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# Recurrent Aphthous Stomatitis

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## Abstract

Recurrent Aphthous Stomatitis (RAS) is the most common ulcerative disease affecting the oral mucosa. It occurs mostly in healthy individuals and has atypical clinical presentation in immunocompromised individuals. The etiology of RAS is still unknown, but several local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors, as well as immunosuppressive drugs, have been proposed as causative agents. Clinical management of RAS is based on severity of symptoms, frequency, size and number of lesions using topical and systemic therapies. The goals of therapy are to decrease pain and ulcer size, promote healing and decrease frequency of recurrence.

### Keywords

Aphthous; Immunological; Crohn's disease; Behçet's disease; Nutritional deficiency; Psychological stress; Topical therapy; Systemic therapy

## Introduction

Recurrent aphthous stomatitis (RAS) remains the most common ulcerative disease of the oral mucosa presenting as painful round shallow ulcers with well-defined erythematous margin and yellowish-gray pseudomembranous center[1]. RAS has a characteristic prodromal burning sensation that lasts from 2 to 48 hours before an ulcer appears. It occurs in otherwise healthy individuals and is typically located on the buccal and labial mucosa and tongue. Involvement of the heavily keratinized mucosa of the palate and gingiva is less common.

Diseases which also cause oral ulcers that may be mistaken for RAS include Behçet's disease, cyclic neutropenia, recurring intraoral herpes infections, HIV-related oral ulcers or gastrointestinal diseases such as Crohn's disease and ulcerative colitis. It is incumbent upon the clinician managing oral disease to distinguish localized RAS from ulcers caused by an underlying systemic disorder.

Several factors have been proposed as possible causative agents for RAS. These include local factors, such as trauma in individuals who are genetically susceptible to RAS, microbial factors, nutritional factors, such as deficiency of folate and B-complex vitamins,

immunologic factors, psychosocial stress, and allergy to dietary constituents[1]. Extensive research has focused predominantly on immunologic factors, but a definitive etiology of RAS has yet to be clearly established.

RAS is classified into minor, major, and herpetiform ulcers. More than 85% of RAS presents as minor ulcers that are less than 1 cm in diameter and heal without scars (Fig. 1). Ulcers classified as major RAS, also known as Sutton's disease or periadenitis mucosa necrotica recurrens, are larger than 1 cm in diameter, persist for weeks to months, and heal with scars (Fig. 2). Herpetiform ulcers are clinically distinct because they appear as clusters of multiple ulcers scattered throughout the oral mucosa; despite the name, these lesions have no association with herpes simplex virus. General characteristics of the three types of RAS are summarized in Table 1.

Management of RAS depends upon the frequency and severity of the lesions. Most cases can be adequately managed with topical therapy, but systemic therapy is sometimes indicated for patients with major RAS or those who experience large numbers of minor lesions that are non-responsive to topical therapies.

## Epidemiology

Approximately 20% of the general population is affected by RAS, but incidence varies from 5% to 50% depending on the ethnic and socioeconomic groups studied [2, 3]. The prevalence of RAS is influenced by the population studied, diagnostic criteria, and environmental factors [1]. In children, prevalence of RAS may be as high as 39% and is influenced by the presence of RAS in one or both parents [4]. Children with RAS-positive parents have a 90% chance of developing RAS compared with 20% of those with RAS-negative parents [2]. In children of high socioeconomic status, RAS is five times more prevalent and represents 50% of oral mucosal lesions in this cohort [5, 6]. RAS prevalence was found to be higher (male, 48.3%; female, 57.2%) among professional school students than in the same subjects 12 years later when they had become practicing professionals. This finding led some investigators to theorize that stress during student life is a major factor in RAS, although the differences due to age changes should also be considered. The onset of RAS appears to peak between the ages of 10 and 19 years and becomes less frequent with advancing age, geographic location or gender[7]. If RAS begins or significantly increases in severity after the third decade and well into adult life (see Table 1), it should increase suspicion that the etiology of the condition maybe attributed to an underlying medical disorder such as hematologic, immunologic, connective tissue disease, or Behçet's syndrome.

## Predisposing etiologic factors

The etiology of RAS lesions is still unknown, but several local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors have been proposed as causative agents. Also, some medications including immunosuppressive drugs such caclineurin and mTOR inhibitors have been associated with severe aphthous-like stomatitis[8, 9] (Table 2).

### Local factors

Local trauma is regarded as a causative agent for RAS in susceptible individuals[10, 11]. Trauma predisposes to RAS by inducing edema and early cellular inflammation associated with an increased viscosity of the oral submucosal extracellular matrix[12]. Not all oral trauma leads to RAS, because denture wearers do not have a high prevalence of RAS in spite of the fact that this cohort is three times more susceptible to oral mucosal ulceration[13]. In addition, habitual smokers who constantly expose their oral mucosa to nicotine have demonstrated a negative association between smoking and RAS[14–16] Therefore, local trauma apparently

predisposes to RAS only in those individuals who have a hereditary predilection for the disease.

Some changes in salivary composition, such as pH, that affect the local properties of saliva and a stress-induced rise in salivary cortisol have been correlated with RAS [17, 18]. Although direct association of salivary gland dysfunction with RAS has not been demonstrated[19], patients with a combination of RAS and xerostomia may experience increased symptoms due to the increased oral dryness.

