Oral Diseases (2006) 12, 1–21. doi:10.1111/j.1601-0825.2005.01143.x

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MUCOSAL DISEASES SERIES

Number VI
Recurrent aphthous stomatitis

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Recurrent aphthous stomatitis (RAS; aphthae; canker sores) is a common condition which is characterized by multiple recurrent small, round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors typically presenting first in childhood or adolescence. RAS occurs worldwide although it appears most common in the developed world. The aetiology of RAS is not entirely clear. Despite many studies trying to identify a causal microorganism, RAS does not appear to be infectious. A genetic predisposition is present, as shown by strong associations with genotypes of IL-1β; IL-6 in RAS patients, and a positive family history in about one-third of patients with RAS. Haematinic deficiency is found in up to 20% of patients. Cessation of smoking may precipitate or exacerbate RAS in some cases. Ulcers similar to RAS may be seen in human immunodeficiency virus disease and some other immune defects, and drugs, especially non-steroidal anti-inflammatory drugs and nicorandil may produce lesions clinically similar to RAS. Topical corticosteroids can often control RAS. However, the treatment of RAS remains unsatisfactory, as most therapies only reduce the severity of the ulceration and do not stop recurrence.
Oral diseases (2006) **12**, 1–21

Keywords: mouth ulcers; aphthae; corticosteroids; immunosuppressants; oral

Introduction

Recurrent aphthous stomatitis (RAS; aphthae; canker sores) is a common condition which is characterized by multiple recurrent small, round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors, appearing first in childhood or adolescence.

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Received 27 November 2004; accepted 10 January 2005

Epidemiology

Depending upon the group examined, RAS may affect 5–60%. In the USA the highest incidence (60%) was found in female student nurses, male student dentists (56%) and professional school students (55%). The lowest incidence (5%) was found in male hospital patients (Ship, 1972). 56% of Danish dental students (Donatsky, 1973) have had a history compatible with RAS. 46.7% of one group of dental patients in Thailand were found to have had RAS (Pongissawaranun and Laohapand, 1991).

Population studies have found RAS in about 2% of Swedish (Axell and Henricsson, 1985b), 1.9% of Spanish (Garcia-Pola Vallejo *et al*, 2002) and 0.5% of Malaysian (Zain, 2000) examined adults, although 17.7% of Swedish and 9.7% of adults in Ljubljana (Slovenia) (Kovac-Kovacic and Skaleric, 2000) have a history of possible RAS. RAS seems to be infrequent in Kuwaiti Bedouins (5%; Fahmy, 1976) and it has been found in only 0.1% of Indians in Malaysia (Zain, 2000). However, RAS may be especially common in North America (Embil *et al*, 1975).

There may be female predominance of RAS in adults (Ship, 1972; Fahmy, 1976; Axell and Henricsson, 1985b; Pongissawaranun and Laohapand, 1991; Donatsky, 1973; Kovac-Kovacic and Skaleric, 2000) and in children (Field *et al*, 1992; Kleinman *et al*, 1994). In the USA, white people are three times more frequently affected than black people (Kleinman *et al*, 1994).

In a population study about 1% of children in the USA were found to have recurrent oral ulcers (Kleinman *et al*, 1994), but about 35–40% may have a history of RAS-like disease (Miller *et al*, 1980; Kleinman *et al*, 1994), with ulceration beginning before 5 years of age [19.7% (Miller *et al*, 1980); 21.7% (Kleinman *et al*, 1994)] and the frequency of affected patients rising with age. However, a study of elderly dental patients in

Thailand found RAS in only 0.7% of persons over 70 years of age (Jainkittivong *et al*, 2002).

Children of higher socioeconomic status may be more commonly affected [21.4% (Axell, 1975; Axell and Henricsson, 1985b); 19% (Crivelli *et al*, 1988)] than those from low socioeconomic groups [5% (de Muniz *et al* 1981); 2% (Crivelli *et al*, 1988)].

Aetiopathogenesis

A genetic predisposition is present, as shown by an increased frequency of certain human leucocyte antigen (HLA) types, and a positive family history in some patients with RAS. Attempts to implicate a variety of bacteria or viruses in the aetiology have failed. Reactions to heat shock proteins (hsp) are one possibility: patients with RAS have circulating lymphocytes reactive with peptide 91–105 of hsp 65–60.

Haematinic deficiency is found in up to 20% of patients, cessation of smoking may precipitate or exacerbate RAS in some cases, and stress may underly RAS in some individuals. It has been suggested in some, but not all, studies that sodium lauryl sulphate (SLS), a detergent in some oral healthcare products may give rise to ulceration akin to that of RAS. Ulcers similar to RAS may be seen in human immunodeficiency virus (HIV) and some other immune defects, and drugs, especially non-steroidal anti-inflammatory drugs (NSAIDS) and nicorandil may produce lesions clinically similar to RAS in appearance, but not periodicity.

In RAS, microscopically, mononuclear (lymphocytic) cells begin to infiltrate the epithelium and oedema develops (Figures 1–3). This preulcerative stage is followed by an increase of pain and the development of a localized papular swelling because of keratinocyte vacuolization surrounded by a reactive erythemathous halo representing localized vasculitis with a dense mononuclear cell infiltrate.

The painful papule then ulcerates and a fibrous membrane covers the ulcer which is infiltrated mainly by neutrophils, lymphocytes and plasma cells. Finally there is healing with epithelial regeneration and coverage of the ulcer.

The immunopathogenesis probably involves a cell-mediated immune response mechanism, and involves generation of T-cells and tumour necrosis factor alpha (TNF-α) by these other leucocytes (macrophages and mast cells) (Natah *et al*, 2000). The TNF-α cytokine, a major inflammatory mediator, induces initiation of the inflammatory process by its effect on endothelial cells adhesion and a chemotactic effect on neutrophils (Natah *et al*, 2000). Studies have shown that RAS can be prevented by treatments that prevent the synthesis of endogenous TNF-α such as thalidomide (Sampaio *et al*, 1991) and pentoxifylline (Natah *et al*, 2000).

Elevated levels of interleukin-2 (IL-2) (Sun *et al*, 2000) as well as those of TNF-α (Taylor *et al*, 1992) (both pro-inflammatory cytokines) and lower levels of IL-10 (an anti-inflammatory cytokine) (Buno *et al*, 1998) have been reported in lesional mucosa of RAS patients. IL-10 usually stimulates epithelial proliferation in a healing process therefore its low levels in RAS patients may delay epithelization and prolong the duration of the ulcers.

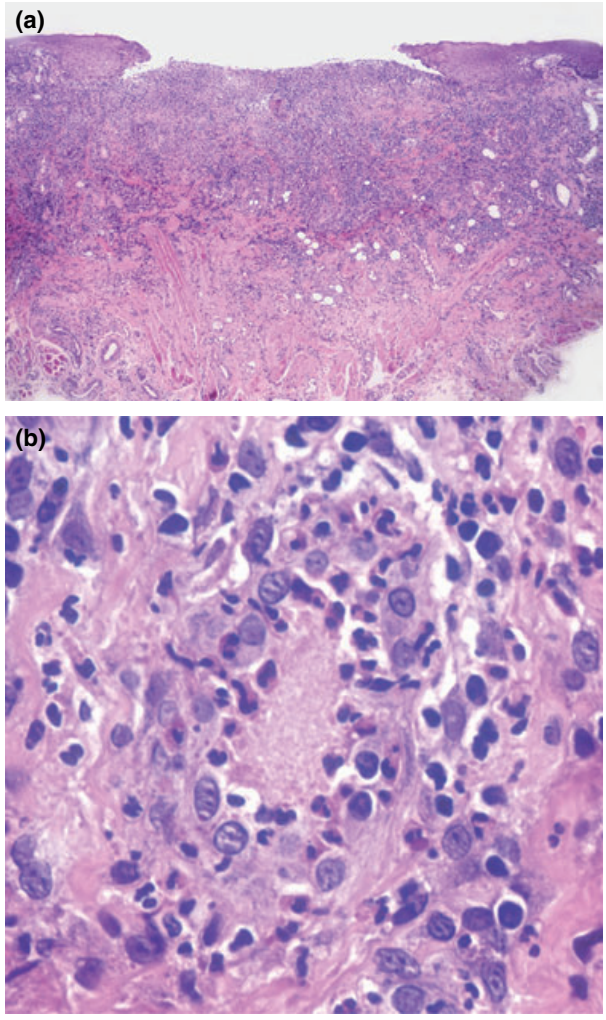

Figure 1 Minor aphthous ulcer (tongue, 33-year-old female). (**a**) Dense inflammatory infiltrate in the ulcer floor, and lateral dilated vessels. (**b**) Vasculitis with small thrombus in a postcapillary venule beneath the ulcer

TNF-α also has some important immune regulatory activities including stimulation of class I major histocompatibility (MHC) expression. An increase in class I and class II MHC antigen expression has been detected in the basal epithelial cells in the preulcerative and ulcerative stages of the RAS lesion (Savage *et al*, 1986). As almost no MHC antigens were detected after healing (Savage *et al*, 1986), they probably play a role in the local tissue damage by targeting these cells for attack by cytotoxic T-cells (CD8+ cells) in the ulcerative process.

