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# Review Article

# Recurrent Apthous Stomatitis- A Review

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***ABSTRACT:***
Recurrent apthous stomatitis (RAS), the most common ailment affecting the oral cavity, is characterized by recurrent disruption of the oral mucosa in the form of painful ulcers. It is a diagnosis of exclusion, and other causes of ulcerative stomatitis should be explored before a diagnosis of RAS is made. The present article highlights the classification, clinical feature, differential diagnosis and management of RAS.
Key words: Apthous ulcer, oral mucosa, RAS.

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## Introduction

The term aphthae is derived from the Greek word aphthi, which means "to set on fire" or "to inflame," and is thought to have been first used by the philosopher hippocrates to describe the pain associated with a common disorder of the mouth during his time (likely, aphthous stomatitis).[1] Local trauma, genetic factors, nutritional deficiencies, viral and bacterial infections, and immune or endocrine disturbances have all been implicated as etiological factors of frequent oral ulcerations. In a subset of patients, no etiology can be identified and a diagnosis of exclusion must be made; such cases are referred to as recurrent aphthous stomatitis. Three forms of RAS exist: minor (>70% of cases), major (10%), and herpetiform (10%). These subtypes differ in morphology, distribution, severity, and prognosis.[2]

## Recurrent aphthous stomatitis

RAS the most common ailment affecting the oral cavity, is characterized by recurrent disruption of the oral mucosa in the form of painful ulcers. It is a diagnosis of exclusion, and other causes of ulcerative stomatitis should be explored before a diagnosis of RAS is made. RAS accounts for 25 percent of recurrent ulcers in adults and 40 percent in children. The severity of the stomatitis is represented by one of three subtypes.[3]

## Minor RAS

Minor RAS is the most prevalent form and typically occurs in patients who are 5 to 19 years old. outbreaks are characterized by a few, superficial, round ulcerations that are <10mm and accompanied by a gray pseudomembrane and erythematous halo. Minor aphthae are usually confined to the lips, tongue, and buccal mucosa.[4]

## Major RAS

Major ras has a wider distribution (commonly extending to the gingiva and pharyngeal mucosa), is larger in size, (>10mm), and has a longer duration of outbreak. Minor aphthae typically resolve within 14 days of presentation, whereas major aphthae may persist for over six weeks. Further, major aphthae pose a significant scarring risk as well.[5] Herpetiform RAS. Herpetiform ras presents with dozens of small, deep ulcers that often coalesce and therefore present as large ulcers with an irregular contour. Outbreaks are non scarring and typically resolve within one month. Regardless of the subtype, lesions can impair one's

ability to effectively speak, swallow, and maintain dental hygiene.[6]

**Behcet's disease**

Behcet's disease, a vasculitis with a complex etiology, is associated with significant oral and genital ulcerations. In 80 percent of cases, mucosal aphthosis is the presenting sign. Ocular involvement in the form of anterior or posterior uveitis, skin lesions such as erythema nodosum, and less commonly, central nervous system deficits may be observed. Vascular lesions in small and large vessels often occur and can manifest as coronary arteritis, arterial or venous thrombosis.[7] A positive pathergy test can be useful, but is not necessary in establishing a diagnosis of Behcet's disease. Patients may present with mucosal aphthosis and hemoptysis as their only complaints.[8]

**Differential diagnosis of oral ulcerations**

Before making a diagnosis of RAS, potentially overlooked causes for oral ulcers must be considered. Several conditions can present with mucosal aphthous ulcers, necessitating a thorough workup to narrow the differential. Physical examination should be used to screen for trauma secondary to dental appliances, widespread vesiculobullous eruptions, and signs of hormone imbalance. The presence of a fever should prompt workup for infection, and if the fever is recurrent, fever syndromes. Blood work should be used to rule out hematologic or nutritional deficiencies and antibodies related to autoimmunity.[9] The differential diagnosis for oral ulcerations includes several entities, including recurrent aphthous stomatitis, drug induced mucocutaneous syndromes, autoimmune disorders, hematologic disorders, nutritional deficiencies, fever syndromes, vesiculobullous diseases, and infection. A diagnosis cannot be made unless other causes for aphthous stomatitis have been considered and dismissed.[10]

**Periodic fever syndromes and other autoinflammatory diseases**

Mucosal aphthosis is often a feature of a systemic syndrome that includes recurrent fever with no known source of infection; such syndromes are referred to as autoinflammatory diseases. PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome, cyclic neutropenia, and hyperimmunoglobulin D are some autoinflammatory diseases to consider in the differential of recurrent aphthous stomatitis when unremitting or cyclical fevers are also present.[11]