## Microbial factors

Despite the fact that RAS has not been etiologically associated with herpes simplex virus based on several well-designed studies, both laymen and clinicians often confuse RAS with herpes simplex virus (HSV) infection. HSV virons and antigens have neither been identified in aphthous lesions nor successfully isolated in RAS biopsy tissues [20, 21]. Although it has been suggested that reactivation of varicella zoster virus (VZV) or human cytomegalovirus (CMV) is associated with frequent recurrence of aphthous ulcers [22], evaluation of RAS biopsy tissue using polymerase chain reaction (PCR) for possible involvement of HV6, CMV, VZV, Epstein-Barr virus (EBV), as causative factors did not find evidence to support the role of these viruses in RAS pathogenesis[20, 23]. Thus, it is the clinician's responsibility to distinguish RAS from herpes infections, reassure RAS patients that they do not have an infectious disease and that antiviral therapy is neither necessary nor effective.

Helicobacter pylori (H pylori), a common risk factor for gastric and duodenal ulcers, has been proposed to have causative role in RAS. Despite the fact that stomach ulcers and RAS are linked to dysregulated immune functions, molecular studies that identified H pylori in both affected and non-affected mucosa of RAS patients found no association with RAS [24, 25]. Interestingly, another study [26] reported that eradication of H pylori in RAS patients positively correlated with increased Vitamin B12 levels and decreased number of aphthous lesions [26–29]. There has been considerable speculation regarding the possible involvement of Streptococci species in the etiology of RAS, especially S sanguis 2A. The proposed hypothesis is that oral streptococci act as antigenic stimulants that cross-react with mitochondrial heat shock proteins of oral keratinocytes. This reaction purportedly induces a T-cell-mediated immune response that causes oral mucosal damage [30], but this theory remains unproven. EBV and lactobacillus are other organisms that have been studied in RAS patients. A study of the possible role of lactobacillus in RAS has yielded no significant finding; but in a small study sample, EBV was associated with epithelial cells of pre-ulcerative RAS [31, 32]. Using PCR techniques, 39% of pre-ulcerative RAS lesions were positive for EB-DNA. Their peripheral blood lymphocytes and serum were also positive for EB-DNA. The report theorized that lymphocytes may serve as a reservoir for latent EBV infection and promote viral shedding into the plasma. However, a causal relationship between EB viral load and RAS was not evaluated.

## Underlying medical disease

The most prominent medical disorder associated with RAS is Behçet's syndrome, characterized by recurring oral and genital ulcers, and eye lesions (Table 2). Behçet's syndrome is a multisystem disorder resulting from vasculitis of small and medium-sized vessels and inflammation of epithelium. The abnormal inflammatory response in Behçet's syndrome is caused by immune complexes induced by T lymphocytes and plasma cells. Although Behçet's syndrome usually affects adults, a number of cases have been reported in children [33–35]. Since distinguishing RAS from Behçet's disease now depends on clinical criteria, investigators have sought an effective laboratory test. A high titer of anti-Saccharomyces cerevisiae antibodies (ASCA) has been detected in Behçet patients

compared with RAS patients and apparently healthy individuals [36]. The report suggested that ASCA test might be a method to distinguish between these two patient populations. This distinction may not be as simple as reported, because up to 70% of patients with Crohn's disease and 15% of patients with ulcerative colitis are ASCA positive and both diseases are associated with recurring oral ulcers. The use of human leukocyte antigen (HLA) system to distinguish RAS from Behçet's disease showed significant differences in frequency of certain HLA antigens, but the distinction between the two disorders is still not clearly defined [37].

Another variant of Behçet's syndrome that includes relapsing polychondritis, a disorder characterized by mouth and genital ulcers with inflamed cartilage, has been labeled MAGIC syndrome (Table 2) [38, 39].

Inflammatory bowel diseases such as Crohn's disease and ulcerative colitis have been associated with oral ulcers that may resemble RAS, but Crohn's lesions often have indurated borders and are histologically different because of the granulomatous nature of the lesion (Fig 3). Approximately 10% of patients with Crohn's disease have oral mucosal ulcers, and the oral manifestations occasionally precede intestinal symptoms. Some researchers believe that inflammation of minor salivary glands is a possible cause of the oral ulcers [40].

Celiac disease, an autoimmune sensitivity to gluten is another medical disorder often associated with RAS, but the causal relationship between these two disorders is not completely clear. Prevalence of RAS in celiac disease patients has been reported to range from 4% to 40%, but oral ulceration in celiac disease patients also vary from 3% to 61% [41]. In addition, oral ulcerations in celiac disease do not have the distinctive features of RAS and often resolve when celiac disease patients are placed on gluten-free diet. Therefore, oral ulceration in celiac disease patients may not be the typical RAS[42].

In HIV-positive individuals, RAS occurs more frequently, lasts longer, and causes more painful symptoms than in healthy individuals (Fig 4). It is also a common finding in HIV-positive children [43, 44]. RAS is usually a late finding in AIDS patients with CD4+ lymphocyte counts below 100 cells/$mm^3$, and it may occasionally be a presenting sign of HIV infection[4].

