The diagnosis and management of recurrent aphthous stomatitis

A consensus approach

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ABSTRACT

Background. Recurrent aphthous stomatitis, or RAS, is a common oral disorder of uncertain etiopathogenesis for which symptomatic therapy only is available. This article reviews the current data on the etiopathogenesis, diagnosis and management of RAS in a primary care setting.

Methods. The authors reviewed publications on Medline from 1995 through 2000, the period since the last major reviews were published.

Results. RAS may have an immunogenetic background owing to cross-reactivity with *Streptococcus sanguis* or heat shock protein. Predisposing factors seen in a minority include haematinic (iron, folate or vitamin B12) deficiency, stress, food allergies and HIV infection. While topical corticosteroids remain the mainstay for therapy, a number of other immunomodulatory modalities now are available.

Conclusions. There is still no conclusive evidence relevant to the etiopathogenesis of RAS, and therefore therapy can attempt only to suppress symptoms rather than to address the basic issues of susceptibility and prevention.

Clinical Implications. In the majority of patients, symptomatic relief of RAS can be achieved with topical corticosteroids alone, with other immunomodulatory topical agents or by combination therapy.

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Recurrent aphthous stomatitis, or RAS, is a common condition in which recurring ovoid or round ulcers affect the oral mucosa. It is one of the most painful oral mucosal inflammatory ulcerative conditions and can cause pain on eating, swallowing and speaking.[1] This article is based on the outcome of a consensus conference between the American Academy of Oral Medicine and the European Association of Oral Medicine, held in Montreal, Canada, in 2001, and summarizes the current data on the etiopathogenesis, diagnosis and management in a primary dental care setting.

There is no conclusive evidence regarding the etiopathogenesis of recurrent aphthous stomatitis, so therapy can attempt only to suppress symptoms.

CLINICAL FEATURES OF RAS

The onset of RAS usually is during childhood, with a tendency for ulcers to diminish in frequency and severity with age.[2] In about 80 percent of patients with RAS, the condition develops before 30 years of age; onset in later years suggests a possibility of definable predisposing factors leading to RAS or that the ulceration is not simple RAS, but rather a part of a more complex disorder such as Behcet's syndrome.

A prodrome of localized burning or pain for 24 to 48 hours can precede the ulcers. The lesions are painful, clearly defined, shallow, round or oval, with a shallow necrotic center covered with a yellow-grayish pseudomembrane and surrounded by raised margins and erythematous haloes. The pain lasts for three to four days, at which point early epithelialization can occur.

Clinical presentations of RAS. RAS has three clinical presentations (Table 1).

Minor aphthae. Minor aphthae (also called Mikulicz's aphthae or mild aphthous ulcers) account for 75 to 85 percent of all cases of RAS.[2] Minor aphthae can involve

every nonkeratinized mucosa of the oral cavity (usually the labial and buccal mucosae, the floor of the mouth and the ventral or lateral surface of the tongue), are smaller than 8 to 10 millimeters and tend to heal within 10 to 14 days without scarring (Figure 1). Minor aphthae heal more slowly than do other oral wounds; an intensive lymphocytic infiltrate may play a role in this.[3]

TABLE 1

CHARACTERISTICS OF THE CLINICAL PRESENTATIONS OF RECURRENT APHTHOUS STOMATITIS.

CHARACTERISTIC	TYPE OF PRESENTATION		
	Minor Aphthae	Major Aphthae	Herpetiform Ulcers
Size (Millimeters)	5-10	> 10	< 5
Duration (Days)	10-14	> two weeks	10-14
Scarring	No	Yes	No
Percentage of All Aphthae	75-85	10-15	5-10

Major aphthae. Major aphthae (sometimes referred to as periadenitis mucosa necrotica recurrens or Sutton's disease) tend to involve mucosa overlying minor salivary glands. Approximately 10 to 15 percent of RAS cases are major aphthae.[2] Usually appearing after puberty, they are round or ovoid with clearly defined margins. The prodromal symptoms are more intense than those of minor aphthae, and the ulcers usually are deeper and larger and last significantly longer than do minor aphthae. They have a raised irregular border and frequently exceed 1 centimeter in diameter, are painful and tend to appear on the lips, soft palate and throat (Figures 2 and 3). They can last for weeks or months and often leave a scar after healing. Fever, dysphagia and malaise sometimes can occur early in the disease process.[2]

Figure 1. Minor aphthous ulceration.