A markedly increased plasma level of IL-2 was recorded in the active stage of RAS (Sun *et al*, 2000). Natural killer (NK) cells activated by IL-2 may play a role in the process of this disease. An increased activity of these cells was noted in active lesions, diminishing during periods of remission (Sun *et al*,

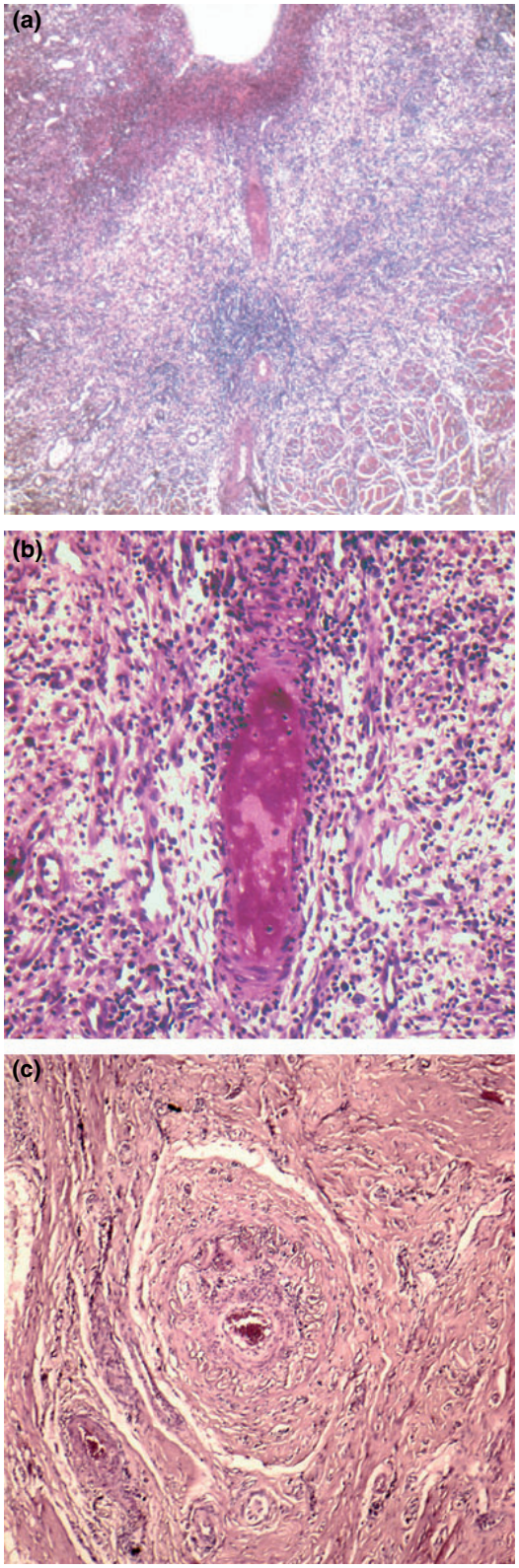

Figure 2 Major aphthous ulcer, active phase (lower lip, HIV positive 44-year-old male). (**a**) Segmental arteritis deeply located beneath the ulcer. (**b**) Detail of arteritis, with occlusive thrombosis of the vessel lumen. (**c**) Recurrent major aphthous ulcer, cicatricial fibrous artery in scar tissue (58-year-old female)

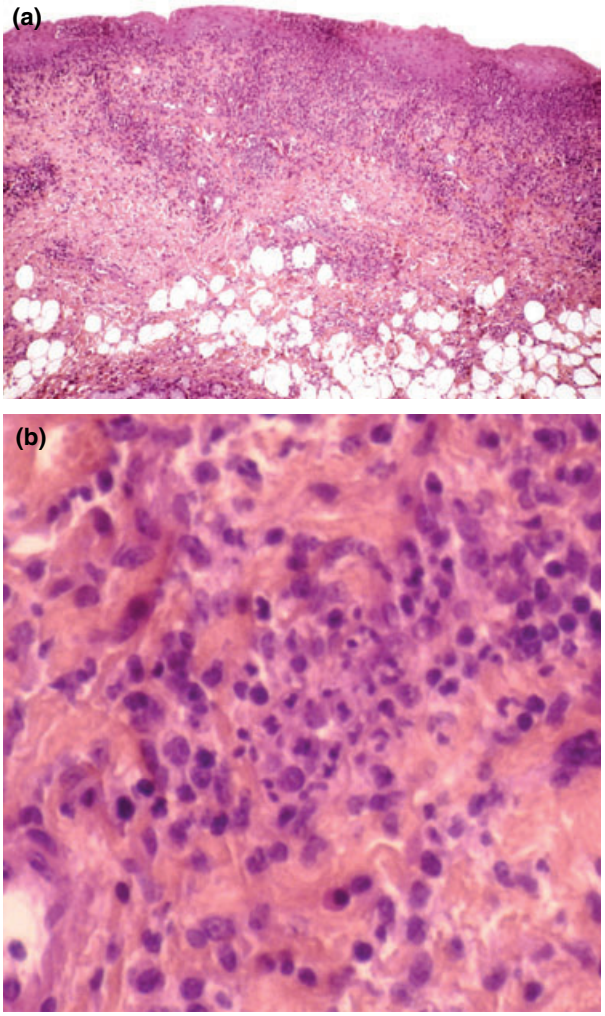

Figure 3 Herpetiform ulcers (lower lip mucosa, 48-year-old female). (**a**) Small erosions and foci of heavy inflammatory exocytosis in the epithelium. (**b**) Polymorphous infiltrate and pyknotic neutrophils around occluded capillaries

1991). As NK cells are also associated with antiviral activity against varicella zoster virus (VZV) and cytomegalovirus (CMV) (Hayward *et al*, 1986), a viral antigenic source may be considered for RAS in some patients. Other studies, however, failed to demonstrate any significant difference in fractions of NK subsets between patients with RAS and controls (Pedersen and Pedersen, 1993).

Studies have shown circulating autoantibodies against the cytoplasm of autologous oral epithelial cells of RAS patients. Enhanced cytotoxic destruction of epithelial cells by TNF produced by peripheral blood mononuclear cells (lymphocytes) (Dolby, 1969) and leucocytes (Taylor *et al*, 1992) from RAS subjects was demonstrated by *in vitro* studies. As a similar enhanced cytotoxicity has been shown against a fibroblast cell line (Thomas *et al*, 1988), the damage to the underlying connective tissue may also be part of the pathogenesis of the disease.

Genetic basis

At least 40% of RAS patients have a vague familial history of RAS (Sircus *et al*, 1957). It has been suggested that patients with a positive family history of possible RAS may develop oral ulcers at an earlier age and have more severe symptoms than affected individuals with no family history of oral ulceration (Ship, 1965). The probability of a sibling developing RAS may be influenced by the parents' RAS status (Ship, 1972) and there is a high correlation of RAS in monozygote but not dizygote twins (Miller *et al*, 1977).