Cyclic neutropenia, a rare disorder that presents at childhood, is also associated with recurring oral ulcers during periods when the neutrophil count is severely depressed [45]. Another condition described as periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) or Marshall's syndrome has a presentation similar to that of cyclic neutropenia and is commonly associated with oral ulcers that cannot be distinguished from RAS [46].

## Hereditary and genetic factors

The role of heredity is the best-defined underlying cause of RAS. Susceptibility to RAS is significantly increased by its presence in one or both parents. Studies of identical twins have also demonstrated the hereditary nature of this disorder [4]. Individuals with a positive family history of RAS, tend to develop RAS at an early age. Specifically, children with two RAS-positive parents have a 90% chance of developing RAS that present with more severe symptoms and recur more frequently[2].

Certain genetically specific HLAs have been identified in RAS patients: HLA-A2, HLA-B5, HLA-B12, HLA-B44, HLA-B51, HLA-B52, HLA-DR2, HLA-DR7, and HLA-DQ series[47]. A confounding finding is that certain ethnic groups have been associated with different HLA

alleles or haplotypes with no HLA consistently associated with RAS[47]. Therefore, additional studies are needed to clarify the variability of RAS in host susceptibility.

## Allergic factors

Allergy has been suspected as a cause of RAS. Hypersensitivity to certain food substances, oral microbes such as Streptococcus sanguis, and microbial heat shock protein have been suggested as possible causative factors, but there is still no conclusive evidence to support allergy as a major cause of RAS[48, 49]. Although some studies reported that RAS patients tend to have hypersensitivity to environmental allergens, other reports did not find significant correlation between hypersensitivity and RAS. In one report, patients wearing nickel-based orthodontic appliances developed RAS that coincided with fitting of the appliance. When the appliance was replaced with a nickel-free type, the mucosal lesion regressed. RAS in this population was attributed to the systemic effect of ingested nickel rather than direct contact, because a patch test to nickel sulfate did not reactivate the mucosal ulceration[50]. In patients presenting with refractory cases of RAS and known allergy to food items such as milk, cheese, and wheat, sequential elimination of these dietary items was found beneficial in a small subset of RAS patients, thereby suggesting a possible link between food allergy and some cases of RAS [51].

The denaturing effect of sodium lauryl sulfate (SLS) commonly found in toothpastes has also been discussed as a cause of RAS. It was proposed that SLS might erode the oral mucin layer, exposing the underlying epithelium, thereby making the individual more susceptible to RAS. This theory still needs further clarification, because it has also been demonstrated that use of SLS-free toothpastes did not affect development of new lesions in RAS patients [52, 53].

## Immunologic factors

There has been significant research on the cause of RAS focusing on detecting an abnormality in the immunologic response. Early work suggested a relationship between several immune-mediated reactions and development of RAS. These include cytotoxicity of T lymphocytes to oral epithelium, antibody-dependent cell-mediated cytotoxicity, and defects in lymphocyte subpopulations [49, 54, 55]. One theory is that multiple immune reactions cause damage induced by deposition of immune complexes within the oral epithelium. In some patients, an elevated level of sIgA has been reported during acute and remission phases of minor RAS[56]. Some other studies have shown an association between RAS severity and abnormal proportions of CD4+ and CD8+ cells, alteration of the CD4+: CD8+ ratio [57, 58], and increased levels of several cytokines including interleukin 2 (IL-2), interferon gamma (INF-$\gamma$), and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) mRNA in RAS lesions[59, 60]. Immunohistochemical studies of RAS biopsy tissues demonstrated numerous inflammatory cells with variable ratios of CD4+: CD8+ T lymphocytes depending on the ulcer duration. CD4+ cells were more numerous during the pre-ulcerative and healing stages, whereas CD8+ cells tended to be more numerous during the ulcerative state of the ulcer. Interestingly, studies on non-affected sites were negative, making researchers focus more on the theory that RAS may be caused by an antigen-triggering effect. Since levels of serum immunoglobulins and natural killer cells are essentially within normal limits in RAS patients, the focus is still on a dysregulated local cell-mediated immune response conducive to accumulation of subsets of T-cells, mostly CD8+ cells. This local immune response is thought to cause tissue breakdown that eventually manifests as RAS.

## Nutritional factors

The role of nutritional deficiency as a cause of RAS has been highlighted by the association of a subset of 5% to 10% of RAS patients with low serum levels of iron, folate, zinc, or

vitamins B1, B2, B6 and B12. This is an indication that nutritional deficiency is apparently an etiological factor for RAS [61, 62]. Some of these nutritional deficiencies may be secondary to other diseases such as malabsorption syndrome or gluten sensitivity associated with or without enteropathy. Hematologic screening of RAS patients for anemia or deficiency of iron, folate, and B vitamins is appropriate for patients with major RAS or cases of minor RAS that worsen during adult life. A deficiency of calcium and vitamin C has also been proposed in patients with RAS, but these findings were in association with vitamin B1 deficiency, supporting the idea of combined nutritional deficiency in RAS patients [63]. The recovery of some RAS patients after treatment of the nutritional deficiency has further corroborated the causative role of nutritional deficiency in a subset of RAS patients [64, 65].

