Recurrent aphthous stomatitis (RAS) is a common disorder affecting 5% to 66% of examined adult patient groups. There may be a female predominance in some adult and child patient groups.1–4 The ulceration usually commences in the second decade,5 although 40% of selected groups of children can have a history of RAS, ulceration beginning before 5 years of age, the frequency of affected patients rising with age. Children of higher socioeconomic status may be more commonly affected that those from low socioeconomic groups.6–9

Clinical Features

The clinical features of RAS comprise recurrent bouts of one or several rounded, shallow, painful oral ulcers at intervals of a few months to a few days; RAS has three main presentations: minor (MiRAS), major (MaRAS), or herpetiform (HU) ulcers (Table 1).

Minor recurrent aphthous stomatitis (MiRAS), the most common variety, affects about 80% of RAS adult and child patients, and is characterized by round or oval shallow ulcers usually less than 5 mm in diameter with a gray-white pseudomembrane enveloped by a thin erythematous halo. Usually, MiRAS occurs on the nonkeratinized mobile surfaces such as the labial and buccal mucosa and floor of the mouth and is uncommon on the gingiva, palate, or dorsum of the tongue. These lesions heal within 1 to 2 weeks without scarring.5

Major recurrent aphthous stomatitis (MaRAS) is an uncommon and severe form of RAS, comprising oval or irregular ulcers that may exceed 1 cm in diameter. These ulcers have a predilection for the lips, soft palate, and fauces (but can affect any site), persist for up to 6 weeks, and often heal with scarring.

Herpetiform (HU) is very uncommon, being characterized by multiple recurrent crops of small, painful ulcers that may be distributed throughout the oral cavity. As many as 100 ulcers may be present at a given time, although they tend to fuse, producing large irregular ulcers. It has been suggested that HU might have a female predisposition and also a later age of onset than other RAS types or represent a spectrum of oral disorders manifesting as recurring ulcers.10

Disorders Giving Rise to RAS-Like Disease

Similar-appearing lesions may arise in systemic disorders including Behcet’s disease,11–15 Sweet’s syndrome,16–18 cyclic neutropenia,19–21 benign familial neutropenia,22,23 MAGIC syndrome,24,25 a periodic syndrome with fever and pharyngitis,26 various nutritional deficiencies with or without underlying gastrointestinal disorders,27–29 some other primary immunodeficiencies,30–33 and infection with human immunodeficiency virus.34,35 Rarely, drugs such as nonsteroidal anti-inflammatory drugs (NSAIDS)36 or nicorandil37 can give rise to oral ulcers, similar to RAS.

Systemic Diseases Possibly Associated With RAS

The precise etiology of RAS is not known. A number of disease associations have been proposed and are suggested to be of etiological significance; however, these links are often tenuous and/or unlikely to be significant to the development of the ulceration of RAS.

Hematin Deficiency

Several studies from the UK, United States, and Spain have demonstrated that hematinc deficiency (iron, folic acid, or vitamin B12) are twice as common in RAS patients than in controls.38–46 About 20% of patients with RAS may have a hematinc deficiency, though one U.S. study did not report any hematinc problem.47 Vitamin B1, B2, and/or B6 deficiency was observed in a cohort of Scottish patients with RAS.48

Gluten-Sensitive Enteropathy

Less than 5% of outpatients who initially present with RAS49–51 are prone to have gluten-sensitive enteropathy (GSE: celiac disease). These RAS patients may not always have gastrointestinal symptoms or other clinical features suggestive of GSE but usually have folate de-
ficiency, sometimes reticulin antibodies, particularly IgA class reticulin antibodies and/or antigliadin antibodies. The haplotype of HLA-DRW10 and DQW1 may predispose patients with GSE to RAS. There may also be occasional patients who have RAS with no detectable clinical or histological evidence of celiac disease on jejunal biopsy, yet who may respond to dietary withdrawal of gluten. Nevertheless, the withdrawal of gluten rarely results in significant benefit and may simply reflect the pronounced placebo response in RAS. Anti-endomysial antibodies are rarely present in patients with RAS, thus adding weight to the evidence that RAS is not commonly associated with GSE. Patients with Crohn’s disease can have superficial ulceration similar to that of RAS.

