symptoms. For these patients, we suggest systemic corticosteroids in addition to topical agents. Oral prednisone given at the dose of 20 to 40 mg per day for four to seven days will often provide relief from discomfort and accelerate healing of aphthous ulcers.

For most patients, the use of topical agents and intermittent use of prednisone (up to three times per year) is sufficient treatment. More prolonged courses of prednisone may be necessary in some cases. Because of the many adverse effects of prolonged use of systemic corticosteroids, in patients requiring more frequent or longer courses of prednisone, alternate systemic agents used on a chronic basis should be considered. (See "Major side effects of systemic glucocorticoids".)

The use of systemic corticosteroids is based on limited evidence from two small, low-quality, randomized trials and clinical experience [64,65]. In one trial including 40 patients with severe RAS uncontrolled by topical corticosteroids, prednisone (25 mg per day for two weeks and then tapered off in six weeks) was more effective than placebo in decreasing pain, time to ulcer healing, and number of new ulcers during treatment and at four months [64]. Treatment was generally well tolerated, but minor adverse events were more frequent in the prednisone group.

Second-line therapies — A number of systemic therapies have been proposed for the management of patients with complex RAS who do not respond to intermittent treatment with systemic corticosteroids or patients in whom systemic corticosteroids are contraindicated. These agents are often used in sequence, based upon the patient's response, consideration of potential adverse effects, and patient's preference. Our approach is to begin with colchicine. We add dapsone to that regimen if there is inadequate response to the colchicine alone or only a low dose of colchicine is tolerated:

- **Colchicine** – Colchicine has been used for the treatment of complex aphthosis and mucosal ulcers in Behçet syndrome and for RAS with variable results [66]. The usual starting dose is 0.6 mg orally once daily. After one week, if tolerated, the dose is increased to 0.6 mg twice daily or 1.2 mg once daily. It can be further increased to 0.6 mg three times daily, but very few patients tolerate this dose without developing significant gastrointestinal complaints.

- **Dapsone** – Dapsone has been used effectively in the treatment of complex aphthosis and mucosal ulcers in Behçet syndrome [67-69]. The usual starting dose is 25 to 50 mg daily, which may be increased to a maximum of 150 mg daily as tolerated. A baseline glucose-6-phosphate dehydrogenase (G6PD) level is recommended, and blood cell counts should be followed carefully, especially during the first three months of therapy.

- **Combination of colchicine/dapsone** – The combination of colchicine and dapsone may be more effective than either agent alone [67]. In addition, the patient may be able to use lower doses of each of these medications, which minimizes potential side effects.

Other therapies — Therapies that have been used in patients with severe recalcitrant RAS include:

- **Thalidomide** – Thalidomide has been used for the treatment of severe aphthous stomatitis and the mucocutaneous lesions of Behçet syndrome based upon its immunomodulatory properties [8,70,71]. It has been extensively used for treatment of oral ulcers seen in the HIV-positive population [39]. Thalidomide is a known teratogen. In the United States, thalidomide can only be prescribed through a Risk Evaluation and Mitigation Strategy (REMS) program (www.thalomidrems.com), a registration and monitoring program for the safe use of thalidomide [72]. There are also concerns about development of a peripheral neuropathy that may be irreversible. However, in select patients with complex aphthosis, it can be very effective. The usual dose is 50 to 100 mg daily, but 25 mg daily may be useful as a maintenance dose [73].

- **Montelukast** – Montelukast, a leukotriene inhibitor, may improve pain and healing of oral ulcers when taken at a dose of 10 mg per day for one month followed by 10 mg every other day [64].

- **Apremilast** – Apremilast is an oral phosphodiesterase 4 inhibitor that inhibits production of proinflammatory cytokines and is approved for the treatment of Behçet disease, psoriasis, and psoriatic arthritis. In a small series of five patients with RAS refractory to treatment with topical corticosteroids and colchicine, apremilast at a dose of 30 mg twice daily induced a complete clearance in four of five patients and an almost complete clearance in one patient over a period of two to six weeks [74].