Herpetiform ulcers. Constituting only 5 to 10 percent of all RAS cases, herpetiform ulcers are rare.[2] Multiple (five to 100) 1- to 3-mm crops of small, rounded, painful ulcers resembling ulcers of herpes simplex are seen anywhere on the mucosa. They tend to fuse and produce much larger ulcers lasting 10 to 14 days.[2] These ulcers tend to appear in women and generally have a later age onset than the other types of RAS.[4]

Most patients have only one to three ulcers, and some have recurrences only two to four times each year (simple aphthosis). Others may have almost continuous disease activity with new lesions developing as older lesions heal, or may have ulcers associated with systemic diseases (complex aphthosis).[2]

Figure 2. Major aphthous ulceration.

ETIOPATHOGENESIS

Family history. There often is a genetic basis for RAS. More than 42 percent of patients with RAS

Figure 3. Herpetiform ulceration.

BOX 1

FACTORS CONTRIBUTING TO RECURRENT APHTHOUS STOMATITIS.

- Trauma
- Stress
- Foods
- Hormonal Imbalance
- Tobacco Smoking

have first-degree relatives with RAS.[5] The likelihood of RAS is 90 percent when both parents are affected, but only 20 percent when neither parent has RAS.[6] It also is likely to be more severe and to start at an earlier age in patients with a positive family history than in those without.[7]

Immunopathogenesis. The pathogenesis of RAS involves a predominantly cell-mediated immune response in which tumor necrosis factor α, or TNF α, plays a major role. A mononuclear (lymphocytic) cell infiltrate in the epithelium in the preulcerative stage is followed by a localized papular swelling due to keratinocyte vacuolation surrounded by a reactive erythematous halo representing vasculitis. The painful papule then ulcerates and a fibrinous membrane covers the ulcer, which is infiltrated mainly by neutrophils, lymphocytes and plasma cells. Finally, there is healing with epithelial regeneration. The immunopathogenesis probably involves cell-mediated responses, involving T cells and TNF-α production by these and other leukocytes (macrophages and mast cells).[8] TNF-α induces inflammation by its effect on endothelial cell adhesion and neutrophil chemotaxis.[8] RAS can be prevented by thalidomide[9] and pentoxifylline,[8] which prevent the synthesis of TNF-α, and these agents now have been introduced into oral medicine specialist practice to control RAS. Other cytokines such as interleukin, or IL, -2[10]; IL-10[11]; and natural killer, or NK, cells activated by IL-2 play a role in RAS.[12]

PREDISPOSING FACTORS

Classic RAS is a localized condition representing a relatively simple disease, although a minority of patients may be predisposed to it by systemic conditions or diseases. The etiology probably is multifactorial, with various predisposing factors and immunological changes provoked by a range of factors (Box 1).

Trauma. Trauma may provoke ulcers in patients with RAS.

Stress. Stress can provoke episodes of RAS, but the association is not invariable.[13]

Foods. Foods such as chocolate, coffee, peanuts, cereals, almonds, strawberries, cheese, tomatoes (even the skin of the tomatoes) and wheat flour (containing gluten) may be implicated in some patients.[14,15] In one study of patients with RAS who previously were diagnosed in patch tests as reactive to agents such as benzoic acid and/or cinnamaldehyde, 50 percent showed clinical improvement when certain foods were excluded from the diet.[16]

Hormonal imbalance. There are a few patients whose RAS remits with oral contraceptives or during pregnancy.[17]

Tobacco smoking. Patients suffering from RAS usually are nonsmokers,[18] and there is a lower prevalence and severity of RAS among heavy smokers as opposed to moderate smokers.[19] Some patients report an onset of RAS after smoking cessation,[20] while others report control on reinitiation of smoking.[20] The use of smokeless tobacco also is associated with a significantly lower prevalence of RAS.[21] Nicotine-containing tablets also appear to control the frequency of RAS.[22]

CONDITIONS THAT MAY MIMIC CLASSIC APHTHAE

Aphthaelike ulcers—usually in adult-onset RAS rather than childhood-onset—may be seen in association with exposure to certain drugs or with some immune or other defects (Box 2).

Exposure to certain drugs. Nicorandil (a

BOX 2

CONDITIONS THAT MAY MIMIC CLASSIC APHTHAE.