Food Hypersensitivities

Some studies have noted an increased prevalence of atopy among RAS patients, but others have failed to find any significant correlation. Some patients correlate the onset of their ulcers to exposure to certain foods, but controlled studies have failed to disclose a causal role despite the fact that certain foods triggering positive skin-prick reactions will elicit pain when they are topically applied to aphthous ulcers. Dietary manipulation significantly improves RAS in only rare instances.

Zinc Deficiency

Any association between RAS and zinc deficiency seems tenuous.

Menstrual Change

A minority of women with RAS have cyclical oral ulceration related to the luteal phase of the menstrual cycle. Nevertheless, a detailed review of all pertinent literature failed to find any association between RAS and altered female sex corticosteroids. A link with autoimmune progesterone dermatitis is most unlikely.

Psychological Illness

Psychological illness has been proposed to initiate some episodes of RAS, but there are sparse data to suggest a strong link between psychological stress and RAS, or that RAS causes significant psychological upset.

Genetic Factors

Recurrent aphthous stomatitis may have a familial basis, perhaps more than 40% of RAS patients having a vague family history of oral ulceration. Patients with a positive family history of RAS may develop oral ulcers at an earlier age and have more severe symptoms than those with no such history. There is an increased likelihood of a child developing RAS if both parents have ulcers, and there is a high correlation of RAS in identical twins. Nevertheless, no consistent significant association between RAS and a particular serologically determined HLA antigen or haplotype has been demonstrated (reviewed elsewhere). This may reflect inadequate patient numbers and/or variable ethnic backgrounds of investigated patients, or most likely the lack of any immunogenetic basis to RAS.

Possible Infectious Basis of RAS

Bacteria

An association between RAS and oral (viridans) streptococci has long been suggested as important in the pathogenesis of RAS, the bacteria acting either as direct pathogens or as antigenic stimuli culminating in an immunologically mediated cross-reaction with keratinocyte antigenic determinants. The initial L-form isolated from RAS patients was typed as Streptococcus sanguis, but later analysis disclosed that this organism was actually a strain of S. mitis, or rather S. oralis, a bacterium frequently present in the dental plaque of patients with Behcet’s disease. In addition, although some studies have disclosed elevated serum antibody titers to viridans streptococci among RAS patients, others have yielded contradictory results. Lymphocyte mitogenic responses to S. sanguis and S. mitis in RAS patients are not significantly different from those in control subjects. Polymerase chain reaction (PCR) studies have also indicated that S. oralis is not specific to RAS, and thus unlikely to be of etiological significance.

Table 1. Characteristics of the Different Types of Recurrent Aphthous Stomatitis

<table>
<thead>
<tr>
<th>Minor</th>
<th>Major</th>
<th>Herpetiform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio</td>
<td>M = F</td>
<td>F = M(?)</td>
</tr>
<tr>
<td>Age of onset (years)</td>
<td>5–19</td>
<td>10–19</td>
</tr>
<tr>
<td>Number of ulcers</td>
<td>1–5</td>
<td>1–10</td>
</tr>
<tr>
<td>Size of ulcers (mm)</td>
<td>&lt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>4–14</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Rate of recurrence (months)</td>
<td>1–4</td>
<td>&lt;Monthly</td>
</tr>
<tr>
<td>Sites</td>
<td>Lips, cheeks, tongue, floor of mouth</td>
<td>Lips, cheeks, tongue, palate, pharynx</td>
</tr>
<tr>
<td>Permanent scarring</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
</tbody>
</table>

* Can be larger if there is a fusion of ulcers.
It has been suggested that there is a molecular basis for the earlier work suggesting a link with S. sanguis, as monoclonal antibodies to part of the 65-kDa heat-shock protein (hsp) of Mycobacterium tuberculosis cross-react with S. sanguis. Thus RAS may be a T-cell-mediated response to antigens of S. sanguis that cross-react with the mitochondrial hsp and induce oral mucosal damage. In the absence of data showing a high frequency of a specific streptococcal infection in RAS patients, however, this proposed etiological mechanism seems unlikely.