- **Pentoxifylline** – Pentoxifylline 400 mg three times daily may have some limited benefits in aphthous stomatitis [75].

- **Cyclosporine** – Cyclosporine has been used to treat mucocutaneous ulcers in patients with Behçet syndrome, and it could be anticipated that it would be effective in patients with complex aphthosis. However, long-term treatment with cyclosporine is generally contraindicated.

- **Biologic agents** – Anti-tumor necrosis factor (TNF)-alpha agents, including etanercept, adalimumab, infliximab, and golimumab, have all been successfully used to treat severe and recalcitrant RAS [76,77]. In one patient series, 16 out of 18 patients with RAS experienced complete or almost complete clearance of their lesions following treatment with one or more of these agents over a period of 3 to 77 months [76].

Although potentially effective, these agents should be reserved for patients with disabling disease that has failed to respond to more conservative measures. The author has used etanercept, adalimumab, and infliximab in patients with complex aphthosis with moderate success.

- **Chemical or laser cauterization** – The efficacy of chemical or laser cauterization in the treatment of RAS has been evaluated in a few randomized trials and systematic reviews [50-52,78-80]:

  - A systematic review of five randomized trials that compared low-level laser therapy using different types of lasers (eg, neodymium-doped yttrium aluminum garnet [Nd:YAG] laser, InGaA1P diode laser) with topical therapies (eg, triamcinolone acetonide, amlexanox) indicated that laser therapy was associated with immediate pain reduction and more rapid re-epithelization compared with topical agents [80]. However, all included studies were deemed to be at high risk of bias.

  - In a randomized trial, 97 patients with minor RAS were treated with a single application of silver nitrate or placebo [79]. One day after the procedure, more patients in the silver nitrate group than in the placebo group experienced a reduction in the severity of pain (70 versus 11 percent). However, the mean healing time was the same in the two groups (5.6 days).

  Although chemical or laser cauterization may provide a rapid relief of the pain associated with RAS, their efficacy in reducing the healing time and preventing new episodes of RAS remains uncertain.

PROGNOSIS

The prognosis for patients with simple aphthosis is excellent. It is a self-limited disease that can periodically result in moderate discomfort but is otherwise well tolerated. In a minority of patients with complex aphthosis, the pain and frequency of outbreaks may have a significant impact on the overall quality of life. The use of systemic medications for symptomatic control can be associated with both short- and long-term side effects. Fortunately, both forms of RAS tend to improve as patients age.

SUMMARY AND RECOMMENDATIONS

- **Clinical presentation** – Recurrent aphthous stomatitis (RAS) is a common disease of the oral mucosa characterized by the recurrent development of one to several discrete, round to oval, painful ulcers with an erythematous rim and adherent yellowish exudate centrally

(picture 1A-C). RAS typically heals within two weeks. (See 'Clinical manifestations' above.)

- **Classification** – RAS is classified as simple aphthosis and complex aphthosis. Simple aphthosis is the more common form of the disease. Patients experience several self-limited episodes per year, and involvement is limited to the oral mucosa. Patients with complex aphthosis may have involvement of both the oral and genital mucosa. The lesions are more numerous, more painful, and larger, often taking up to four to six weeks to resolve. (See 'Classification' above.)

- **Diagnosis** – The diagnosis of RAS is usually made on clinical grounds, based upon a typical history and physical examination. Most patients are otherwise healthy. In patients with more severe or recalcitrant disease, it is appropriate to evaluate for underlying disease. In patients with complex aphthosis, the diagnosis of Behçet syndrome must be excluded. Biopsy of a lesion will not distinguish between these two entities. (See 'Diagnosis' above and 'Differential diagnosis' above.)