### Psychological stress

Stress and psychological imbalance have been associated with RAS[6, 10, 66]. Stressful life events can increase the chances that a RAS susceptible patient will develop a new lesion. One study reported that mental stress is strongly associated with episodes of RAS more than physical stress; and these stressful events tend to correlate more with onset of RAS rather than duration of the lesions[10]. In women, appearance of RAS may coincide with menses; and stress of academic load may be the precipitating factor for the higher prevalence of RAS in professional school students[63]. A clinician should consider questioning patients with worsening episodes of RAS regarding psychosocial, physical or environmental stress.

### Other factors

The role of antioxidants in RAS is still attracting attention because blood and salivary levels of antioxidants such as erythrocyte superoxide dismutase and catalase seem to be higher in patients with RAS and Behçet's syndrome than in normal controls [67–69], but their causative roles in RAS are yet to be clearly defined. There have also been several reported cases of drug-induced RAS. A case-control study associated a higher risk of RAS with drug exposure and found significant association with nonsteroidal anti-inflammatory drugs and beta-blockers[70]. Nicorandil, a vasodilator used extensively outside the United States to manage angina as well as caclineurin and mTOR inhibitors used as immunosuppressors have been associated with severe aphthous-like ulcers [8, 9, 71]. Therefore, it is imperative to closely scrutinize the medication history as well as current medications of RAS patients to identify any pattern associated with frequency and duration of RAS lesions.

## Clinical manifestation and pathogenesis

RAS patients usually experience prodromal burning sensations that last from 2 to 48 hours before an ulcer appears. Ulcers are round with well-defined erythematous margins and a shallow ulcerated center covered with yellowish-gray fibrinous pseudomembrane. RAS ulcers usually develop on non-keratinized oral mucosa, with the buccal and labial mucosa being the most common sites, and last approximately 10 to 14 days without scar formation (see Table 1). The oral ulcers seen in Behçet's disease are clinically similar, but they are more likely to be major aphthae [72]. Microscopic characteristics of RAS are non-specific. The pre-ulcerative lesion demonstrates subepithelial inflammatory mononuclear cells with abundant mast cells, connective tissue edema and lining of the margins with neutrophils[73]. Damage to the epithelium usually begins in the basal layer and progresses through the superficial layers, leading eventually to ulceration and surface exudate. The presence of extravasated erythrocytes around the ulcer margin, subepithelial extravascular neutrophils, numerous macrophages loaded with phagolysosomes, and the non-specific binding of stratum spinosum cells to immunoglobulins and complements may be a result of vascular leakage and passive diffusion of serum proteins. These findings suggest that pathogenesis of RAS may be mediated by immune complex vasculitis [74]. The onset of a RAS lesion is

associated with cell-mediated immune response, generation of T cells and production of TNF-α. Peripheral blood mononuclear cells of RAS patients has been shown to secrete high amounts of TNF-α, an indication that TNF-α plays a key role in RAS pathogenesis [54, 74–76]. Consequently, TNF-α-mediated endothelial cell adhesion and neutrophil chemotaxis initiate the cascade of inflammatory processes that lead to ulceration[77]. Majority of the TNF-α is produced in response to activation of toll-like receptors (TLRs), a set of functional membrane receptors associated with immune response and protection of epithelial barrier. TLRs have both pro- and anti-inflammatory properties. While pro-inflammatory TLRs were found to be greatly increased in the epithelium and lamina propria of RAS lesions in some patients[78], a decrease in expression levels of TLRs with anti-inflammatory activities was also found in another cohort of RAS patients[79]. Therefore, the role of TLRs in RAS pathogenesis still needs to be better defined, but it is possible that an imbalance in pro- and anti-inflammatory activities of TLRs could increase susceptibility to RAS in some individuals.

## Management

The proper treatment of RAS depends on the severity of symptoms, frequency, size, and number of the ulcers. Patients who experience occasional episodes of minor aphthous ulcers experience significant relief with appropriate topical therapy. Symptoms resulting from occasional small lesions are often adequately controlled with use of a protective emollient such as Zilactin (Zila Pharmaceuticals, Phoenix, Arizona) or Orabase (Bristol Myers Squib, Princeton, New Jersey), used either alone or mixed with a topical anesthetic such as benzocaine. Other topical agents that can minimize patient discomfort include diclofenac, a nonsteroidal anti-inflammatory drug, or amlexanox paste, which has been shown to decrease the healing time of minor aphthae[80, 81]. Patients can also get some pain relief by swishing 3 to 4 times a day with Magic Mouth Wash (MMW), which can be custom-mixed by the pharmacy. Several formulations of MMW are available, but the most common is a mixture of equal parts of viscous lidocaine, diphenhydramine and Maalox or similar antacid.

In patients with more frequent or more severe disease, use of a topical glucocorticoid is an effective therapy to decrease both the size and healing time of the ulcers, especially when the medication is used early in the developing stage of the lesion.[82, 83] Patients should be counseled regarding the proper use of high-potency topical steroids and instructed to apply medication sparingly on the mucosal areas involved. This precaution will significantly decrease the risk of developing local and systemic side effects. Some clinicians advocate mixing high-potency steroids with an adhesive such as Orabase to promote contact between the lesion and medication. When patients have large, slowly healing lesions of major RAS, topical steroids may not be effective, so the use of intralesional steroid injections may help decrease the healing time.