A variety of associations or non-associations with HLA antigens and RAS have been reported. An association with HLA-B12 was reported (Lehner *et al*, 1982; Malmstrom *et al*, 1983) but not confirmed by others (Gallina *et al*, 1985; Ozbakir *et al*, 1987). In groups of RAS patients of different ethnic origin a significant association between HLA-DR2 (usually in the haplotype HLA-DR2/B12) and RAS was observed, but the study groups were only comprised of a few patients (Lehner *et al*, 1982; Albanidou-Farmaki *et al*, 1988). In a study of Turkish patients with RAS the frequency of HLA-B5 was not significantly raised compared with healthy control subjects (Ozbakir *et al*, 1987). The frequency of HLA-DR4 was reduced in a cohort of Greek patients (Albanidou-Farmaki *et al*, 1988). In Sicilian patients with RAS the frequency of HLA-B5 was reduced, but HLA-DR7 was significantly increased (Gallina *et al*, 1985). A small study of 22 Israeli Arabs with probable RAS found a non-significantly raised frequency of HLA-B52 and B44 (Jaber *et al*, 2001). In some, but not all groups (Shohat-Zabarski *et al*, 1992), there may be a negative association of RAS with MT2 and MT3 (now HLA-DQ series). A comparison of HLA phenotypes of patients of Chinese origin established that the frequency of HLA-DR5; DRw8; DQw1 were increased in mucocutaneous Behcet's disease, compared with RAS as well as haplotypes DR5/DRw1 and DRw8/DRw1 (Sun *et al*, 2001). There would seem to be no consistent significant association between RAS and any particular serologically determined HLA antigen haplotypes except possibly HLA-B51 (Shohat-Zabarski *et al*, 1992).

The close association both of Behcet's syndrome and RAS with HLA-B51 (Shohat-Zabarski *et al*, 1992) suggests a relationship in which this locus may not be the primary locus responsible – rather some other gene close to those controlling hsp and TNF (Mizuki *et al*, 1995). However no association was observed in polymorphism of TNFα, TNFβ or vitamin D receptor genes in a study of 95 white patients with RAS attending a clinic in London (Bazrafshani *et al*, 2002a) but a strong correlation was observed in the inheritance of an allele of interleukin-1 (IL-1β-51). In addition, the allele of IL-6-174 was strongly associated with RAS, this being greatest with a/a homozygosity. Other less strong associations occurred with IL-iIRN-wNTR 1/1 homozygosity.

Such strong associations with these genotypes of IL-1β and IL-6 thus suggest that RAS does indeed have some sort of genetic basis (Bazrafshani *et al*, 2002b). It may be that an unopposed or excessive production of IL-1β or IL-6 (e.g. response to local trauma) may be pivotal to the development of RAS (see below).

There is evidence that patients with RAS have changes in cell-mediated immunity. Patients with RAS may have increased levels of peripheral blood CD8+ T lymphocytes and/or decreased CD4+ T lymphocytes (Bachtiar *et al*, 1998; Sistig *et al*, 2002) although levels of total (CD3+) lymphocytes may be reduced (Sistig *et al*, 2002). There may be a reduced percentage of CD4+ (CD5+ 2H4T) 'virgin' T cells and an increased percentage of CD4+ (CD29+4B4+) 'memory' T lymphocytes (Pedersen *et al*, 1989). Patients with active RAS have an increased proportion of $\gamma\delta$ cells compared with healthy control subjects and RAS patients with inactive disease (Pedersen and Ryder, 1994). The $\gamma\delta$ T cells may play a role in antibody-dependent cell-mediated cytotoxicity (ADCC), however, the exact stimulus for the increased generation of $\gamma\delta$ T cells in RAS is unclear.

In contrast to peripheral blood there is a decrease in the number of mononuclear cells, including CD4+ and CD8+ T lymphocytes in the affected and non-affected oral mucosa of RAS patients (Hayrinen-Immonen *et al*, 1991). In the preulcerative phase of RAS there is a local mononuclear infiltrate consisting initially of large granular lymphocytes (LGL) and T4 (CD4+) helper-induced lymphocytes (Hayrinen-Immonen *et al*, 1991). The ulcerative phase is associated with the appearance of CD4+ cytotoxic suppressor cells, but these are replaced by CD4+ cells during healing (Savage *et al*, 1985). Polymorphnuclear lymphocytes (PMNL) also appear in the lesion (Figures 1, 2 and 3).

As noted above, there can be an increase in $\gamma\delta$ T cells, important in ADCC. *In vitro* studies have indicated that peripheral blood leucocytes of patients with RAS may demonstrate increased cytotoxicity towards oral mucosal epithelium (Lehner, 1967; Dolby, 1969; Rogers *et al*, 1974, 1976; Greenspan *et al*, 1981; Burnett and Wray, 1985) or sheep red blood cells (Sistig *et al*, 2002), and it is thus possible that RAS may represent an ADCC-type reaction to the oral mucosa. This concept is supported by the knowledge that peripheral blood mononuclear cells of patients with RAS (but no active disease) lyse oral mucosal cells expressing class I and II MHC antigens. More importantly peripheral blood CD4+ T cells from RAS patients can also cause epithelial lysis (Savage and Seymour, 1994). It is thus feasible that CD4+ and CD8+ T cell mediated cytotoxic reactions occur in RAS.

The aggregation of lymphocytes is likely to be mediated by the adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function-antigen-3 (LFA-3) binding to their counterpart ligands LFA-1 and CD-2 on lymphocytes (Hayrinen-Immonen *et al*, 1992; Verdickt *et al*, 1992). ICAM-1 is expressed on the submucosal capillaries and venules suggesting that it may control the trafficking of leucocytes into the submucosa (Savage *et al*, 1986; Eversole, 1994) while LFA-3 and its lingual counterpart CD-2 are likely to be involved in T-cell activation in RAS.

There is an elevation of serum levels of IL-6, IL-2R and soluble ICAM compared with controls, but these changes do not correlate with disease activity, and their pathogenic significance remains unclear (Yamamoto *et al*, 1994).

The HLA class I and II antigens appear on basal epithelial and then perilesional cells in all layers of the epithelium in the early phases of ulceration (Savage *et al*, 1986) presumably mediated by interferon gamma (IFN-γ) released by T-cells. Such MHC antigens may target these cells for attack by cytotoxic cells: indeed, activated mononuclear cells infiltrate the epithelium, especially the prickle cell layer (Honma, 1976) and are in contact with apoptotic prickle cells, which they and neutrophils sometimes phagocytose (Honma *et al*, 1985). Factor XIIIa – positive (FXIIIa+) cells are present in significantly greater numbers in RAS lesions than traumatic ulcers (Natah *et al*, 1997). The FXIIIa+ cells are present in the mononuclear – rich inflammation cell infiltrate and perivascular areas of the RAS lesions. As FXIIIa cells are considered to have antigen presenting functions these observations do suggest that the pathogenic trigger of RAS may indeed be some as yet unknown local factor. A local trigger for RAS may also be suggested by the increased number of activated mast cells in RAS as compared with traumatic ulcers (Natah *et al*, 1998).

Although there are cell-mediated immune changes within RAS, a B lymphocyte-mediated mechanism involving ADCC and, possibly, immune complexes have also been observed. Although circulating immune complexes have not reliably been demonstrated in RAS (Levinsky and Lehner, 1978; Lehner *et al*, 1979; Burton-Kee *et al*, 1981; Bagg *et al*, 1987), immune deposits do occur in lesional biopsy specimens (Ullman and Gorlin, 1978) especially in the stratum spinosum (Schroeder *et al*, 1984) and there can be evidence of leucocytoclastic or immune complex vasculitis (Lunderschmidt, 1982; Schroeder *et al*, 1984) leading to the non-specific deposition of immunoglobulins and complement.

Serum immunoglobulin (Ig) levels are generally normal although increases in serum IgA, IgG, IgD and IgE have all been reported in different groups of RAS patients (Lehner, 1969a,b; Ben Aryeh *et al*, 1976; Scully *et al*, 1983). Normal or reduced immunoglobulin levels have been observed in other groups of RAS patients. Serum levels of C9 have been reported to be raised in some patients (Adinolfi and Lehner, 1976; Lehner and Adinolfi, 1980) and, together with elevated serum levels of β_2 microglobulin, (Scully, 1982) may represent a non-specific acute phase response. IgG subclass deficiencies were not observed in one study of UK patients with quiescent RAS (Porter *et al*, 1992b), but a significant reduction in IgG_2 (important in bacterial immunity) was observed in a study of Spanish patients (Vicente *et al*, 1996). The IgG_2 subclass deficiency may predispose to infection by (an unknown) bacteria and the resultant immune response raises IgG_2 antibody levels. However, oral ulceration is not a common feature of patients with known IgG_2 subclass deficiency and is uncommon in selective IgA deficiency – where IgG_2 and IgG_4 can predispose to significant bacterial infection (Porter *et al*, 1992b). Salivary levels of total IgA are not abnormal in RAS (Lehner, 1969b; Bennet and Reade, 1982).