- **Management** – There is no uniformly effective therapy for RAS. General measures aimed at oral hygiene, avoidance of trauma to the oral mucosa, and use of topical pain relievers are appropriate for all patients with RAS (see 'General measures' above):

  - **Simple aphthosis** – For patients with simple RAS, we suggest topical corticosteroids as first-line therapy rather than other topical agents (**Grade 2C**). Other topical agents that can be used as an alternative or in combination with topical corticosteroids include sucralfate suspension, amlexanox (not available in the United States), and topical doxycycline. Based on limited clinical trial data, these agents appear to be safe, and they appear to improve pain and ulcer healing compared with placebo. No specific therapy is also a reasonable alternative since many patients improve with general measures alone. (See 'Patients with simple aphthosis' above.)

  - **Complex/recalcitrant aphthosis** – For patients with complex RAS, we suggest oral corticosteroids, in addition to topical corticosteroids, as first-line therapy (**Grade 2C**). If the episodes are frequent or severe despite treatment with oral corticosteroids, other treatment options include colchicine, dapsone, or a combination of both drugs. We typically start with colchicine and add dapsone if there is an inadequate response to the colchicine alone or only a low dose of colchicine is tolerated. (See 'Patients with complex aphthosis' above.)

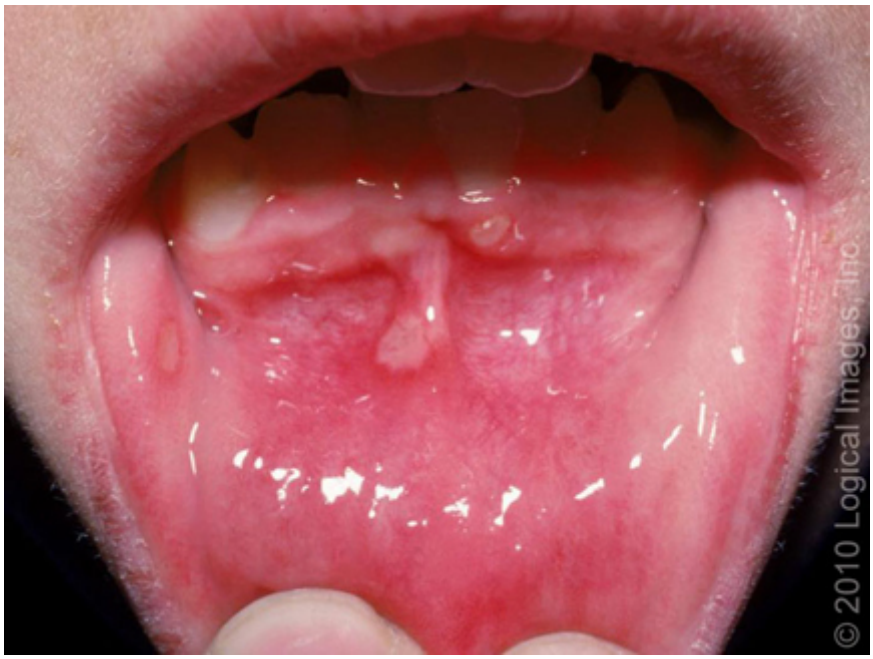
    Other systemic agents that have been used with some success in patients with severe recalcitrant RAS include thalidomide, montelukast, pentoxifylline, cyclosporine, and anti-tumor necrosis factor (TNF)-alpha agents. (See 'Other therapies' above.)

- **Prognosis** – In most patients, RAS resolves or subsides spontaneously with age. In a minority of patients with complex aphthosis, the pain and frequency of outbreaks may have a significant impact on the overall quality of life. (See 'Prognosis' above.)