Helicobacter pylori has been detected in lesional tissue of ill-defined oral ulcers and by PCR in up to 72% of examined RAS ulcers; however, the frequency of serum IgG antibodies to H. pylori is not increased in RAS.

Viruses

An association of RAS with adenoviruses has been suggested, but adenoviruses are ubiquitous organisms. The possible association of RAS with herpesviruses-1–6 is reviewed elsewhere. Herpesvirus virions are not demonstrable in RAS, and although RNA complimentary to herpes simplex virus (HSV) has been detected in circulating mononuclear cells in some RAS patients and in circulating immune complexes, serum levels of interferon are not increased, HSV is not demonstrable in RAS lesions, and RAS patients are not always HSV seropositive.

There is contradictory serological and molecular biological data on the frequency of detection of cytomegalovirus and varicella zoster infection in patients with RAS, and there is little substantive data to suggest that anti-herpesvirus antivirals such as acyclovir are of therapeutic benefit in the management of RAS.

An association between Epstein-Barr virus (EBV) and the early ulcerative lesions of RAS and Behcet’s disease has been proposed, but the data are based upon a very small group of patients. Human herpesvirus-6 (HHV-6) DNA has not been detected in 6 of 21 RAS lesions and 95% of the patients had IgM antibodies to HHV-6, but both HHV-6 and HHV-7 DNA are rarely detected in peripheral blood monocytes of RAS patients with and without ulceration.

Local Factors Associated With RAS

Local physical trauma may initiate ulcers in people susceptible to RAS, and RAS are uncommon on keratinized surfaces or in patients who smoke tobacco.

Immunopathogenesis

A review of the immunology and possible pathogenesis of RAS is beyond the scope of this clinical review. A detailed discussion of this subject can be found elsewhere.

Management of RAS

A systematic review of the management of RAS is available. Patients with oral ulceration possibly associated with systemic disease require referral to an appropriate specialist. All patients should be advised to use an oral hygiene procedure that is as atraumatic as possible, and all dental appliances should fit well and be non-tissue-damaging.

Hematinic Replacement

The correction of any hematinic deficiency is of limited benefit unless the cause is corrected. Zinc sulphate therapy is not effective, and LongoVital®, a herbal-based vitamin tablet with a wide range of trace elements, seems to be of limited benefit.

Topical Antimicrobials

Chlorhexidine used as a 0.2% w/w mouthrinse or 1% gel can reduce the duration of ulcers and increase the number of ulcer-free days. (Table 2) One study, however, found little objective value of chlorhexidine gluconate mouthrinse over placebo in the management of RAS. Regular use of chlorhexidine gluconate may
cause exogenous dental staining, and the bitter taste may limit compliance.

Topical tetracyclines (eg, aureomycin, chlortetracycline, and tetracycline) may reduce healing times and/or reduce the associated pain of RAS, but they may cause dysgeusia, oral candidosis, and a burning-like sensation of the pharynx, and they are not suitable for young children who might ingest them, with resultant tooth staining.

**Topical Corticosteroids**

Topical corticosteroids remain the mainstay of RAS treatment in most countries, although there are few well-controlled studies of their precise efficacy. A wide range of different topical corticosteroids may reduce symptoms.

**Topical Analgesics**

Benzydamine hydrochloride mouthwash is of no more benefit on ulcer healing than placebo; nevertheless, it (or lignocaine gel) can produce transient relief of pain.

**Toothpastes**

Toothpastes that enhance the salivary peroxidase system are not effective. It has been suggested that elimination of sodium lauryl sulphate (SLS) can reduce or prevent RAS, but although one later study confirmed this, another did not.