Topical antibiotics have been advocated as therapy for RAS [84]. Tetracycline mouth rinses have been reported to decrease both the healing time and the pain of the lesions in several trials, but the association of these rinses with oral candidiasis and reports of allergic reactions have limited the use of this form of therapy. The effectiveness of topical tetracycline may result from a combination of the anti-bacterial and the anti-inflammatory effects of this group of antibiotics. A placebo-controlled study of the topical use of penicillin G troches to treat minor RAS showed efficacy in reducing both pain and healing time of RAS [85]. The risk of allergic reactions from this potentially useful form of therapy has not been reported, even in studies involving large numbers of RAS patients.

Topical therapy is effective treatment for most patients with RAS; however, topical therapy alone does not decrease the formation of new lesions and may not be adequate treatment for

patients with major RAS or patients who experience frequent episodes of multiple minor RAS. Systemic therapy should be considered for this relatively small group of patients, but the potential benefit of the drug should always be carefully weighed against potential side effects, and systemic therapies should be used only by clinicians trained in their use.

A short course of systemic corticosteroids such as prednisone may occasionally be used to treat a particularly severe episode of major RAS, but long-term use of systemic steroids is rarely indicated for RAS because the serious side effects of long-term steroid therapy outweigh the benefits for RAS patients[86].

Clinicians who treat patients with major RAS have been searching for a substitute for systemic corticosteroids that will prevent formation of new RAS lesions and lower incidence of serious side effects. Medications that have been reported to have potential effectiveness in reducing the formation of new RAS lesions include pentoxifylline (PTX), colchicine, dapsone and thalidomide[87].

PTX, a methylxanthine related to caffeine, has been used for many years to treat intermittent leg cramps in patients with peripheral vascular disease. PTX improves the circulation of blood to the extremities by increasing the flexibility of red blood cells, making it easier for them to physically pass through atherosclerotic vessels. PTX has also been shown to decrease inflammation by its effect on white blood cell function and inflammatory cytokines, making it a useful therapy for inflammatory diseases such as rheumatoid arthritis, vasculitis, and diabetic leg ulcers. There have been several clinical reports of the successful use of PTX, 400 mg three times/day, to manage RAS. Patient with major RAS treated with PTX tend to have fewer and smaller ulcers and significant pain reduction without major side effects (Fig 5)[87, 88].

Another drug that has been advocated for management of major RAS is colchicine, which has been used for decades to manage gouty arthritis. Because colchicine has anti-inflammatory activity and inhibits the cell-mediated response, it has proven useful in the management of a number of dermatologic diseases including psoriasis, Behçet's syndrome, dermatitis herpetiformis, and leukocytoclastic vasculitis.[89] There are still no controlled clinical trials of colchicine therapy for RAS, but open trials have shown encouraging results [87, 90]. Low doses of colchicine 0.6 – 1.2 mg/day have been shown to reduce number and duration of aphthous lesions, therefore long term therapy with 1.2 –1.8 mg/day is often recommended[91]. Colchicine has a low therapeutic-toxicity window because of myelosuppression, hepatoxicity, decreased sperm count and adverse drug interactions[8]. Before starting colchicine therapy, baseline liver function tests and hematology screening of RAS patients should be performed and monitored frequently. Also, careful medication history should be obtained to avoid adverse drug interactions. Colchicine has been associated with teratogenicity in animal studies but limited adverse fetal and maternal effects reported in human studies were not significantly higher than normal[9]. However, some clinicians still recommend that RAS patients use appropriate contraceptive methods before colchicine therapy[91]

The medication that has been most carefully studied for the management of major RAS is thalidomide, a drug with a long history of major side effects, including severe life threatening and crippling birth defects[92]. Thalidomide was originally marketed in Europe in the 1950s as a non-addicting sedative but was withdrawn from the market when the risk of major teratogenic defects, including phocomelia and neural tube abnormalities, were discovered. Later, investigators discovered its potent anti-inflammatory and immunomodulatory properties, by its ability to inhibit angiogenesis and reduce the activity

of TNF-α. Due to its effectiveness, limited use of the drug was permitted for patients with recalcitrant diseases such as erythema nodosum leprosum, lupus and Behçet's syndrome[93].

Controlled clinical trials have demonstrated the effectiveness of thalidomide in treating major RAS in HIV-infected patients and in otherwise normal individuals. Thalidomide therapy results in either complete remission or substantial improvement in a majority of major RAS patients [94, 95]. To minimize the risk of birth defects resulting from thalidomide therapy, clinicians prescribing the drug must register in the program for Risk Evaluation and Mitigation Strategy (REMS) formerly known as the STEPS program[96]. This program educates physicians and dentists on the proper use of the drug, provides counseling for patients, and closely monitors thalidomide use. For example, the program mandates that women in childbearing years must use two forms of birth control and have a monthly pregnancy test. Both women and men taking thalidomide must be evaluated every four weeks and both the patient and the prescribing clinician must complete a questionnaire before thalidomide can be prescribed for another 28 days. In addition to birth defects, thalidomide can also cause peripheral neuropathy, neutropenia, and drowsiness[97].