Topic 112654 Version 10.0

GRAPHICS

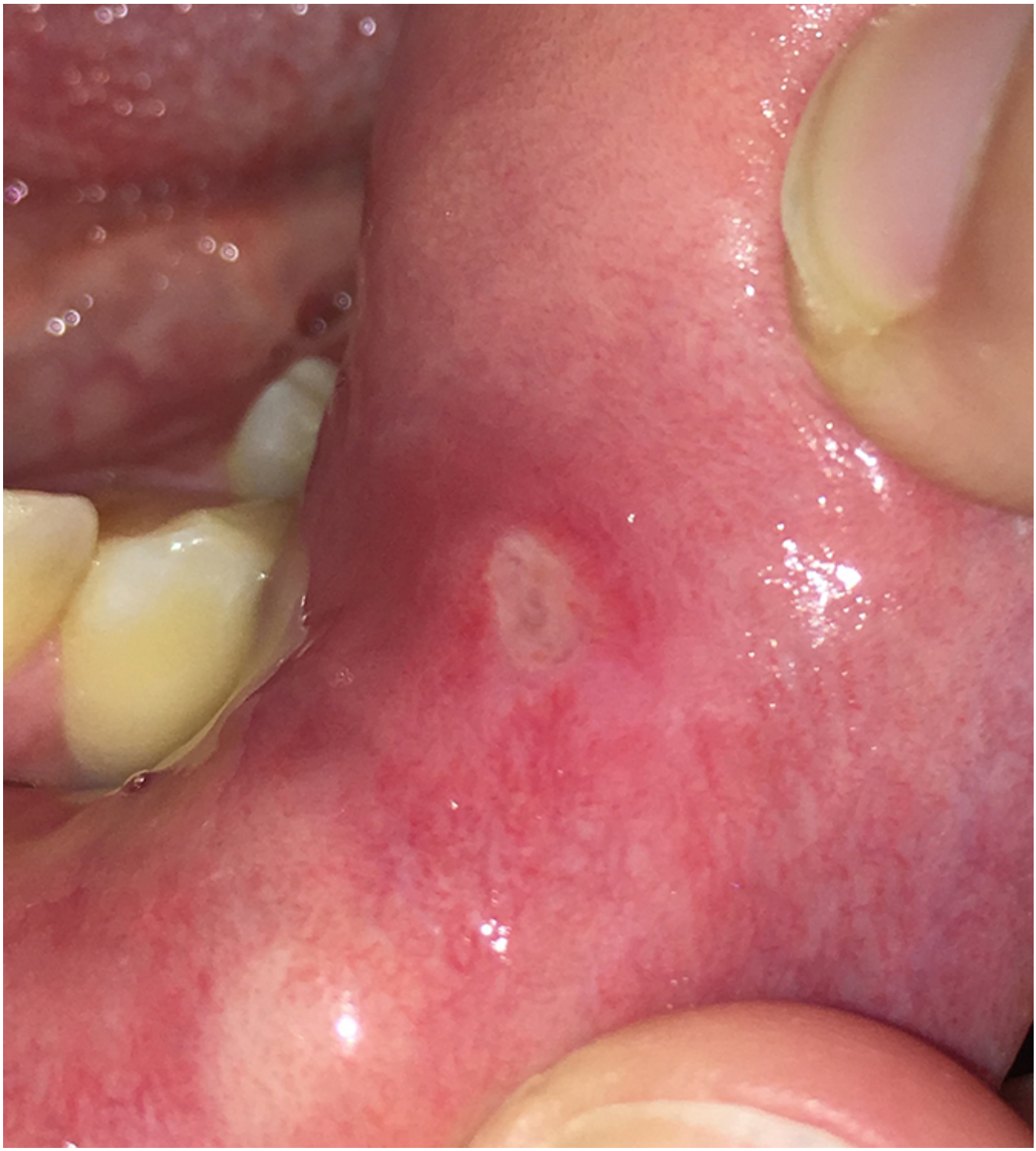
Aphthous ulcers



Round, yellow-gray ulcers are present on the oral mucosa.