**Other Topical Agents**

Sodium cromoglycate lozenges may provide mild symptomatic relief, but cromoglycate-containing toothpaste is of no benefit. Carbenoxolone sodium mouthwash reduced the severity of RAS in one study. Topical immunomodulatory agents that have been suggested to be of some benefit in the management of RAS include azelastine, human alpha-2-interferon in cream, topical cyclosporine, deglycyrrhizinated licorice, topical 5-aminosalicylic acid (5-ASA), and prostaglandin E2 (PGE2) gel. There have been several studies of the efficacy of amlexanox in the management of RAS including one detailed randomized controlled study suggesting that the 5% paste may significantly reduce the pain and time of healing of RAS ulceration.

A cross-over study found that sucralfate reduced the duration of symptoms and improved duration of remission of RAS. A previous study did not report sucralfate to be clinically useful, although a recent investigation of Italian patients suggested that 20% sucralfate is of some benefit in reducing the symptoms of RAS. Cimetidine has found favor with some workers.

**Physical Therapies**

Surgical removal, debridement, or laser ablation of ulcers is not practical and is of very limited practical benefit. The efficacy of a chemical cauterity agent (Debacterol) is unclear.

**Systemic Therapies**

Systemic immunosuppression is sometimes warranted in view of the limited efficacy of topical agents, and the sometimes profound pain and/or long-standing ulceration; however, whereas many such agents have been proposed to be clinically useful, there is little evidence base.

**Prednisolone and/or Azathioprine**

Systemic prednisolone and azathioprine have been suggested to be effective, but there are no detailed published studies on their precise clinical benefits.

**Levamisole**

Levamisole rarely causes objective clinical improvement, and the associated adverse effects (nausea, hyperosmia, dysgeusia, and agranulocytosis) discourage its use.

**Colchicine**

Colchicine has proved clinically beneficial when investigated in small groups of patients with RAS, and in an open study of 20 patients, colchicine (1.5 mg/day for 2 months) caused a significant reduction in pain scores and frequency of self-reported ulcers. Unfortunately, not all patients benefit from colchicine therapy, and at least 20% can have painful gastrointestinal symptoms or diarrhea. Long-term use can induce infertility in young men. Combined colchicine and thalidomide therapy may occasionally benefit recalcitrant RAS.

**Pentoxifylline**

Results of limited open studies suggest that pentoxifylline (400 mg three times daily) may significantly reduce the number of RAS for up to 9 months after a month of therapy. The results of a recent study, however, did not confirm that pentoxifylline reduces the recurrence of RAS when therapy is stopped. About 10% of patients will have some degree of gastrointestinal upset with pentoxifylline therapy.

**Dapsone**

Dapsone has been reported to reduce the oral lesions in a few patients with RAS-like lesions, but the clinical features of this group of patients were poorly described.
**Thalidomide**

Thalidomide remains the most effective agent for the management of RAS, producing a remission in almost 50% of treated patients in one randomized controlled trial. Open and double-blind studies of patients with HIV-related oral ulceration and in non-HIV-related RAS, and in several case studies, all confirm that thalidomide is of clinical benefit. Thalidomide gives rise to mild adverse side effects (eg, intolerance, loss of libido) in up to 75% of treated patients, and polyneuropathy can arise in about 5% of cases. Clearly the risk of teratogenicity also limits the clinical application of thalidomide in the management of RAS.

**Other Agents**

Transfer factor and gammaglobulin therapy have been suggested to be beneficial, but more detailed studies are needed to confirm these preliminary observations.

The reported clinical benefit of monoamine oxidase inhibitor therapy in the treatment of three patients with RAS was probably due to accompanying dietary modifications rather than any alteration in psychological status.

**Conclusions**

Recurrent aphthous stomatitis remains a common oral mucosal disorder in most communities of the world; however, as its precise etiology (or etiologies) remains unknown, therapy is nonspecific and often of limited efficacy. Fortuitously, patients with RAS are generally otherwise quite well.

**References**

60. Tuft L, Etteslon LN. Canker sores from allergy to weak organic acids (citric and acetic). J Allergy 1956;27:536–43.


141. Henricsson V, Axell T. Treatment of recurrent aphthous...