Other drugs that have been advocated for the management of major RAS not responding adequately to topical therapy include dapsone, a sulfone derivative which is used to manage a number of mucocutaneous disorders; azathioprine, an immunosuppressive drug; and etanercept, a recombinant TNF-soluble receptor that binds to TNF-α to limit the amount of active TNF-α. Etanercept has been used successfully to manage rheumatoid arthritis and psoriasis[87, 98, 99]

## Summary

RAS is the most common ulcerative disease affecting the oral mucosa. Its etiology is still unknown, occurs mostly in healthy individuals and has a more severe clinical presentation in immunocompromised individuals. Several local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors as well as immunosuppressive drugs have been proposed as causative agents. Clinical management of RAS is aimed at improving patient function and quality of life using topical and systemic therapies. The goals of therapy are to decrease pain and ulcer size, promote healing, and decrease frequency of recurrence.

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**Key Points**

Recurrent aphthous stomatitis (RAS) is the most common ulcerative disease of the oral mucosa. Several etiological theories proposed are reviewed. Topical and systemic therapies that are used to manage RAS are also presented.

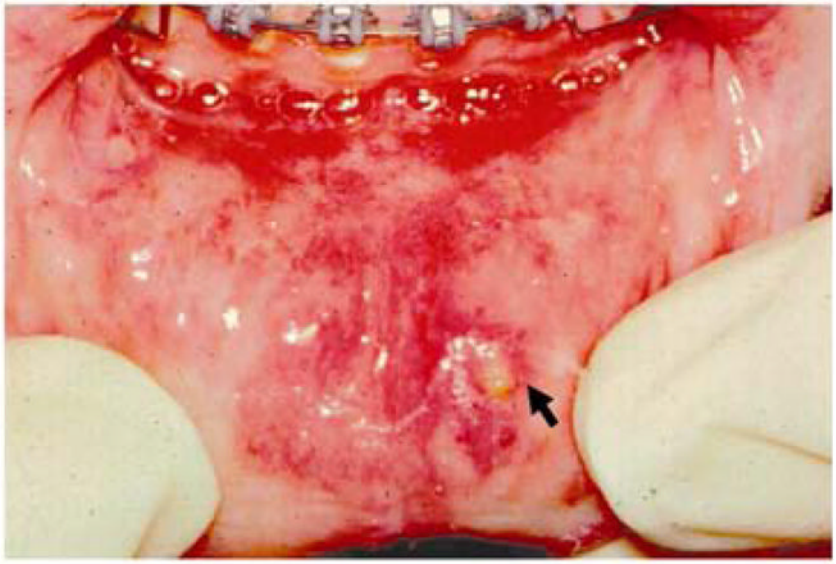

**Figure 1.**
Minor aphthous ulcer on the lower lip

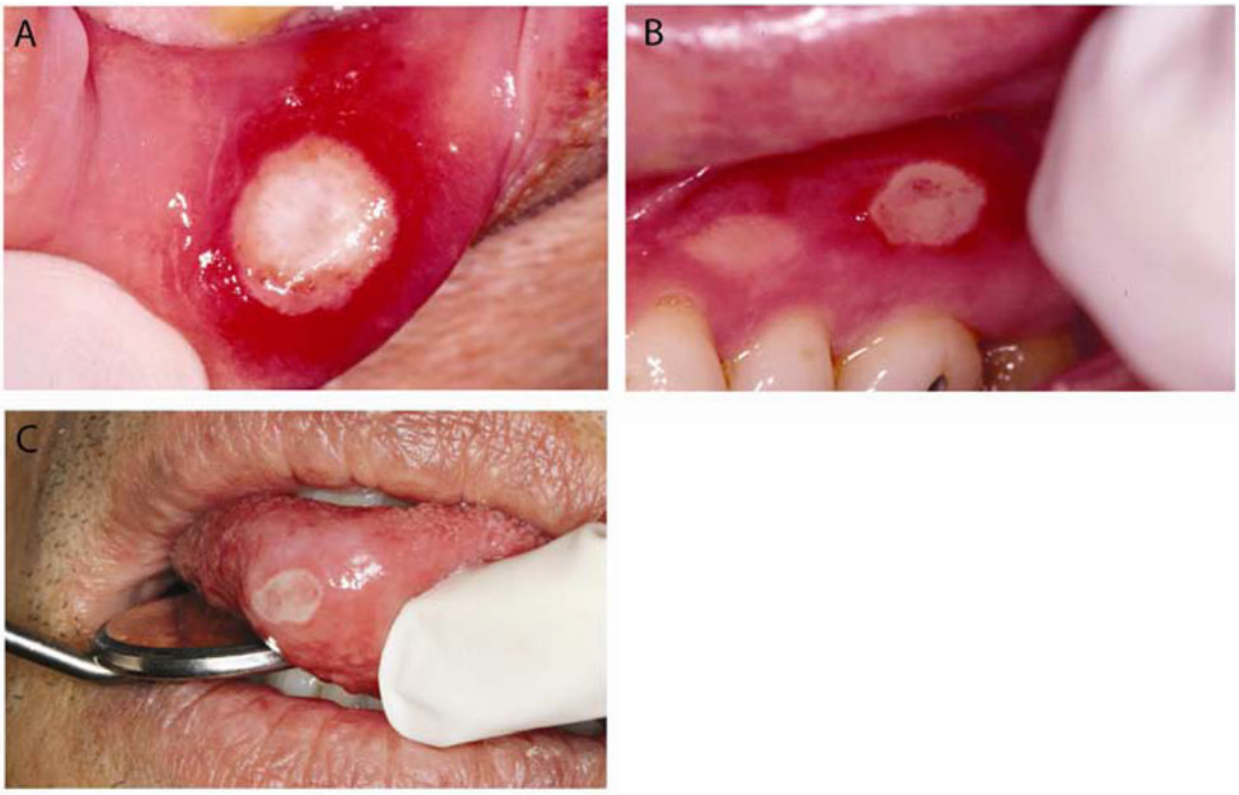


**Figure 2.**
Major aphthous ulcer on the lower lip (A), maxillary unattached gingiva (B) and anterior tongue (C). The ulcers display characteristic erythematous halo and central yellowish-gray pseudomembrane.