Graphic 63475 Version 6.0

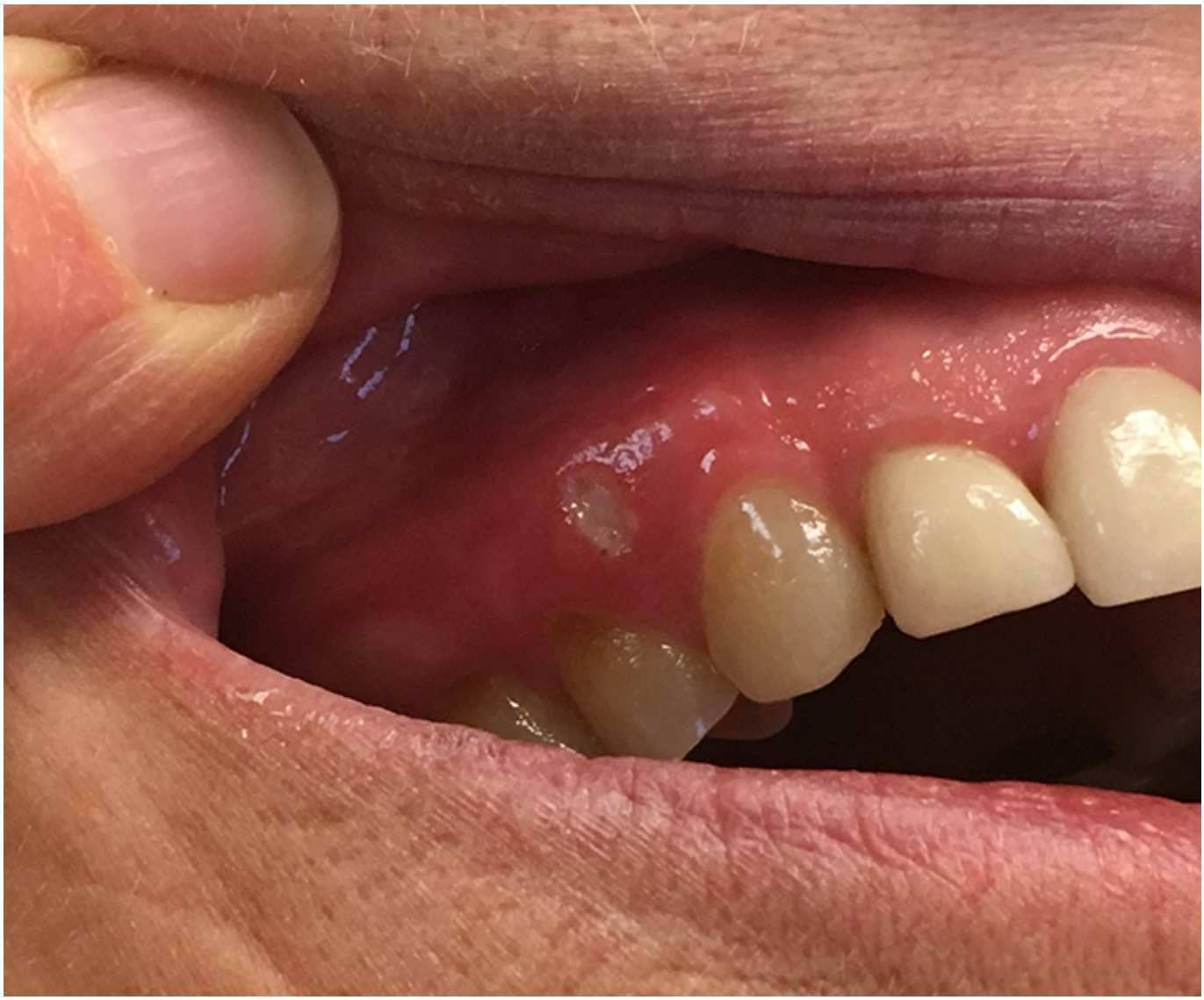
Recurrent aphthous stomatitis



A round ulceration is visible on the oral mucosa of this patient with recurrent aphthous stomatitis.