In the ulcerative phase of RAS salivary levels of IgG_{1-4} as well as IgA_1 and IgA_2 may increase, but levels of IgA_2, IgG_1, IgG_3 remain increased in the non-ulcerative phase of disease (Sistig *et al*, 2002). However, it remains unclear if such changes have any true bearing upon the pathogenesis of RAS. If local humoral immunity was to be of relevance to the development of RAS it would be expected that patients with xerostomia would develop RAS-like ulcers – but they do not.

Salivary prostaglandin E_2 and epidermal growth factor (that may potentially aid mucosal healing) are reportedly reduced in the early stages of ulceration of RAS and then rise in the healing phase (Wu-Wang *et al*, 1995). A stage-dependent fall in salivary levels of vascular endothelial growth factor (VEGF) was also observed in patients with major (but not minor) RAS (Brozovic *et al*, 2002). It remains to be determined however, if the fluctuation in these potentially tissue-healing agents is of any true significance to the pathogenesis of RAS. It would seem more likely that these changes are merely the normal homeostatic response to the tissue damage of RAS. Such a notion would also explain the increase in levels of circulatory vascular cell adhesion molecule-1 (VCAM-1) and E-selectin (Healy *et al*, 1997) in patients with RAS.

The role of NK cells seems doubtful in the pathogenesis of RAS. In RAS levels of peripheral blood NK cells may be increased (Thomas *et al*, 1990) or similar to those of control subjects and NK subsets (e.g. CD16+, CD56+ and CD14+) are not altered in RAS (Pedersen and Pedersen, 1993). Likewise the function of NK cells in RAS shows no consistent pattern, baseline NK cell function is not notably altered in RAS (Pedersen and Pedersen, 1993; Ueta *et al*, 1993), although may be reduced during exacerbation of major RAS, late ulcerative stage of minor RAS (Sun *et al*, 1991) or indeed during quiescent phases of disease (Sistig *et al*, 2002).

In contrast to Behcet's disease, peripheral blood neutrophils of patients with RAS do not have any enhanced *in vitro* chemotaxis (Dagalis *et al*, 1987). Phagocytosis by neutrophils has likewise been reported to be not significantly defective, though one recent study reported that peripheral blood neutrophil haemotaxis and phagocytosis may be reduced in the ulcerative phase of RAS, although ingestion may be enhanced during the non-ulcerative phase (Sistig *et al*, 2002).

It is thus evident, that although there is no unifying theory of the immunopathogenesis of RAS, it would seem that the ulceration is because of the cytotoxic action of lymphocytes and monocytes upon the oral epithelium, but the trigger for these responses remains unclear. Patients with RAS may be liable to uncontrolled or excessive release of locally active inflammatory mediators, perhaps in response to local trauma (Bazrafshani *et al*, 2002a). Levels of IL-2, IFN-γ and TNF-α mRNA are raised in lesional tissue of RAS (Buno *et al*, 1998), while levels of IL-10 mRNA were

reduced in the normal mucosa of RAS patients when compared with that of control subjects. Local levels of IFN-γ are higher in the mucosa of RAS patients as compared with suitable controls, and in contrast IL-10 levels remain low in the former but not the latter. Local production of TNF-α is higher in RAS lesions than traumatic ulcers (Natah *et al*, 2000) and unstimulated peripheral blood leucocytes of patients with RAS produce much greater amounts of TNF-α than healthy controls (Taylor *et al*, 1992).

Microbial aspects of RAS

A local microbial basis for RAS might explain why only the oral mucosa is affected in patients with RAS. However, as there is no evidence of clustering of affected patients (other than via vague family associations), an infectious basis for RAS seems unlikely.

Oral streptococci were previously suggested as important in the pathogenesis of RAS, either as direct pathogens or as antigenic stimuli in the genesis of antibodies that may conceivably cross-react with the oral mucosa (Martin *et al*, 1979; Lindemann *et al*, 1985). An L-form streptococcus isolated from RAS patients was initially typed as *S. sanguis* (Barile *et al*, 1963) (but later this was found to be *S. mitis* (Hoover and Greenspan, 1983). While some studies have disclosed elevated serum antibody titres to viridans streptococci among RAS patients, other investigations have yielded contradictory results (Barile *et al*, 1968; Donatsky, 1976). Furthermore, lymphocyte mitogenic responses to *S. sanguis* and *S. mitis* in RAS patients are not significantly different from those in control subjects (Barile *et al*, 1968; Gadol *et al*, 1985; Greenspan *et al*, 1985), although this may simply indicate that there is no predominant cell-mediated pathogenesis to RAS.

Cross-reactivity between a streptococcal 60–65 kDa hsp and the oral mucosa has been demonstrated and significantly elevated levels of serum antibodies to hsp have been detected in patients with RAS (Lehner *et al*, 1991). Lymphocytes of RAS patients have reactivity to peptide 91–105 (Hasan *et al*, 1995), and there is a significantly increased lymphoproliferative response to this peptide in the ulcerative stage as opposed to the period of remission. There is some cross-reactivity between the 65 kDa hsp and the 60 kDa human mitochondrial hsp. As monoclonal antibodies to part of the 65 kDa hsp of *Mycobacterium tuberculosis* react with *S. sanguis* (Lehner *et al*, 1991), it has been suggested that 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 (Hasan *et al*, 1995).

An association between RAS and *Helicobacter pylori* has also been suggested, but the evidence suggests such a link is unlikely. A study of 39 patients with both RAS and HIV disease found that 71.8% of samples of ulcers had polymerase chain reaction (PCR) evidence of local *H. pylori* carriage, and that 68.8% of the patients had circulating antibodies to *H. pylori* (Birek *et al*, 1999). In contrast no raised frequency of local carriage of *H. pylori* has been detected in four other studies of non-HIV infected individuals with RAS (Mravak-Stipetic *et al*, 1998; Pavelic *et al*, 2000; Shimoyama *et al*, 2000; Victoria *et al*, 2003) and no raised frequency of *H. pylori* seropositivity was observed in a study of patients from the UK (Porter *et al*, 1997).

It has been suggested that viruses may play a role in RAS (Hooks, 1978). An association with adenoviruses (Sallay *et al*, 1971, 1973, 1975) has been suggested, but these are ubiquitous organisms and the results need confirmation. The possible association of RAS with herpes viruses 1–6 has been reviewed (Pedersen, 1993). Herpes virus virions and antigens are not demonstrable in RAS (Dodd and Ruchman, 1950; Driscoll *et al*, 1961; Ship *et al*, 1961a; Griffin, 1963). RNA complimentary to herpes simplex virus (HSV) has been detected in circulating mononuclear cells (Eglin *et al*, 1982) and HSV-1 in circulating immune complexes (Hussain *et al*, 1986) in some RAS patients. However, serum levels of IFN-γ which tend to rise in viral infections, are not increased in RAS (Hooks *et al*, 1979). HSV has not been successfully isolated from lesional material (Donatsky *et al*, 1977; Rothe *et al*, 1978), only about a third of RAS patients are HSV seropositive (Ship *et al*, 1967), and HSV is rarely detected in lesional tissue by PCR (Studd *et al*, 1991).

IgM and IgG antibodies to VZV may be elevated in some RAS patients (Pedersen and Hornsleth, 1993) suggesting an association between reactivation of VZV and RAS. Furthermore VZV-DNA can be detected in lesional tissue by PCR (Pedersen *et al*, 1993), but contamination is possible and may underlie these observations (Pedersen *et al*, 1993). The evidence on the potential therapeutic benefits of aciclovir also requires further investigation (Wormser *et al*, 1988; Pedersen, 1992).