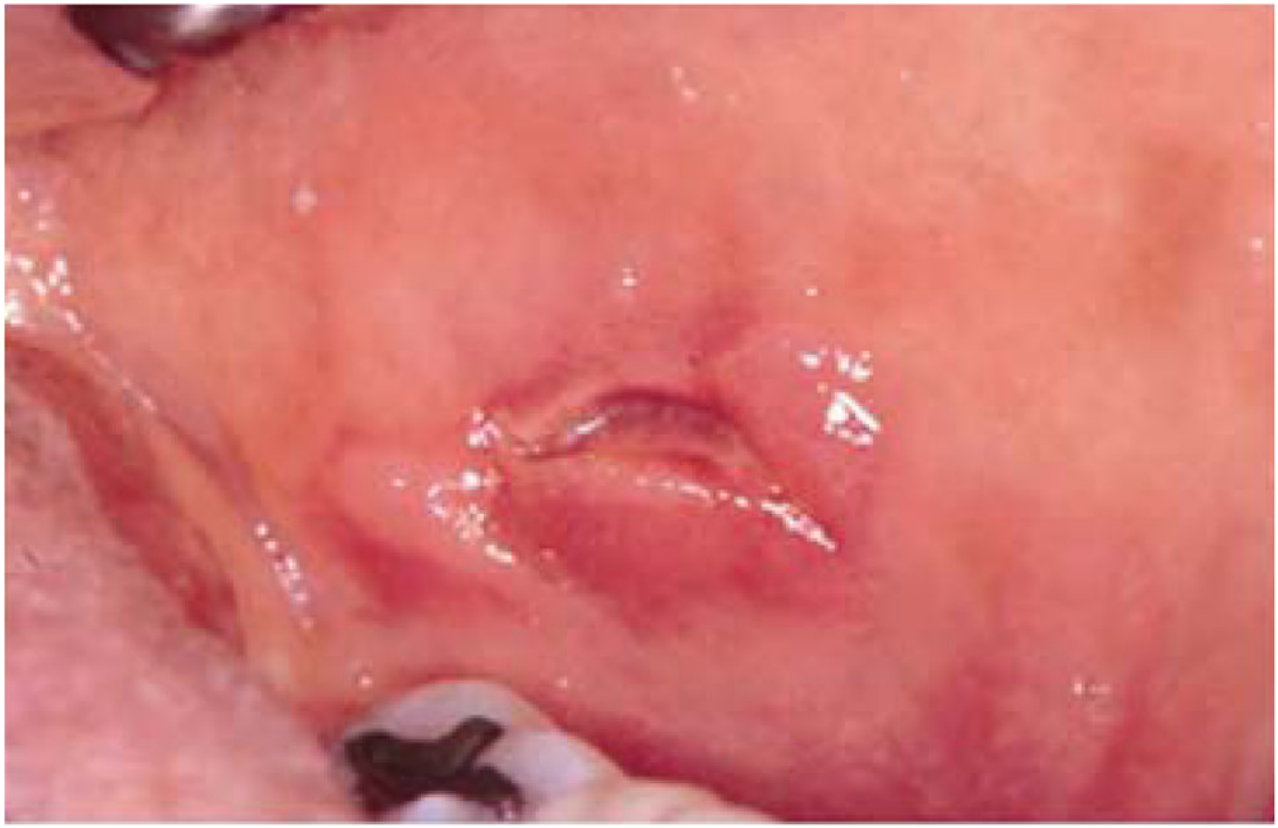

**Figure 3.**
Ulcer with indurated margin on the buccal mucosa of a patient with Crohn's disease.

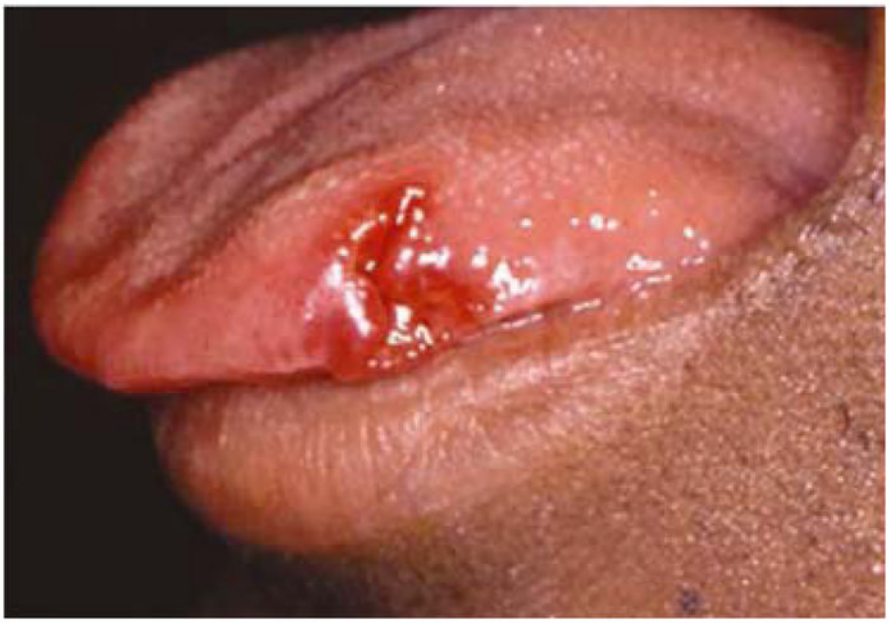

**Figure 4.**
Aphthous-like lesion in a patient with advanced HIV disease.

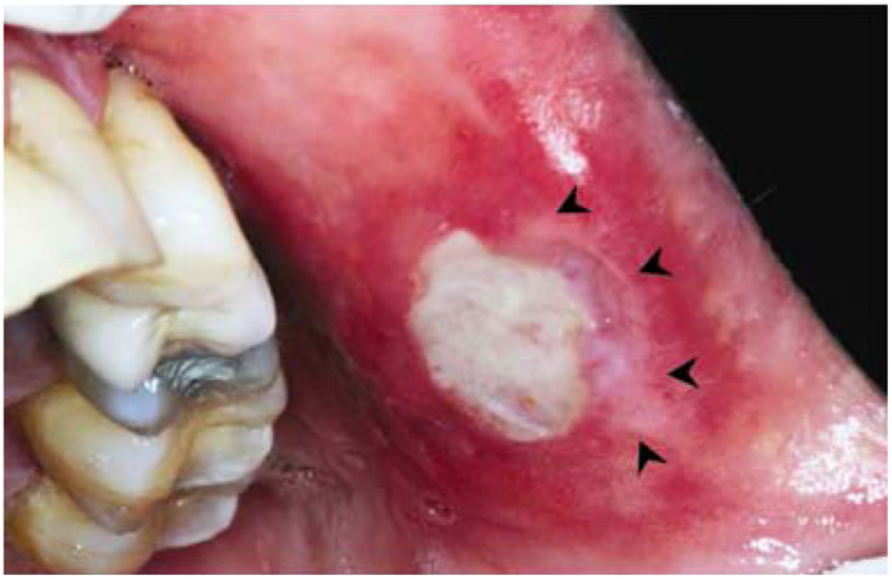

**Figure 5.**
Major RAS on left buccal mucosa responding to pentoxifylline therapy. Note the progressive healing and absence of pseudomembrane in a section of the ulcer (black arrowheads)

## Table 1

**Types of Recurrent Aphthous Stomatitis***

| | Minor | Major | Herpetiform |
|---|---|---|---|
| **Gender predilection:** | M=F | M=F | F > M (usually) |
| **Age of onset (years):** | 5–19 | 10–19 | 20–29 |
| **Number of ulcers:** | 1–5 | 1–10 | 10–100 |
| **Size of ulcers (mm):** | <10 | >10 | 1–2 (larger if coalesced) |
| **Duration (days);** | 4–14 | >30 | <30 |
| **Recurrence rate (months):** | 1–4 | <1 | <1 |
| **Site predilection:** | Lips, cheeks, tongue, floor of mouth | Lips, cheeks, tongue, palate, pharynx | Lips, cheeks, tongue, pharynx, palate, gingiva, floor of mouth |
| **Permanent scarring:** | Unusual | Common | Unusual |

* Adapted from: Porter SR, Scully C, Pedersen A. Recurrent aphthous stomatitis. *Crit Rev Oral Biol Med.* 1998;9(3):306–321.

