

# Etiological Factors of Recurrent Aphthous Stomatitis: A Common Perplexity

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## ABSTRACT

Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal disorders. Nevertheless, while the clinical characteristics of RAS are well-defined, the precise etiology and pathogenesis of RAS remain unclear. The present article provides a detailed review of the current knowledge of various etiological factors of RAS.

**Keywords:** Mouth ulcers, Recurrent aphthous stomatitis, Etiology.

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## INTRODUCTION

Recurrent aphthous stomatitis (RAS; Aphthae; Canker sores), a common oral mucosal disorder that is characterized by multiple, recurrent, small, round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or gray floors that present first in childhood or adolescence. Although it is one of the most common recurrent oral ulcerative conditions of adults and children recognized throughout the world, RAS is also one of the least understood oral diseases and is among the most vexing problems faced by affected patients and clinicians alike.<sup>1,2</sup> The triggering factors that precipitate recurrent episodes in RAS patients seem to be as diverse and unique as the affected individuals themselves, which has posed a challenge for researchers in their attempts to identify a specific causation for this disease. Although the exact etiology of RAS remains obscure, there is growing lucidity with regard to its pathogenesis which has significantly influenced contemporary approaches toward its management. This article reviews the clinical features and various etiological factors of RAS.

## CLINICAL FEATURES

‘Aphthous’ comes from the Greek word ‘aphtha’, which means ulcer. Despite the redundancy, the medical literature continues to refer to these oral lesions as aphthous ulcers. ‘Aphthous stomatitis’ has been used interchangeably with ‘aphthous ulcers’ and may be a more accurate terminology. Aphthous ulcers are round or oval, with a grayish yellow,

crateriform base surrounded by an erythematous halo of inflamed mucosa. For 24 to 48 hours preceding the appearance of an ulcer, most patients have a pricking or burning sensation in the affected area. The ulcer usually occurs on the nonkeratinized oral mucosa, including the lips, the buccal mucosa, floor of the mouth, soft palate and the ventral surface of the tongue.

RAS is seen worldwide and may affect up to 25% of the population.<sup>1-3</sup> Recurrent aphthous ulceration has three different variants—minor aphthous ulcers, major aphthous ulcers and herpetiform ulcers, according to the classification described by Stanley<sup>4</sup> in 1972. Minor RAU (MiRAU) is the common variety, affecting about 80% of RAU patients. It is characterized by painful round or oval shallow ulcers, regular in outline, less than 10 mm in diameter, with a gray-white pseudomembrane surrounded by a thin erythematous halo. MiRAU usually occurs on nonkeratinized mucosa such as labial mucosa, buccal mucosa and floor of the mouth. It is uncommon on the keratinized mucosa. Minor RAU is the most common form of childhood RAU. The lesions recur at varying frequencies (from every few years to almost constantly) and heal within 7 to 10 days without scarring. Major RAU (MaRAU), also known as periadenitis mucosa necrotica recurrens, occurs in approximately 10% of RAU patients. The lesions are similar in appearance to those of minor RAU, but they are larger than 10 mm in diameter, single or multiple and very painful. MaRAU has a predilection for the lips, soft palate, and fauces, but can affect any site. The ulcers of MaRAU persist for up to 6 weeks or longer and often heal with scarring. Herpetiform aphthae accounts for 7 to 10% of all RAU cases. In herpetiform RAU there are 10 to 100 ulcers at a time, ulcer size is usually 1 to 3 cm, and the ulcers form clusters that coalesce into widespread areas of ulceration lasting 7 to 10 days. These ulcers are only herpes-like in appearance; herpes simplex virus has not been cultured from them.

## ETIOLOGY

To date, the precise etiology of RAS has not been disclosed, despite years of collective effort on the part of many researchers. Historically, conjecture about the origin of RAS focused on a wide spectrum of potential local and systemic factors that encompassed microbial agents, hematologic and hormonal disturbances, physical injury, emotional stress and other influences. Also confounding the search for a singular

cause is the observation that aphthous-like oral ulcers often occur in conjunction with diverse conditions of a systemic nature. Included among those conditions are cyclic neutropenia, selected anemias,<sup>5</sup> inflammatory bowel diseases,<sup>6</sup> Behçet's disease,<sup>7,8</sup> gluten-sensitive enteropathy (celiac sprue),<sup>9,10</sup> relapsing polychondritis syndromes (including the so-called 'MAGIC' syndrome, which consists of mouth and genital ulcers with inflamed cartilage),<sup>11</sup> HIV infection,<sup>12</sup> the purported symptom complex of recurring fevers, aphthous stomatitis, pharyngitis and lymphadenopathy (FAPA syndrome).<sup>13</sup>

In recent years, body of evidence has emerged to suggest a genetic and an immunologic basis for RAS. These revelations largely have eclipsed speculation that RAS is caused by an infectious microorganism or one of the other previously suspected etiologic factors. They also have led to more rational and effective contemporary approaches to the management of RAS.