Graphic 114283 Version 1.0

Recurrent aphthous stomatitis



A small, oval ulceration is present on the gingival mucosa of a patient with recurrent aphthous stomatiti

Graphic 114284 Version 1.0

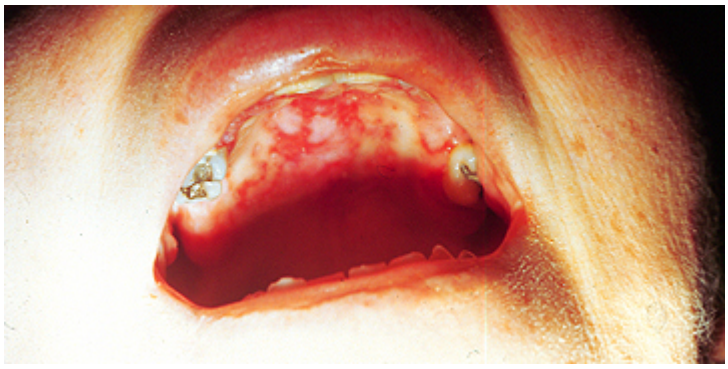
Diagnostic criteria for Behçet syndrome

Criterion	Required features
Recurrent oral ulceration	Aphthous (idiopathic) ulceration, observed by clinician or patient, with at least three episodes in any 12-month period
Plus any two of the following:	
Recurrent genital ulceration	Aphthous ulceration or scarring, observed by clinician or patient
Eye lesions	Anterior or posterior uveitis cells in vitreous in slit-lamp examination; or retinal vasculitis documented by ophthalmologist
Skin lesions	Erythema nodosum-like lesions observed by clinician or patient; papulopustular skin lesions or pseudofolliculitis with characteristic acneiform nodules observed by clinician
Pathergy test	Interpreted at 24 to 48 hours by clinician

Adapted from International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. Lancet 1990; 335:1078.

Graphic 54762 Version 6.0

Oral ulcers in lupus

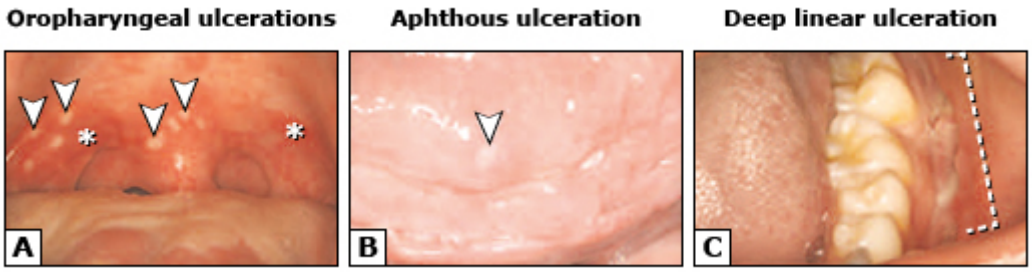


Multiple white, hyperkeratotic lesions and erosive lesions are present on the mucosa of the hard palate.

Courtesy of Samuel Moschella, MD.

Graphic 63605 Version 5.0

Aphthous ulcerations of the mouth in inflammatory bowel disease



Examples of different oral aphthous lesions in patients with IBD:

(A) Erythema (*) and multiple aphthous ulcers of the soft palate mucosa (arrowheads).

(B) Aphthous ulcer of the ventral tongue (arrowhead).

(C) Deep, linear mucosal ulceration.

From: Shazib MA, Byrd KM, Gulati AS. Diagnosis and Management of Oral Extraintestinal Manifestations of Pediatric Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2022; 74:7. DOI: 10.1097/MPG.0000000000003302.