## Table 2

| Etiological Factors Associated with Recurrent Aphthous Stomatitis* | |
|---|---|
| **Local:** | Trauma |
| | Smoking |
| | Dysregulated saliva composition |
| **Microbial:** | Bacterial: Streptococci |
| | Viral: Varicella zoster, Cytomegalovirus |
| **Systemic:** | Behçet's disease |
| | Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome |
| | Crohn's disease |
| | Ulcerative colitis |
| | HIV infection |
| | Periodic fever, aphthosis, pharyngitis, and adenitis (PFAPA) or Marshall's syndrome |
| | Cyclic neutropenia |
| | Stress; psychological imbalance, menstrual cycle |
| **Nutritional:** | Gluten sensitive enteropathy |
| | Iron, folic acid, zinc deficiencies |
| | Vitamin B1, B2, B6 and B12 deficiencies |
| **Genetic:** | Ethnicity |
| | HLA haplotypes |
| **Allergic/Immunologic:** | Local T-lymphocyte cytotoxicity |
| | Abnormal CD4:CD8 ratio |
| | Dysregulated cytokine levels |
| | Microbe-induced hypersensitivity |
| | Sodium lauryl sulfate (SLS) sensitivity |
| | Food sensitivity |
| **Others:** | Antioxidants |
| | Non-steroidal anti-inflammatory drugs (NSAIDS) |
| | Beta blockers |
| | Immunosuppressive drugs |

*Adapted from: Ship, II. Socioeconomic status and recurrent aphthous ulcers. *J Am Dent Assoc.* Jul 1966;73(1):120–123.