- Immune Disturbances
- Hematinic Deficiency States
- Gastrointestinal Diseases
- Behcet's Syndrome
- Periodic Fever, Aphthae, Pharyngitis and Adenitis Syndrome
- Sweet's Syndrome

potassium channel blocker used in cardiac disease),[23,24] nonsteroidal anti-inflammatory drugs[25] and some other drugs[26] may produce aphthaelike ulcers, but the onset typically is in older people and related temporally to the drug use, which differentiates them from true aphthae.

Immune disturbances. Large aphthouslike ulcers may be seen where CD4 T lymphocyte counts are lower than 100 cells per milliliter,[27] in HIV-positive patients[28] and in non–HIV-infected patients with other immunodeficiencies,[29] myelodysplastic syndromes,[30] benign neutropenia[31] and other forms of neutropenia such as cyclical neutropenia.[32]

Hematinic deficiency states. Though some studies deny an etiologic relationship between RAS and deficiencies of folic acid or iron,[33] deficiencies of vitamin B_1, B_2, B_6 or B_{12}, folic acid or iron have been found in 18 to 28 percent of cases of classical RAS compared with about 8 percent in healthy people.[34,16] Replacement of the deficiency improves RAS in some patients.[35]

Gastrointestinal diseases. Celiac disease, or gluten-sensitive enteropathy, is seen in more than 4 percent of patients whose initial presentation was classical RAS,[36] and RAS in patients with celiac disease remits completely on a gluten-free diet. One uncontrolled study reported that dietary gluten withdrawal produced a favorable response in patients with RAS without celiac disease,[37] but another study conducted on these otherwise healthy RAS patients showed no significant response to gluten withdrawal above that with placebo.[38] Crohn's disease and ulcerative colitis also may occasionally be accompanied by RAS or other mouth ulcers.[39]

Behcet's syndrome. Behcet's syndrome manifests with classical RAS and a range of systemic complications, notably affecting the eyes, joints, neurological system and skin.[40]

Periodic fever, aphthae, pharyngitis and adenitis syndrome. Periodic fever, aphthae, pharyngitis and adenitis, or PFAPA, syndrome is a syndrome occasionally seen in young children who have classical RAS.[41]

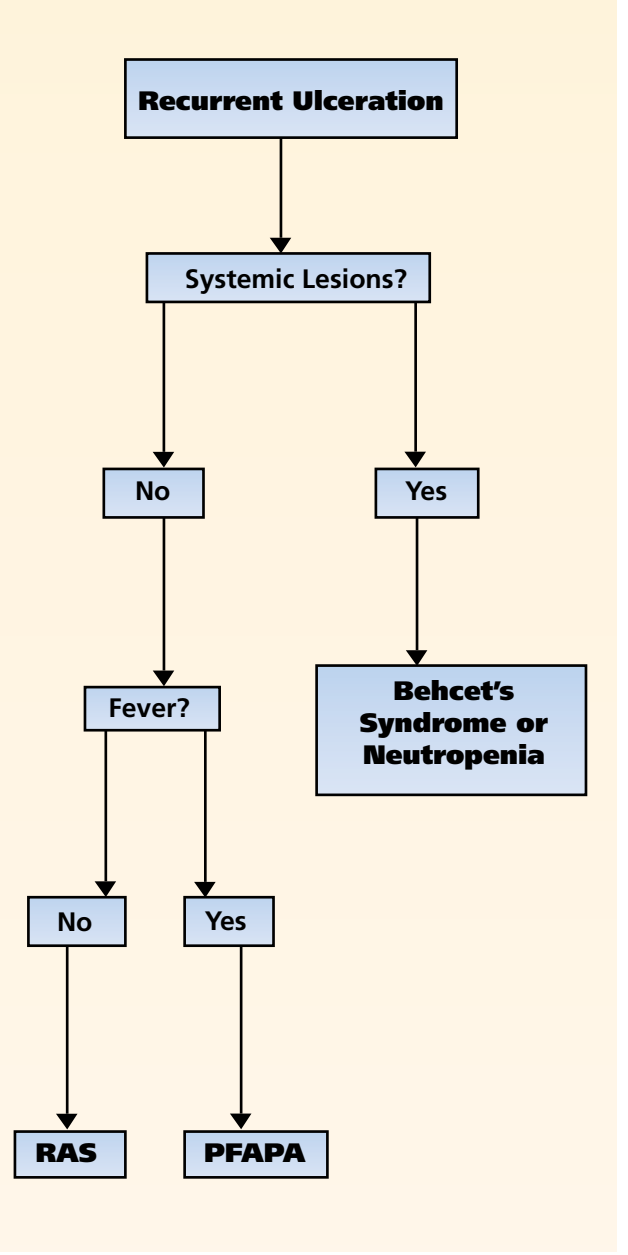

Figure 4. Differentiation of causes of oral ulceration. RAS: Recurrent aphthous stomatitis. PFAPA: Periodic fever, aphthae, pharyngitis and adenitis syndrome.