Graphic 138812 Version 1.0

Comparison of representative topical corticosteroid preparations (classified according to the United States system)

Potency group*	Corticosteroid	Vehicle type/form	Brand names (United States)	Available strength(s), percent (except as noted)
Super-high potency (group 1)	Betamethasone dipropionate, augmented	Ointment (optimized)	Diprolene	0.05
		Gel, lotion	[Generic only]	0.05
	Clobetasol propionate	Cream, ointment	Temovate	0.05
		Gel, solution (scalp)	[Generic only]	0.05
		Cream	Tasoprol	0.05
		Cream (emollient base)	Temovate E¶	0.05
		Lotion, shampoo, spray aerosol	Clobex	0.05
		Foam aerosol	Olux, Olux-E, Tovet	0.05
		Lotion	Impeklo	0.05
		Ointment	Clobetavix	0.05
		Shampoo	Clodan	0.05
		Solution (scalp)	Cormax¶	0.05
	Diflucortolone valerate (not available in United States)	Ointment, oily cream	Nerisone Forte (United Kingdom, others)	0.3
	Fluocinonide	Cream	Vanos	0.1
	Flurandrenolide	Tape (roll)	Cordran	4 mcg/cm^2
	Halobetasol propionate	Lotion	Ultravate	0.05
		Cream, ointment	[Generic only]	0.05
		Foam	Lexette	0.05
High potency (group 2)	Amcinonide	Ointment	Cyclocort¶, Amcort¶	0.1
	Betamethasone dipropionate	Ointment	Diprosone¶	0.05

		Cream, augmented formulation (AF)	Diprolene AF	0.05
	Clobetasol propionate	Cream	Impoyz	0.025
	Desoximetasone	Cream, ointment, spray	Topicort	0.25
		Gel	Topicort	0.05
	Diflorasone diacetate	Ointment	ApexiCon¶, Florone¶	0.05
		Cream (emollient)	ApexiCon E	0.05
	Fluocinonide	Cream, gel, ointment, solution	Lidex¶	0.05
	Halcinonide	Cream, ointment, solution	Halog	0.1
	Halobetasol propionate	Lotion	Bryhali	0.01
High potency (group 3)	Amcinonide	Cream	Cyclocort¶, Amcort¶	0.1
		Lotion	Amcort¶	0.1
	Betamethasone dipropionate	Cream (hydrophilic emollient)	Diprosone¶	0.05
	Betamethasone valerate	Ointment	Valisone¶	0.1
		Foam	Luxiq	0.12
	Desoximetasone	Cream, ointment	Topicort, Topicort LP¶	0.05
	Diflorasone diacetate	Cream	Florone¶, Psorcon	0.05
	Diflucortolone valerate (not available in United States)	Cream, oily cream, ointment	Nerisone (United Kingdom, others)	0.1
	Fluocinonide	Cream (aqueous emollient)	Lidex-E¶	0.05
	Fluticasone propionate	Ointment	Cutivate¶	0.005
	Mometasone	Ointment	Elocon¶	0.1

	furoate			
	Triamcinolone acetonide	Cream, ointment	Aristocort HP¶, Kenalog¶, Triderm	0.5
Medium potency (group 4)	Betamethasone dipropionate	Spray	Sernivo	0.05
	Clocortolone pivalate	Cream	Cloderm	0.1
	Fluocinolone acetonide	Ointment	Synalar	0.025
	Flurandrenolide	Ointment	Cordran	0.05
	Fluticasone propionate	Cream	Cutivate¶	0.05
	Hydrocortisone valerate	Ointment	Westcort¶	0.2
	Mometasone furoate	Cream, lotion, solution	Elocon¶	0.1
	Triamcinolone acetonide	Cream	Kenalog¶, Triderm	0.1
		Ointment	Kenalog¶	0.1
Lower-mid potency (group 5)		Ointment	Trianex, Tritocin	0.05
		Aerosol spray	Kenalog	0.2 mg per 2 second spray
		Dental paste	Oralone	0.1
	Betamethasone dipropionate	Lotion	Diprosone¶	0.05
	Betamethasone valerate	Cream	Beta-Val¶, Valisone¶	0.1
	Desonide	Ointment	DesOwen¶, Tridesilon¶	0.05
		Gel	Desonate, DesRx	0.05
	Fluocinolone acetonide	Cream	Synalar	0.025
	Flurandrenolide	Cream, lotion	Cordran, Nolix	0.05
	Fluticasone propionate	Lotion	Beser¶, Cutivate¶	0.05
	Hydrocortisone butyrate	Cream, lotion	Locoid, Locoid Lipocream	0.1

