

# Challenges in Diagnosis and Treatment of Recurrent Aphthous Stomatitis

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## Abstract

*Modern medicine and advanced research nowadays allow clinicians to correctly diagnose and treat recurrent aphthous stomatitis, which can impact affected individuals functionally, psychosocially and economically. This review has been designed to investigate the diagnosis and treatment options of RAS based on the etiopathogenesis of the aphthous ulcers. The success of treatment depends on the timely and correct diagnosis of the lesions. Although pin-pointing a precise etiological factor is difficult, various plausible of them are discussed in this review. Treatment modalities allow efficient and effective palliative care, along with rapid healing of affected mucosa. Further research should be made to isolate the aetiology of RAS for every case and the efficiency of conventional and unconventional treatment options, and possible side effects of such.*

**Keywords:** recurrent aphthous ulcers, oral mucosa, stomatitis, management

## Background

Recurrent aphthous stomatitis (RAS) is an inflammatory disease characterized by recurrent single or multiple, round or ovoid, painful ulcers with yellow or grey floors. Surrounded by sharply circumscribed erythematous haloes with grey fibrinous exudate. (1)

RAS is the most common recurring idiopathic intra-oral ulcerative disease which typically presents first in childhood and sometimes in adolescence. (2) Oral ulcers can hinder the quality of life of affected individuals in functional, psychosocial and economic dimensions. White people are three times more frequently affected than black people, children of higher socioeconomic status are also at a higher risk.

There are three clinical presentations of RAS: minor RAS, major RAS, and herpetiform ulceration. Minor RAS is the most common form (up to 85% of all RAS lesions) and involve the non-keratinized mucosa of the oral cavity (the labial and buccal mucosa, the floor of the mouth and the ventral or lateral surface of the tongue – concentrated mostly anteriorly). The ulcers are superficial, usually <1 cm in diameter, their size is approximately 4-5 mm in diameter. Minor aphthae do not result in scarring despite years of recurrent ulceration of oral mucosa and can heal within 10 to 14 days. Major RAS are less common condition than the minor RAS lesions (10 to 15% of all RAS). These lesions are similar in clinical features to minor RAS, but they are larger than 10 mm in diameter, deeper, often scarred after healing, and can prolonged for several weeks. These lesions affect more often lips, tongue, soft palate, and the palatal fauces and can cause significant pain and dysphagia. Herpetiform ulceration is not so common condition and is only 5 to 10% of all RAS cases. A resemblance with herpes simplex virus (HSV type 1) infection can be detected. Herpetiform ulcers presents as a small (1 to 2 mm) and multiple ulcers (5-100) and more common in females. (3-6) The affected sites are the lateral margins and ventral surface of the tongue and the floor of the mouth although any non-keratinized oral mucosa may be involved. Ulcers are grey in colour and without a erythematous surrounding border, which make them difficult to visualize. (7,8) These ulcers are small in size and are very painful and make speaking and eating difficult. Herpetiform ulceration may last for 7 to 14 days, and the period of remission between the attacks is variable. The lesions may coalesce to form larger confluent areas of ulceration and in this with marked erythema around.

The etiology of RAS remains unclear, it is multifactorial. Several plausible triggers have been studied that influence its precipitation. Trauma of the mucosa in sites of dental treatment, cheek-biting or harsh toothbrushing, have likewise been reported to be linked to RAS. There is no association between RAS with dysmenorrhea, pregnancy and the menstrual cycle. (9) Drugs such as NSAID's, phenobarbital and nicorandil potentially trigger lesions very similar to RAS, however with different periodicity. Nutritional and vitamin deficiencies are also a strong risk factor, anemias and vitamin B deficiencies are the most common causes. (10-13) Oral L- form streptococci have been considered as potential microbial agents in the pathogenesis of RAS. Helicobacter pylori, Epstein-Bar virus and cytomegalovirus are suggested as possible etiological agents of RAS. (14)

Herpes simplex virus (HSV type 1) infections present with similar lesions however in HSV the lesions are preceded by fever and diffuse gingival erythema, also HSV lesions are localized on attached gingiva as opposed to the mobile gingiva. Varicella zoster virus (VZV) can be differentiated from RAS as VZV lesions are distributed unilaterally, extra and intraorally, following the course of the trigeminal nerve. Various other oral infections, such as coxsackie virus infection (hand-foot-mouth disease) must also be ruled out before initiating the treatment of RAS.(14)