Antibodies to CMV may be significantly elevated in some RAS patients (Pedersen and Hornsleth, 1993) and CMV-DNA has been detected in ill-defined oral ulceration in non-HIV-infected persons (Leimola-Virtanen *et al*, 1995). Additional support for a link with CMV was suggested by the detection of elevated levels of circulating antibodies to CMV in patients with RAS (Sun *et al*, 1996). However, CMV was not detected more frequently in RAS when compared with the titres in some of the same group of patients (Sun *et al*, 1996). Two further studies did not report an increased local carriage of CMV (as detected by PCR) in patients with RAS (Ghodratnama *et al*, 1997; Brice *et al*, 2000). Human herpes virus 6 (HHV-6) and HHV-7 DNA have not been demonstrated in RAS, but HHV-8 DNA is present in HIV-related oral ulcers (Di Alberti *et al*, 1998). However, the detection of herpes viruses in oral lesions may well not be of clinical relevance as these viruses are commonly latent, and can often be detected in oral fluids of even healthy individuals.

There are thus no definitive data to support the notion of RAS having an infectious aetiology. A viral cause seems unlikely. Current evidence suggests that cross-reactivity between bacterial heat shock proteins and epithelial components may play a role.

Local factors predisposing to RAS

Local, physical trauma may initiate ulcers in susceptible people (Ross *et al*, 1958; Wray *et al*, 1981) and RAS are uncommon where mucosal keratinization is present (Sallay, 1968; Banoczy and Sallay, 1969) or in patients who smoke tobacco (Brookman, 1960; Dorsey, 1964; Chellemi *et al*, 1970; Shapiro *et al*, 1970; Axell and Henricsson, 1985a; Salonen *et al*, 1990). A recent study of 34 patients in Turkey with minor and/or major RAS found a significantly reduced frequency of tobacco smoking in individuals with RAS compared with an appropriate control group (8.8% *vs* 25.2% respectively) (Tuzun *et al*, 2000). In an effort to correct for any error caused by the self-reporting of patients about their tobacco habits, cotinine levels of 84 UK patients with RAS were compared with a group of 81 control subjects. The study found that the frequency of tobacco smokers was significantly less in RAS than control group. In addition, the mean cotinine levels of RAS patients who smoked, was significantly less than that of healthy control smokers (Atkin *et al*, 2002). Of course it may be that these individuals who did smoke may be less psychologically stressed than those did not smoke and thus some psychological trigger may be at play.

An increased frequency of recurrent oral ulceration because of use of SLS-containing toothpaste was previously reported, together with some reduction in ulceration following the use of SLS-free toothpaste. This supposed adverse effect of SLS does not reflect any increased oral retention of SLS (Fakhry-Smith *et al*, 1997). However, while another study also suggested that SLS-free dentifrice might reduce the number of ulcers that patients with RAS might develop (Chahine *et al*, 1997), a large double-blind study did not observe any significant change in the frequency or severity of RAS (Healy *et al*, 1999). In view of the widespread use of SLS in dentifrices it seems unlikely that this agent truly predisposes to, or causes, most RAS.

Systemic factors predisposing to RAS

Most patients with RAS appear otherwise well. Oral ulceration similar in clinical appearance to RAS can arise in a number of disorders in which the patient has other systemic problems (Table 1). These include Behcet's disease (Hoopen-Neumann *et al*, 1999; Krause *et al*, 1999; Whallett *et al*, 1999; Al-Otaibi *et al*, 2005); mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome (Orme *et al*, 1990; Le Thi *et al*, 1993); Sweet's syndrome (acute febrile neutrophilic dermatosis) (Delke *et al*, 1981; Driban and Alvarez, 1984; Mizoguchi *et al*, 1988; von den Driesch *et al*, 1989; Bruyn *et al*, 1990; von den Driesch, 1994; Femiano *et al*, 2003a, b); cyclic neutropenia (Lange and Jones, 1981; Scully *et al*, 1982; Sucker and Djawari, 1999; Lubitz *et al*, 2001), benign familial neutropenia (Porter *et al*, 1994); a periodic fever with aphthae, pharyngitis and adenitis (sometimes termed PFAPA syndrome) (Marshall *et al*, 1987; Feder, 2000; Kawashima *et al*, 2001) various nutritional deficiencies with or without underlying gastrointestinal disorders (Grattan and Scully, 1986; Eversole, 1994); and some other primary immunodeficiencies (Porter and Scully, 1993a–d) and secondary immunodeficiencies (Porter *et al*, 1994) including infection with HIV (MacPhail and Greenspan, 1997; Zakrzewska *et al*, 1997). Rarely, drugs such as NSAIDS can give rise to oral ulcers, similar to RAS, along with genital ulceration (Healy and Thornhill, 1995). Superficial ulceration similar to that of RAS can arise in response to nicorandil therapy (Cribier *et al*, 1998; Scully *et al*, 2001; Boulinguez *et al*, 2003). However, unlike RAS, this drug associated ulceration is not recurrent and resolves upon cessation of nicorandil therapy.

There is particular interest in the association between RAS and Behcet's disease. RAS-like ulceration can occur in Behcet's disease, however patients with the latter have multisystem disease, particularly affecting

Table 1 Some disorders with similar characteristics to recurrent aphthous stomatitis

Disease	*Comment*
Behcet's disease	RAS-like ulceration is a cardinal feature of Behcet's disease. The ulceration may be more severe, and more likely to comprise major and/or herpetiform ulcers from RAS. Patients with Behcet's disease also have recurrent genital ulceration, cutaneous disease (usually papulopustular lesions or erythema nodosum), ocular disease (typically posterior uveitis) and a range of other gastrointestinal, neurological, renal, joint and haematological abnormalities
MAGIC syndrome	Comprises major aphthae and generalized inflamed cartilage. A variant of Behcet's disease
Sweet's syndrome	Also termed acute neutrophilic dermatosis. Affected patients have superficial ulceration similar to RAS. In addition, there is sudden onset fever, leucocytosis and well demarcated cutaneous, plum-coloured papules or plaques. Usually arises in middle-aged females. In 50% of patients there is an associated malignancy (e.g. acute myeloid leukaemia)
PFAPA syndrome	Comprises periodic fever, aphthae like oral mucosal ulceration, pharyngitis and cervical adenitis. Although rare, PFAPA tends to occur in young children. Tends to be self-limiting, and non-recurrent. May respond to cimetidine (via suppression of T lymphocyte function)
Cyclic neutropenia	Cyclic reduction in circulating levels of neutrophils about every 21 days. Affected patients develop oral ulceration, fever, cutaneous abscesses, upper respiratory tract infections and lymphadenopathy. Other oral complications include severe gingivitis and aggressive periodontitis. Treated with recombinant granulocyte colony stimulating factor (rG-CSF). Other neutropenias (e.g. chronic neutropenia) can give rise to superficial oral mucosal ulceration without any significant periodicity
HIV disease	Aphthous-like ulceration may occasionally arise in HIV disease. However, it remains unclear, if there is a significantly raised frequency of recurrent idiopathic oral ulceration in HIV disease

other mucocutaneous surfaces, the eyes (e.g. uveitis), and musculoskeletal, neurological, haematological, gastrointestinal, and other systems. As detailed in this paper, RAS does not have a notable geographic distribution, has no HLA associations similar to those of Behcet's disease and has few of the immunological abnormalities that arise in Behcet's disease. Unlike Behcet's disease, RAS does not lead to significant morbidity nor mortality (Mittal *et al*, 1985; Schreiner and Jorizzo, 1987; Arbesfeld and Kurban, 1988; Jankowski *et al*, 1992; Stratigos *et al*, 1992).

Haematinic (iron, folic acid or vitamin B_{12}) deficiencies may be twice as common in some groups of patients with RAS as in healthy control subjects (Wray *et al*, 1975; Challacombe *et al*, 1977a, 1983; Hutcheon *et al*, 1978; Tyldesley, 1983; Rogers and Hutton, 1986; Field *et al*, 1987; Porter *et al*, 1988). About 20% of patients with RAS may have a haematinic deficiency, although one US study did not report any haematinic problem (Olson *et al*, 1982). A study of Japanese patients with RAS suggested that affected individuals may have reduced dietary intake of iron and vitamin B_1, which might underlie some of the aforementioned observations (Ogura *et al*, 2001). However, this investigation did not examine for correlations between dietary intake and haematological evidence of deficiency.