### Genetic Factors

Some people have a well-established familial basis for RAU. As compared to the general population, the prevalence of RAS is higher when there is a positive family history, especially when both parents are affected. There is also increased disease correlation observed in identical twins as compared to fraternal twins. In familial cases of RAS, the onset of disease is earlier and attacks tend to occur more frequently than in nonfamilial cases.<sup>14-16</sup> The likelihood that RAS is a genetically grounded disease is further supported by the recognized, although not entirely consistent, identification of certain histocompatibility antigen (HLA) types (e.g. HLA B12, B51, Cw7), among some groups of aphthous patients.<sup>17</sup>

### Immunologic Factors

Despite the inconsistent finding and conflicting theories, mounting scientific evidences support immune dysregulation as a key mechanism underlying the pathogenesis of RAS. It is believed that the altered immune reactivity arises perhaps in response to, or in concert with, a state of presumably heightened antigenic stimulation<sup>18</sup> exacted on a diminished mucosal barrier. A constellation of cell-mediated immunologic phenomena seems to be a consistent factor in the disease. Serologic studies that compared RAS patients and unaffected controls revealed diminished ratios of circulating CD4<sup>+</sup> helper cells to CD8<sup>+</sup> suppressor cells in the former group.<sup>19,20</sup> It has been proposed that in RAS some unspecified antigenic influence<sup>21</sup> is at the epicenter of an antibody-dependent, T cell-mediated immune response that involves a shift in local lymphocytic subpopulations that eventuates in tissue damage.<sup>22-24</sup> From the observations

of several investigators it has been hypothesized that the entire process of aphthous ulceration, from initiation through progression, is instigated by the expression on oral epithelial cells of not only normally found HLA class I antigens but also HLA class II antigens.<sup>25</sup> Presumably, this renders the cells antigenically 'foreign' and consequently they become the targets of a cell-mediated immune reaction perpetrated by lymphocytes and Langerhans cells. It has been shown that in patients with aphthous stomatitis there is a heightened lymphocytotoxic effect directed against oral epithelial cells when compared to unaffected controls.<sup>24-26</sup>

Evidence for this pathogenetic mechanism is also inferred from observations that tissue biopsies of newly erupted aphthous ulcerations demonstrate agglomeration of activated T lymphocytes at the periphery of the lesions, whereas in well-established aphthae the initially predominant CD4<sup>+</sup> helper/suppressor cell population is subsumed and succeeded by cytotoxic CD8<sup>+</sup> lymphocytes.<sup>23,24</sup> Additional indirect support for primary immune dysregulation is reflected in the long-recognized correlation between stress and outbreaks of aphthous ulcers that is reported by many RAS patients, in contrast to the notable decrease in frequency of episodes during periods of reduced stress.<sup>27</sup> This observed association is not entirely surprising, because stress is known to affect immunologic function. It also has been observed that HIV-infected patients experience oral aphthous-like ulcerations with relatively high frequency. With advancing immune depletion, their aphthous outbreaks are often dominated by larger ulcers that run a more protracted course.<sup>28,29</sup> Attempts to explore the possibility that RAS is fundamentally an antibody-driven disorder have disclosed findings that are at best inconsistent and largely unresponsive. It seems that any previously held conjecture that aphthous ulcers stem from a centrally generated humoral immune mechanism rather than from local cellular immune responses to an antigenically modified oral mucous membrane was predicated on assumptions that have since been discredited.<sup>17,30-32</sup>

### Microbial Factors

There is little consistent evidence to support the hypothesis that RAS represents an infectious disease. In particular, from studies to determine whether there might be a connection between previously suspect L-forms of streptococci and RAS, or the adenoviruses, herpes simplex virus (HSV), varicella-zoster virus, or cytomegalovirus and RAS, the available evidence suggests that none of these microorganisms seems to be directly culpable for RAS despite continued speculation about their possible role. One should note that an antiviral agent, acyclovir, offers no beneficial effect in preventing or attenuating episodic flares of the

condition,<sup>33</sup> which serves to weaken arguments in favor of a possible viral causation for RAS. From occasional anecdotal cases in which patients report an apparent consistent temporal relationship between their aphthous outbreaks and an immediately antecedent reactivated (recurrent) HSV infection, it is tempting to postulate that in a narrow subset of individuals who get RAS, the herpes virus may serve as an antigenic 'trigger' that initiates the cascade of immunologic events that result in ulceration. In a limited subset of RAS patients, it is possible that this is actually the case. Presumably, such patients would benefit from appropriate therapeutic and prophylactic antiviral therapy, coupled with treatments specifically aimed at lessening the severity and frequency of the RAS episodes by modulating their supposedly heightened immune responses to the viral 'trigger'. Such therapeutic strategies probably would be best carried out in consultation with an infectious disease specialist. It must be emphasized, however, that regarding most aphthous patients, any suggestion of a causative nexus between RAS and HSV seems to represent unsubstantiated conjecture rather than proven fact.<sup>34,35</sup>