The total oxidative status and oxidative stress index values is significantly higher in the recurrent aphthous stomatitis. (15) Many researches have pointed the significance of psychological disorders (stress) to the etiology of RAS, as stress may cause a temporary rise in salivary cortisol which incites changes in immunoregulatory activity. Although this is difficult to quantify as some studies have found no association between stress and RAS. Albeit, it is proven that stress causes an increase in inflammatory response, resulting in the mast cell's releasing Ig E into the skin and mucosa. Interestingly, smokers who quit complain of RAS possibly due to the increase in keratinization as a result of the tobacco which results in the mucosa being less prone to ulceration. Flavoring agents such as cinnamon aldehyde and cosmetic additives such as sodium lauryl sulphate have been identified as plausible etiological factors. Finally, genetics and family history are also believed to influence on the predisposition of the patient. Some systemic disorders are proven to be associated with RAS, these include Behcet's syndrome, Reactive arthritis and Sweet's syndrome. In HIV-infected and other immunocompromised people, the lesions are larger, more painful, heal slower and recur more frequently. (16)

Specific tests are unavailable to diagnose RAS, but it is of utmost significance that correct diagnosis is made and we exclude other oral lesions such as erosive lichen planus and erythema multiforme, and most importantly, malignancies such as squamous cell carcinoma. (17) The important features that the clinician should follow when examining a patient with oral ulceration include family history, occurrence of ulceration, duration of ulceration, number and site of ulcers(non-keratinized or keratinized), size and shape of ulcers, edge and base of ulcer, surrounding tissue, associated medical conditions(comorbidity), current medication, genital ulceration, skin problems, gastrointestinal disturbances, drug history.

In most of cases aphthous ulcerations of oral mucosa (or RAS-like ulcerations) have an underlying systemic cause and they should be considered as a distinct medical condition. The differential diagnoses should be established with autoimmune syndromes and diseases as: periodic fever with adenitis, pharyngitis and aphthae (PFAPA) syndrome, Behcet's syndrome and Crohn's disease, immunodeficiency states, including nutritional deficits (malabsorption conditions) such as celiac disease and other gastrointestinal disorders, immune defects- as human immunodeficiency virus infection/acquired immune deficiency syndrome and neutrophil defects (such as cyclic neutropenia). The term RAS should be used for these cases of ulceration in which no systemic disease is detected. (18)

Paraclinical examinations which can be made to investigate patients with persistent RAS include full blood screen, ESR, CRP, B12, folate and anti-endomysial antibodies and if needed pathohistological examination. Therefore, RAS is usually diagnosed based on history and clinical examination. For patients who have a current oral lesion a clinical diagnosis of an active RAS lesion is often made based on the clinical appearance of the lesion and supporting history. Differential diagnosis must be made with other mucocutaneous and hematological diseases that can affect the oral cavity.

Likewise, no definitive treatment has emerged, however, objectives are pain reduction, decrease in number and size of ulcers and reduction in frequency of attacks. A careful medical and dental history, including the use of oral hygiene products, may aid in detecting systemic or local precipitation factors. The most important factor to aid in the management of the disease is the maintenance of good oral hygiene which can be aided by chlorhexidine mouthwashes. Equally important for the patient, is to obtain adequate analgesia to ensure maximum palliation of the pain and minimum impact on the quality of life of the patient. A topical anesthetic such as 2% viscous lidocaine hydrochloride is used for this purpose. After achieving good oral hygiene and pain-free lesions, the treatment can focus on the remission of the ulcers and the aided healing of the oral

mucosa. The traditional treatment of RAS is glucocorticoids and antimicrobial therapy applied as topical pastes (flucinonide) and mouth rinses (triclosan and betamethasone valerate). Thalidomide used at a dose of 50mg-100mg daily also treated severe refractory RAS successfully, however, due to its neurotoxic and mutagenic potentials, it is not the treatment of choice. Levamisole, an anthelmintic drug has been tried with promising results in patients with severe RAS providing long-term benefits. (19-20)

Other unconventional treatment methods have been proposed such as destruction of local nerve endings by chemical cauterization using a mixture of Sulphuric acid and sulphonated phenolics in aqueous solution. Another method is by using silver nitrate sticks on the mucosal surface for 20 seconds, as the silver salts have been shown to exert an inhibitory effect on proliferation and differentiation of several cell lines (lymphocytes, leucocytes, keratinocytes and dermal fibroblasts). (21)

## Conclusion

Correct management, prevention and treatment of RAS are fundamental to implement in order to increase quality of life of affected individuals. A careful diagnosis is equally important to exclude clinically similar oral lesions. Essentials associated with RAS are, the etiology is unknown, it cannot be prevented, it is an immunologically mediated disease and the diagnosis is clinical and the management includes a combination of topical anesthesia plus an antiseptic and corticosteroids. Taking these key concepts into account, several questions require further biomedical research. These include determining if there are molecular differences between a healthy individual and a patient with RAS, determining what biomarkers are involved in the ulcerative phase of the disease and the remission period, assessing if there are biomarkers that can predict the clinical course and the severity of oral ulcers, which can help in therapeutic and preventive measurements.

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