A novel study of Indian patients reported a correlation between high nitrate concentration of drinking water, resultant increased blood cytochrome b_5 reductase activity, and susceptibility to recurrent episodes of 'stomatitis' (presumed to be RAS) (Gupta *et al*, 1999). The rationale for these associations was that excess oxidation of NADH would predispose to oral mucosal inflammation (Courtois *et al*, 1994).

Deficiencies in vitamin B_1 (thiamine), B_2 and B_6 were observed in 28.2% of a group of patients with RAS from Scotland (Nolan *et al*, 1991), but the cause of the deficiencies was never established, and it is interesting to note, that this group of workers found vitamin B complex deficiencies in other patients with quite disparate clinical disease. Low levels of thiamine were observed in substantial number of adult patients from Israel with RAS (Haisraeli-Shalish *et al*, 1996). The reasons why thiamine deficiency could cause RAS are not known.

Reduced iron storage is the most commonly reported relevant abnormality, arising in up to 37% of reported patient groups (Porter *et al*, 1988, 1993) and can affect children (Field *et al*, 1987) as well as adults. Vitamin B_{12} deficiency has been observed in 1– 6% of adults or children with RAS (Field *et al*, 1987; Porter *et al*, 1988, 1993; Barnadas *et al*, 1997; Weusten and van de Weil, 1998) in developed countries, but a more recent study observed low serum vitamin B_{12} levels in about 23% of a group of teenagers and adults with RAS (Piskin *et al*, 2002). The reasons for such a high frequency of vitamin B_{12} deficiency in this group of patients were not established.

The present evidence thus suggests that some patients with RAS may have deficiency of one or more haematinics, or occasionally an unrelated vitamin. That these deficiencies are truly important in the pathogenesis of RAS however, seems doubtful, as current data suggest that iron or vitamin supplement significantly only infrequently produce resolution of RAS (Nolan *et al*, 1991; Porter *et al*, 1992a; Haisraeli-Shalish *et al*, 1996).

Oral ulceration akin to RAS can be a feature of gluten sensitive enteropathy (GSE; coeliac disease) but only 5% of outpatients who initially present with RAS (Ferguson *et al*, 1976, 1980; Veloso and Saleiro, 1987; Nolan *et al*, 1991) have GSE. Folate deficiency can occur in RAS and reticulin antibodies (Ferguson *et al*, 1980) including IgA class reticulin antibodies (Merchant *et al*, 1986) and/or antigliadin antibodies (O'Mahony *et al*, 1985) are occasionally detected in patients with RAS. The haplotype of HLA-DRw10 and DQw1 has been suggested to predispose patients with GSE to RAS (Majorana *et al*, 1992; Meini *et al*, 1993), but this haplotype is not similar to the suggested HLA associations of RAS (see above). There may also be occasional patients who have RAS with no detectable clinical or histological evidence of coeliac disease on jejunal biopsy, yet who may respond to dietary withdrawal of gluten (Wray, 1981; Wright *et al*, 1986). However, the withdrawal of gluten does not often result in significant benefit (Hunter *et al*, 1993), may be difficult for the patient to comply with and may simply reflect the pronounced placebo response in RAS.

Hypersensitivity reactions to other identifiable exogenous antigens appear not to have a significant aetiological role in RAS. There is no consistent association with atopy (Tuft and Ettleson, 1956; Spouge and Diamond, 1963; Wilson, 1980; Eversole *et al*, 1982; Wray *et al*, 1982; Hay and Reade, 1984). Some RAS patients correlate the onset of ulcers with exposure to certain foods, but controlled studies have failed to disclose a causal role (Wilson, 1980) and dietary manipulation rarely produces clinical improvement (Spouge and Diamond, 1963; Eversole *et al*, 1982; Hay and Reade, 1984).

Aphthous-like ulceration can be a feature both of Crohn's disease (Rehberger *et al*, 1998; Hegarty *et al*, 2003) and ulcerative colitis (Thornhill *et al*, 1992) but this ulceration may reflect associated haematinic deficiencies.

It is unlikely that an association between RAS and zinc deficiency exists, although one reported patient with RAS and zinc deficiency did have clinical benefit from zinc supplementation (Endre, 1991).

A minority of women with RAS have cyclical oral ulceration related to the luteal phase of the menstrual cycle, presumed progestogen driven defective oral mucosal epithelial turnover (Dolby, 1968; Segal *et al*, 1974; Ferguson *et al*, 1984). However, a detailed review of relevant data did not find any association between RAS and altered female sex corticosteroids (McCartan and Sullivan, 1992). It is of course possible, that occasional patients with RAS-like disease may have autoimmune progesterone dermatitis (Moghadam *et al*, 1998).

Psychological illness has been suggested to initiate some episodes of RAS (Ship *et al*, 1961b; Miller and Ship, 1977) but there has never been an appropriate study to

examine this possible link. A study of Irish patients with RAS, using the hospital anxiety and depression (HAD) scale, observed an increased level of anxiety (and increased salivary cortisol levels) in some patients (McCartan *et al*, 1996). There are sparse data to suggest that antidepressant therapy may lessen symptoms of RAS (Yaacob and Ab, 1985). Nevertheless, no significant objective measure of neurosis has been observed in patients with RAS (Pedersen, 1989; Buajeeb *et al*, 1990).

Clinical features

RAS comprises recurrent bouts of one or several rounded, shallow, painful ulcers at intervals of a few months to a few days. RAS has three main presentations – minor (MiRAS), major (MaRAS) or herpetiform (HU) ulcers.

The MiRAS is the most common (Field *et al*, 1992), affecting about 80% of patients with RAS: ulcers are round or oval usually < 5 mm in diameter with a grey-white pseudomembrane and an erythematous halo (Figure 4). MiRAS usually occur on the labial and buccal mucosa and floor of mouth, but are uncommon on the gingiva, palate or dorsum of the tongue. The ulcers heal within 10–14 days without scarring.

Major RAS is a rare, severe form of RAS, sometimes termed periadenitis mucosa necrotica recurrens (Figure 5). These ulcers are oval and may exceed 1 cm in diameter and have a predilection for the lips, soft palate and fauces. The ulcers persist for up to 6 weeks and often heal with scarring. MaRAS usually has its onset after puberty and is chronic, persisting for up to 20 or more years (Scully and Porter, 1989).

Herpetiform ulceration is the least common variety and is characterized by multiple recurrent crops of widespread small, painful ulcers. As many as 100 ulcers may be present at a given time, each measuring 2–3 mm in diameter (Figure 6), although they tend to fuse producing large irregular ulcers. HU may have a predisposition for women and have a later age of onset than other types of RAS (Lehner, 1977; Scully and Porter, 1989).

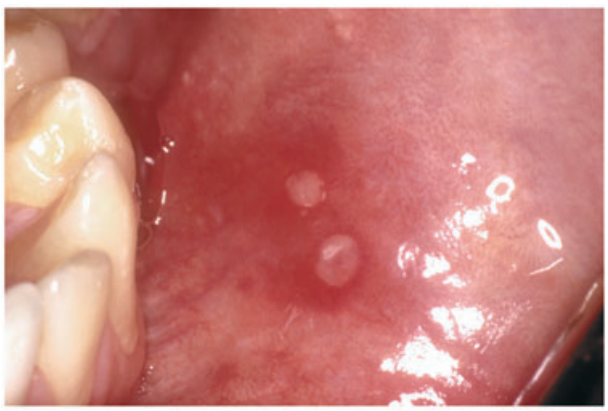

Figure 4 Typical minor aphthae (buccal mucosa, 22-year-old male)

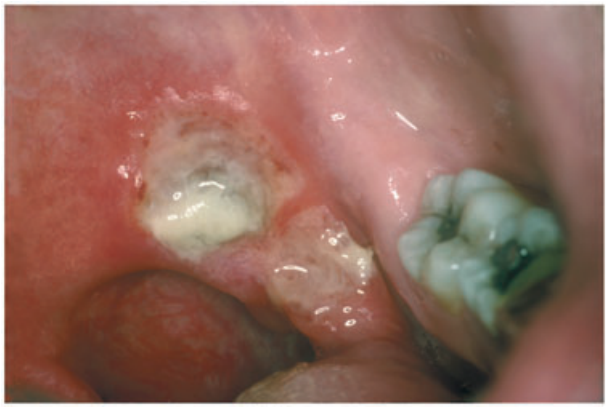

Figure 5 Major aphthae (soft palate and fauces, 32-year-old male)