PFAPA syndrome, also known as Marshall syndrome, is a hereditary autoinflammatory disease characterized by three- to six-day episodes of fevers every four to eight weeks. Episodes of fever are accompanied by aphthous stomatitis, cervical adenitis, pharyngitis, abdominal pain, and joint pain. It is the most common fever syndrome in children, yet the exact genetic marker responsible has not been determined. Patients are completely asymptomatic between episodes and attacks typically respond rapidly to a single dose of corticosteroids. Although corticosteroids decrease severity of attacks, they do not prevent future attacks.[12] In some cases, the administration of steroids actually increased the frequency of attacks. It has been suggested that levels of interleukin 1, specifically il- 1β, are elevated in PfaPa, and treatment with a recombinant il-1 receptor antagonist has yielded promising patient responses. Colchicine administration, by decreasing neutrophil migration and adhesion, has also shown promise in decreasing the number of PFAPA attacks, although additional studies with more subjects are needed. In certain refractory cases, adenotonsillectomy is a possible solution. When recurrent aphthous ulcers occur with a periodicity of approximately every three weeks, the dermatologist should be alerted to the possibility of cyclic neutropenia.[13]

Cyclic neutropenia is inherited in an autosomal dominant pattern, so there is usually a family history present and episodes of neutropenia are present at or soon after birth. Mutations in the ElanE gene, which codes for neutrophil elastase, are responsible for causing cyclic neutropenia. Episodes occur every 21 days and last between three to five days. Patients present with painful oral and colonic ulcers, pharyngitis, recurrent fever, and abdominal pain.[14]

**Pathogenesis of recurrent aphthous stomatitis**

Several theories describing the etiopathogenesis of RAS have been described in the literature. The pathogenesis of ras is multifaceted with significant physiological interplay between the immune system, genetics, and environmental factors. Similar to other chronic inflammatory conditions, deoxyribonucleic acid (DNA) damage secondary to oxidative stress is thought to play a large role in recurrent ulcerations. In a recent case-control study, total oxidative status (tos), total antioxidant status (tas), and the tos: tas ratio (oxidative stress index, osi) were used as parameters to assess oxidative damage in RAS patients against unaffected controls. The results strongly suggested that RAS patients have a systemic imbalance in the oxidant-to-antioxidant ratio favoring oxidative damage. The cause for this imbalance is likely multifactorial.[15]

Evidence also suggests an immunological basis for the chronic inflammation in RAS patients. it is currently thought that an unknown antigen stimulates keratinocytes, resulting in cytokine secretion and leukocyte chemotaxis. Tnf-α has been found to be significantly increased in the saliva of RAS patients. A recent study explored the significance of single nucleotide polymorphisms (snP) in the genes for proinflammatory cytokines il-1 and il-6 in ras.34 the average frequency of il-6 C-174C haplotype, which is associated with an increase in il-6 secretion, was detected in higher amounts in affected patients than in controls. This suggests a genetic component to the immunopathogenesis of RAS. Further implicating a genetic component, there is evidence in the literature that RAS may be associated with a specific HLA haplotype. HLA

haplotype a*038B*07DrB1*13 is the most commonly associated with minor, major, and herpetiform RAS.[16]

**Local pharmacological treatment**

Treatment should always start with topical medication. The first line treatment options comprise antiseptics and antiinflammatory drugs/analgesics such as 0.2% chlorhexidine in rinses or gel, three times a day (without swallowing), for as long as the lesions persist. Triclosan can also be used in gel or rinse format three times a day (without swallowing), for as long as the lesions persist, and affords antiinflammatory, antiseptic and analgesic effects. In turn, topical 3% diclofenac with 2.5% hyaluronic acid can be applied to lessen the pain. There have also been reports of the use of oral rinses with benzidamine hydrochloride, which offers temporary pain relief.[17]

Amlexanox is a widely studied drug that offers short-term efficacy, particularly when used in the prodromic (early symptoms) phase. Its mechanism of action is not known, though it is a topical agent with established anti-inflammatory and antiallergic properties. It is usually supplied in the form of an ointment at a concentration of 5%, and is applied 2-4 times a day. The drug has been shown to be effective in accelerating the healing of aphthae and in lessening the pain, erythema and size of the lesions.[18]

Topical antibiotics such as tetracyclines and their derivatives (doxycycline and minocycline), in gel or rinse format, have also been found to lessen the pain and outbreaks of RAS. These drugs act through the local inhibition of collagenases and metalloproteinases (MPs) that form part of the inflammatory response and contribute to tissue destruction and ulcer formation, and moreover exert immune modulating effects.[19] Of the commercially available tetracyclines, doxycycline has shown the best inhibition of MPs. The administration of fixed-dose doxycycline in mucoadhesive gel format has been shown to be effective in treating RAS. Other authors recommend its application at a dose of 100 mg in 10 ml of water, performing rinses for 2-3 minutes (without swallowing), four times a day during three days. The topical use of tetracyclines and retinoic acid also exerts an antiinflammatory effect, in addition to the known antibiotic action.[20]

Other topical treatments that have been used in RAS are 0.2% hyaluronic acid in gel formulation, applied twice a day during two weeks (19); topical anesthetics such as 2% lidocaine (as a spray or gel); adhesive toothpaste containing polydocanol; or benzocaine tablets. In turn, the Nd:YAG laser has been found to afford immediate pain relief and faster healing, and is well tolerated by patients with RAS, since it is a brief form of treatment, results in lesser pain after application, and has few side effects (20). Other treatments include natural substances such as myrtle (*Myrtus communis*), a bush from northern Iran that possesses blood glucose-lowering, antibacterial, analgesic and antioxidant properties, thus suggesting potential usefulness in application to diseases characterized by inflammation and allergy.[21]

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