### Nutritional Factors

Other issues explored in the quest to determine a cause for RAS include the possible relationship of attacks to excess or deficiency of various nutritional factors, such as serum iron, folate and vitamin B<sub>12</sub>, and speculation that aphthous ulcers represent the manifestation of an allergic reaction to certain foods or other ingested or contacted substances. Apart from variably favorable responses to the avoidance of gluten products in aphthous patients with documented intestinal malabsorption disease (compared to controls<sup>36</sup> and in some aphthous stomatitis patients with normal intestinal function,<sup>37</sup> evidence that RAS primarily represents an allergic response or is etiologically linked to diminished serum iron, vitamin B<sub>12</sub> or folate levels is lacking or, at best, equivocal.<sup>23,27,38</sup> For any RAS patient who exhibits physical signs and symptoms that suggest the possibility of an underlying malabsorption or nutritional deficiency state or a blood dyscrasia, it is prudent to obtain a complete blood count and assays for serum folate, vitamin B<sub>12</sub> and ferritin. Should any of these tests yield findings that suggest an underlying systemic abnormality, referral to an internist or a hematologist is indicated.

The improvement of RAU with zinc sulfate supplementation has been described in an open trial<sup>39</sup> and in a case report of aphthous ulcers with zinc deficiency and immunodeficiency,<sup>40</sup> but such improvement was not been confirmed in later studies.<sup>41,42</sup> In a Chinese study the level of serum zinc in 75 cases of RAU was found to be at a low

level but, within the normal range, and serum copper levels were also normal.<sup>43</sup> So far no information exists on the associations between RAU and other trace elements.

### Environmental Factors

#### Stress

Earlier studies have documented an association between RAU and a variety of psychological factors including anxiety, repressed hostility, as well as job-related and other stress factors. Conversely, other studies have failed to reveal any association between anxiety, depression, psychological life stress and recurrences of RAU. In one study, in which a relaxation/imagery treatment program was used, a significant decrease in the frequency of ulcer recurrence among all treated subjects was noted.<sup>44</sup> Although the majority of investigators have been unable to validate the concept that stress plays an important role in the development of RAU, the literature continues to indicate that stress may play a role in precipitating RAU.

#### Local Trauma

A subset of patients with RAU is predisposed to develop aphthae at sites of trauma. The reason why local trauma, such as anesthetic injections, sharp foods, tooth-brushing and dental treatment, can trigger aphthous ulceration in these patients is still unknown.<sup>45</sup>

#### Tobacco

Several investigators have documented a negative association between smoking and the occurrence of RAU.<sup>46</sup> Such a negative association has also been documented as regards the use of smokeless tobacco (chewing tobacco and snuff), as well as in patients who are smokers.<sup>47</sup> Paradoxically, the majority of patients with RAU are non-smokers, and in a recent study only 9% of RAU patients were found to be active smokers, compared with 25% among the control subjects.<sup>48</sup>

Nicotine has been reported to be beneficial in RAU and in inflammatory bowel disease, and its effects may result from influences on nerve function, although these may also exert direct anti-inflammatory effects. However, the mechanism by which cigarette smoking protects against RAU is still unknown.

#### Food Hypersensitivity

Some investigators have correlated the onset of ulcers to exposure to certain foods, such as cows' milk, gluten, chocolate, nuts, cheese, azo dyes, flavoring agents and preservatives. Eversole et al (1982) found no significant association between RAU and three specific food items



(tomatoes, strawberries and walnuts).<sup>49</sup> Some investigators have noted an increased prevalence of atopy among RAU patients, whereas Wray et al (1982) found no significant difference in the incidence of atopy in RAU patients compared with the normal population.<sup>50</sup>

### Drugs

Some drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs, e.g. propionic acid, phenylacetic acid and diclofenac) can give rise to oral ulcers similar to those of RAU, along with genital ulceration or only oral ulcers in the case of piroxicam.<sup>51</sup> An association between beta-blockers and aphthous ulcers has also been suggested. Such ulcers usually occur as an adverse side effect and disappear with discontinued usage of the drug.<sup>52,53</sup>

Recently, an increased frequency in the occurrence of RAS has been reported on using sodium lauryl sulfate (SLS)-containing toothpaste. Some reduction in ulceration has been noticed on use of SLS-free toothpaste. However, because of the widespread use of SLS-containing dentifrice, it has been proposed that this may not be a true predisposing factor of RAS.<sup>54</sup>

### CONCLUSION

While RAS remains a common oral mucosal disorder in most communities of the world, its precise etiology remains unclear. No precise trigger has ever been demonstrated, and there is no conclusive evidence for a genetic predisposition to RAS in most patients. Currently, RAS is recognized as an immunologically mediated, inflammatory oral condition rather than an infectious disease. It is reasonable to suggest that for the future, anticipated new insights into the condition's origin and pathogenesis, combined with ongoing research directed toward the development of safer, more effective immunomodulating agents, render the prospect of a cure for RAS increasingly plausible.

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