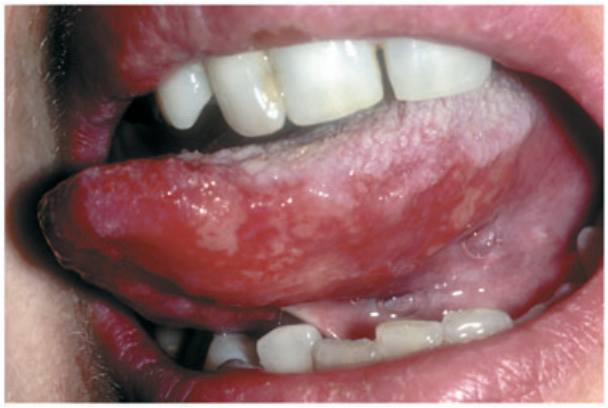

Figure 6 Herpetiform ulcers (tongue, 42-years-old female)

Management

The diagnosis of RAS is invariably based upon the history and clinical findings. It is essential however to always consider a possible systemic cause, especially when adult patients suddenly develop what appears to be RAS. It is common practice to assess the full blood cell count, red cell folate and serum levels of ferritin (or equivalents) and vitamin B_{12} (Porter *et al*, 1993). These investigations may also reveal potential gastrointestinal causes of oral ulceration but, in the absence of other manifestations, screening of patients with RAS for GSE is usually fruitless (Sedghizadeh *et al*, 2002).

There are currently few agents that have been found in randomized controlled trials (RCTs) to be clinically effective in the management of RAS. Nevertheless there is a need to provide patients with treatment to lessen the severity and/or frequency the associated painful symptoms, and reduce the likelihood of associated tissue damage. A wide variety of different agents have been suggested for the treatment of RAS (Table 2) (Porter and Scully, 2005). A consensus approach to the management of RAS was recently published (Scully *et al*, 2003). There is no curative treatment available. The best that can be achieved is to suppress the local immune

Table 2 Some reported therapies for recurrent aphthous stomatitis (RAS)

Local physical treatment	Surgical removal
	Debridement
	Laser ablation
	Low dense ultrasound
	Chemical cautery (e.g. silver nitrate sticks)
	Physical barriers (e.g. cyanoacrylate adhesives)
Antimicrobials	Chlorhexidine gluconate (mouthrinse)
	Triclosan (mouthrinse)
	Topical tetracyclines (e.g. aureomycin, chlortetracycline, tetracycline)
Topical corticosteroids	Hydrocortisone hemisuccinate (pellets)
	Triamcinolone acetonide (in adhesive paste)
	Flucinonide (cream)
	Betamethasone valerate (mouthrinse)
	Betamethasone-17-benzoate (mouthrinse)
	Betamethasone-17-valerate (mouthrinse)
	Flumethasone pivolate (spray)
	Beclomethasone diproprionate (spray)
	Clobetasol proprionate (cream)
	Mometasone furoate (cream)
Topical analgesics	Benzydamine hydrochloride (spray or mouthrinse)
	Topical anaesthetics (gel)
Other topical anti-inflammatory agents	Amlexanox
	Sodium cromoglycate (lozenges)
	Carbenoxolone sodium mouthrinse
	Azalestine
	Human alpha-2-interferon (cream)
	Ciclosporin (mouthrinse)
	Deglycirrhizinated liquorice
	Topical 5-aminosalicylic acid
	Prostaglandin E2 (gel)
	Topical granulocyte-macrophage colony-stimulating factor
	Aspirin mouthrinse
	Diclofenac in hyaluronase
	Sucralfate
Systemic immunosuppression	Prednisolone
	Azathioprine
	Levamisole
	Colchicine
	Thalidomide
	Pentoxifylline
	Dapsone
	Cimetidine

response, to ease discomfort and to prevent secondary infection. Presently topical corticosteroids, or topical chlorhexidine, or topical amlexanox if used with care, may be advantageous and systemic steroids or thalidomide would seem to be of possible clinical benefit in recalcitrant cases.

Topical corticosteroids

Topical corticosteroids are the mainstay of RAS treatment in most countries (Siegel, 1999), but there are few well-controlled studies. There is only one systematic review of aspects of therapy of RAS (Porter and Scully, 2005), showing topical corticosteroids to be the most frequent means of treating RAS, although the available data do not demonstrate consistent benefits.

The corticosteroids vary in their degree of potency and may be given as mouth rinses, ointments, creams or in adhesive vehicles. Several different topical corticosteroids may reduce symptoms and hasten healing of RAS (Cooke and Armitage, 1960; Zegarelli *et al*, 1960; Merchant *et al*, 1978; Yeoman *et al*, 1978; Fisher, 1979; Pimlott and Walker, 1983; Scaglione *et al*, 1985; Miles *et al*, 1993). The major concern of possible adrenal suppression with long-term and/or repeated application has rarely been addressed, although there is evidence that even some of the more potent, such 0.05% fluocinonide in adhesive paste and betamethasone-17-valerate mouth rinse do not cause this problem (Porter *et al*, 2000).

Cyclodextrin-based corticosteroid mouthrinses may be useful as corticosteroids are better released from the cyclodextrin preparations than from carboxymethylcellulose-based pastes (Holbrook *et al*, 1998). Topical clobetasol proprionate 0.05% in an adhesive denture paste seems to be even more effective and does not cause adverse effects (Lo *et al*, 2001), however, some authors disagree (Gonzales-Moles *et al*, 2002). A 0.1% solution of mometasone furoate has been suggested as an effective treatment of RAS (Teixeira *et al*, 1999). However, corticosteroids applied topically do not stop the recurrence of RAS.

Other topical anti-inflammatory agents

Benzydamine
Benzydamine hydrochloride mouthwash may provide transient relief of painful symptoms but does not aid ulcer healing (Matthews *et al*, 1987) and is the only 'over the counter' topical agent (Edres *et al*, 1997) to have been formally assessed.

Amlexanox
Amlexanox has been suggested to be of some benefit in the treatment of RAS. Amlexanox has anti-allergic and anti-inflammatory activities, but its exact mode of action in the treatment of RAS remains unknown (Khandwala *et al*, 1997). One RCT of 335 patients with RAS in the US reported that 5% amlexanox significantly reduced the pain and time of healing. Other open studies have also suggested that amlexanox may result in some improvement in the signs and symptoms (Greer *et al*, 1993; Binnie *et al*, 1997; Khandwala *et al*, 1997).

Cromoglycate
Lozenges of the anti-allergic sodium cromoglycate may provide mild symptomatic relief (Dolby and Walker, 1975; Kowolik *et al*, 1978), but cromoglycate-containing toothpaste is not of benefit (Potts *et al*, 1984). In one double blind study carbenoxolone sodium mouthwash reduced the severity of RAS (Poswillo and Partridge, 1984).

Others
Topical non-corticosteroid based immunomodulatory agents which have been suggested to be of some benefit in the management of RAS include azelastine (Ueta

et al, 1994), human alpha-2-interferon in cream (Hamuryudan *et al*, 1990, 1991), topical ciclosporin (Eisen and Ellis, 1990), deglycirrhizinated liquorice (Das *et al*, 1989), topical 5-aminosalicylic acid (5-ASA; (Collier *et al*, 1992), prostaglandin E2 (PGE2) gel (Taylor *et al*, 1993) and topical granulocyte-macrophage colony-stimulating factor (at least in HIV disease) (Herranz *et al*, 2000). However, few of these agents have been subjected to detailed clinical evaluation. Despite the knowledge that non-steroidal anti-inflammatory agents can cause oral ulceration, one study suggests that aspirin mouth rinse may reduce the pain of RAS (Angirish, 1996). A more detailed RTC observed that diclofenac in hyaluronase reduced the pain associated with RAS; indeed this preparation was more effective than lidocaine (Saxen *et al*, 1997).

In a double-blind study sucralfate mouth rinse was found to reduce the duration of pain and healing time of RAS (Ricer, 1989). A recent study of Italian patients suggested that 20% sucralfate is of some benefit in reducing the symptoms of RAS (Campisi *et al*, 1997).