		Ointment, solution	[Generic only]	0.1
	Hydrocortisone probutate	Cream	Pandel	0.1
	Hydrocortisone valerate	Cream	Westcort¶	0.2
	Prednicarbate	Cream (emollient), ointment	Dermatop¶	0.1
	Triamcinolone acetonide	Lotion	Kenalog¶	0.1
		Ointment	Kenalog¶	0.025
Low potency (group 6)	Alclometasone dipropionate	Cream, ointment	Aclovate¶	0.05
	Betamethasone valerate	Lotion	Beta-Val¶, Valisone¶	0.1
	Desonide	Cream	DesOwen, Tridesilon	0.05
		Lotion	DesOwen¶, LoKara¶	0.05
	Fluocinolone acetonide	Foam	Verdeso	0.05
		Cream, solution	Synalar	0.01
		Shampoo	Capex	0.01
		Oil[Δ]	Derma-Smoothe/FS Body, Derma-Smoothe/FS Scalp	0.01
	Triamcinolone acetonide	Cream, lotion	Kenalog¶, Aristocort¶	0.025
Least potent (group 7)	Hydrocortisone (base, ≥2%)	Cream	Ala-Cort, Hytone¶, Nutracort¶	2.5
		Ointment	Hytone¶	2.5
	Hydrocortisone (base, <2%)	Lotion	Hytone¶, Ala Scalp, Scalacort DK	2
		Solution	Texacort	2.5
		Ointment	Cortaid¶, Cortizone 10,	1

			Hytone¶, Nutracort¶	
		Cream	Ala-Cort, Cortaid¶, Cortizone 10, Hytone¶, KeriCort, Synacort¶	1
		Gel	Cortizone 10	1
	Hydrocortisone acetate	Lotion	Aquanil HC, Cortizone 10, Sarnol-HC	1
		Spray	Cortaid¶	1
		Solution	Cortaid¶, Noble¶, Scalp Relief, Scalpicin	1
		Cream, ointment	Cortaid¶	0.5
		Cream	Instacort	0.5
		Cream	MiCort-HC¶	2.5
		Cream	Vanicream HC	1
		Lotion	Nucort	2

* Listed by potency according to the United States classification system: group 1 is the most potent, group 7 is the least potent. Other countries use a different classification system with only 4 or 5 groups.

¶ Inactive United States brand name for specific product; brand may be available outside United States. This product may be available generically in the United States.

Δ 48% refined peanut oil.

Data from:

1. *Lexicomp Online. Copyright © 1978-2023 Lexicomp, Inc. All Rights Reserved.*
2. *Tadicherla S, Ross K, Shenefelt D. Topical corticosteroids in dermatology. Journal of Drugs in Dermatology 2009; 12:1093.*
3. *U.S. Food & Drug Administration Approved Drug Products with Therapeutic Equivalence (Orange Book). Available at: https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (Accessed on June 18, 2017).*
4. *The British Association of Dermatologists' information on topical corticosteroids – established and alternative proprietary names, potency, and discontinuation. British Association of Dermatologists. Available at: https://www.bad.org.uk/shared/get-file.ashx?id=3427&itemtype=document (Accessed on April 26, 2021).*

Graphic 62402 Version 65.0

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