A gel of silicone dioxide, aloe and allantoin – suggested to be useful in aiding wound healing – failed to significantly influence the clinical course of RAS (Garnick *et al*, 1998).

Systemic immunomodulation

Patients with especially frequent or severe RAS may require systemic immunosuppressive therapy.

Corticosteroids

Prednisolone (Stanley, 1973) and/or azathioprine (Brown and Bottomley, 1990) can help healing of large ulcers but their long-term use should be avoided as the risk of their many associated adverse systemic side-effects will usually outweigh any clinical benefit.

Anti-TNF agents

As TNF-α may be implicated in the pathogenesis of RAS (see above), it might be expected that anti-TNF-α agents could be beneficial in the treatment of RAS.

Results of limited open studies from two centres suggested that the anti-TNF-α agent pentoxifylline (400 mg three times daily) significantly reduced the number of RAS for up to 9 months after 1 month of therapy (Pizarro *et al*, 1995, 1996; Wahba-Yahav, 1995a,b). Nevertheless, this interesting carry-over effect was not confirmed in a more recent study (Chandrasekhar *et al*, 1999) and furthermore, about 10% of treated patients had some degree of gastrointestinal upset. Thalidomide is effective and is proven to be the most reliably effective agent for the management of RAS, producing remission in almost 50% (Revuz *et al*, 1990). Thalidomide probably acts by virtue of its anti-TNF-α actions but, in one study, the reduction in blood TNF-α levels did not correlate with ulcer healing (Jacobson *et al*, 1997), suggesting that thalidomide could also be acting via its action upon Th_1/Th_2 immune response and /or its anti-angiogenic properties (Porter and Jorge, 2002). Open and double-blind studies on patients with HIV-related oral ulceration (Nicolau and West, 1990; Paterson *et al*, 1995), and non-HIV-related RAS (de Wazieres *et al*, 1999), and several case studies, confirm that thalidomide (e.g. 50–100 mg daily) is of clinical benefit (Mascaro *et al*, 1979; Grinspan, 1985; Grinspan *et al*, 1989). Nevertheless, its adverse effects seriously limit its application to short-term use. The main concern is the real risk of teratogenicity (just one tablet taken about day 20 of pregnancy can cause phocomelia) (Porter and Jorge, 2002), particularly as most females with RAS are of childbearing age. Polyneuropathy – typically a peripheral neuropathy, is an unpredictable but significant adverse effect of long-term thalidomide treatment, necessitating regular assessment of sensory nerve action potentials (SNAPs) (Porter and Jorge, 2002). Recently the risk of polyneuropathy has been shown to be minimal at doses below 25 mg day^{-1} (Bastuji-Garin *et al*, 2002). Somnolence is common but can be reduced by dosing prior to sleep.

Levamisole

In the 1970s there was considerable interest in the possible benefits of levamisole in the management of RAS (Sun *et al*, 1994). The exact mode of action of levamisole remains unclear but the current data do not suggest this agent to be the clinical panacea once suggested. Five RCTs did not report a significant benefit with levamisole while four suggested that this agent might decrease the duration, number, size and frequency of ulceration of RAS. However the benefit, while statistically significant, was not likely to be of clinical significance, and the associated adverse effects (nausea, hyperosmia, dysgeusia and agranulocytosis) discourage its use (Lehner *et al*, 1976; Meyer *et al*, 1977; Drinnan and Fischman, 1978; Gier *et al*, 1978; Kaplan *et al*, 1978; Miller *et al*, 1978; Olson and Silverman, 1978). Levamisole combined with Chinese medical herbs has produced a decrease in the frequency, duration and number of oral ulcers (Sun *et al*, 2003).

Colchicine

Results of one open study and several smaller investigations suggested that colchicine may be of some clinical benefit in the management of RAS, causing a significant reduction in pain scores and frequency of self-reported ulcers (Gatot and Tovi, 1984; Ruah *et al*, 1988). It was suggested that colchicine shortens the recovery period of RAS by reducing neutrophil phagocytic function (Altinor *et al*, 2003). Unfortunately, not all patients benefit from colchicine, and at least 20% can have painful gastrointestinal symptoms or diarrhoea (Katz *et al*, 1994) and long-term use can induce infertility in young males. Combined colchicine and thalidomide therapy has been suggested to be of occasional benefit in the treatment of recalcitrant RAS (Genvo *et al*, 1984), although long-term therapy might be expected to give rise to clinically significant adverse side-effects.

Others
Dapsone (Handfield-Jones *et al*, 1985), transfer factor (Schulkind *et al*, 1984), sulodexide (Femiano *et al*, 2003a,b) and gammaglobulin therapy (Kaloyannides, 1971) have been suggested to be beneficial but more detailed studies are needed to confirm this preliminary observation. Cimetidine has been suggested to be useful (Feder, 1992), (presumably via some suppression of T-cell function) but there is little supportive evidence.

Antimicrobials

Chlorhexidine
Despite there being no evidence that RAS is caused by any bacterial infection there are good data to indicate that some topical antimicrobials (particularly chlorhexidine gluconate) will lessen the duration of ulceration of RAS. Several RCTs have established that chlorhexidine either as a 0.2% w/w mouth rinse or a 1% gel can reduce the duration of ulcers and increase the number of ulcer-free days (Addy *et al*, 1974, 1976; Addy, 1977; Hunter and Addy, 1987) in patients with RAS. However, one study found little objective benefit of chlorhexidine mouth rinse over placebo (Matthews *et al*, 1987).

Tetracyclines
Placebo-controlled studies of topical tetracyclines (e.g. aureomycin, chlortetracycline and tetracycline) suggest that these may also reduce healing times and/or reduce the associated pain of RAS (Guggenheimer *et al*, 1968; Graykowski and Kingman, 1978; Denman and Schiff, 1979; Hayrinen-Immonen *et al*, 1994). An open study indicated that the local application of doxymycin under cyanoacrylate caused rapid healing of the ulceration of RAS (Ylikontiola *et al*, 1997). However this approach is of limited clinical application (dental professionals or patients have to apply the agent to the lesions) (Ludlow *et al*, 2000; Kutcher *et al*, 2001) and the other agents may cause dysgeusia, oral candidosis and a burning-like sensation of the pharynx, and/or are not suitable for young children who might ingest the antibiotic leading to later dental staining. One placebo-controlled study of 25 patients with RAS suggested that the oxygenating agent carbamide peroxide in glycerol was not effective in the treatment of RAS (Miller and Chilton, 1980). In a study by Skaare *et al* (1996a) triclosan-containing mouthrinse was found to significantly reduce the number of ulcers, relief pain and shorten the ulcerative phase. It has been suggested that triclosan has not only antimicrobial, but also anti-inflammatory and analgesic effects (Kjaerheim *et al*, 1995).

Other agents

Monoamine oxidase inhibitor (antidepressant) therapy in the treatment of three patients with RAS produced benefit (Rosenthal, 1984; Lejonc and Fourestie, 1985) but this may have been because of accompanying dietary modifications rather than any alteration in psychological status. The lack of association between significant mental illness and RAS suggests that therapeutic approaches of this type are likely to be fruitless.

There are reports that systemic zinc sulphate (Orbak *et al*, 2003), irsogladine maleate (Hara *et al*, 1999), *Eupatorium laevigatum* (Paulo *et al*, 2000) paste and photophoresis of oxolin ointment (Prikuls, 2000) may be of benefit in the treatment of RAS, but any real benefit from these agents is unclear.

Physical treatment

A range of physical methods of locally managing RAS have been proposed for the treatment of RAS, but most are impractical. Suggested physical therapies have included surgical removal, debridement or laser ablation of ulcers (Potoky, 1981; Howell *et al*, 1988; Convissar and Massoumi-Sourey, 1992), low dense ultrasound (Brice, 1997) chemical cautery (Debacterol) (Rhodus and Bereuter, 1998) and the use of physical barriers such as cyanoacrylate adhesives (Yel *et al*, 1994).

Conclusion

Although common, RAS remains an elusive disorder, as the precise aetiology and long-term behaviour of disease are ill understood. No therapies are available to stop the bouts of ulceration and not give rise to adverse side-effects. The management of RAS is thus presently directed towards lessening physical trauma to the oral mucosa, and reducing the inflammatory response.

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