Sweet's syndrome. Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by fever, neutrophil leukocytosis, erythematous skin plaques or nodules and, often, classical RAS.[42] It may occur in conjunction with malignant conditions, such as leukemia.[43]

BOX 3

RECENTLY RESEARCHED TREATMENTS FOR RECURRENT APHTHOUS STOMATITIS.

- Aciclovir
- Amelexanox 5 Percent Topical*
- Azelastine
- Chlorhexidine
- Colchicine
- Corticosteroids
- Dapsone
- Diclofenac in Hyaluronan*
- Doxymycine-Cyanoacrylate
- Eupatorium Laevigatum
- Helium-Neon Lasers
- Interferon-Alpha
- Irsogladine Maleate
- Levamisole
- Nicotine
- Pentoxifylline
- Photophoresis of Oxolin Ointment
- Relaxation/Imagery
- Shark Liver Oil
- Sucralfate
- Tetracyclines
- Thalidomide*
- Triclosan
- Ultrasound

* Controlled trial.

DIAGNOSIS

The diagnosis of RAS is made on the basis of history and clinical criteria, since there are no specific laboratory tests available.

A medical history should be taken to rule out other ulcerative disorders and conditions such as Crohn's disease, celiac disease, neutropenia, HIV infection and Behcet's syndrome (Figure 4).

A complete blood cell count, hematinic estimation and test for anti-endomysial antibodies are indicated to rule out immune disturbances, vitamin and iron deficiencies, and malabsorption (such as in celiac disease).[44]

MANAGEMENT

Since the etiology of RAS remains unknown, and the cyclic nature of the disease makes it difficult to conduct well-designed prospective double-blind controlled clinical studies, there is no definitive treatment. Although a miscellany of supposed therapies have been tried, few have been subjected to double-blind randomized controlled trials (Box 3). Misclassification bias may explain the inconsistency of results found in the vast literature on treatment outcomes.[45,46] Some patients have mild outbreaks, whereas others have severe and longer episodes. Some present with a few small ulcers, while others present with larger ulcers or a combination of small and large.[47] In some patients, the severity and frequency of outbreaks ease with the passing of years; in others, severity and frequency worsen. Thus, therapy should be tailored to each patient individually.

Treatment is symptomatic, the goal being to

- decrease symptoms;
- reduce ulcer number and size;
- increase disease-free periods.

The best treatment is that which will control ulcers for the longest period with minimal adverse side effects. The treatment approach should be determined by disease severity (pain), the patient's medical history, the frequency of flare-ups and the patient's ability to tolerate the medication. In all patients with RAS, it is important to rule out predisposing factors and treat any such factors, where possible, before introducing more specific therapy.

Perhaps surprisingly, few randomized controlled clinical trials have been conducted to determine the best treatments for RAS. Those that exist showed that chlorhexidine gluconate mouthwashes and topical corticosteroids both can reduce the severity and duration of RAS ulcers, but that neither significantly influences the frequency of RAS episodes.[48]

To help determine management strategies, the practitioner may find it useful to classify RAS in three clinical presentations: type A, type B and type C.

Type A. RAS episodes lasting for only a few days, occurring only a few times a year, are classified as "type A."

In this scenario, pain is tolerable. The clinician should try to identify what precipitates the ulcers, what the patient uses to treat them, and how effective that treatment is. If it is effective and safe, the health care provider, or HCP, should encourage the patient to continue it. If a precipitating factor(s) is identified, the HCP should try eliminating it first. For example, if trauma-induced RAS is suspected, the HCP can suggest a softer toothbrush and gentler brushing. Medication may not be indicated.

Type B. Painful RAS each month, lasting between three and 10 days, is type B. In this scenario, the patient may have changed diet and oral hygiene habits because of the pain. If a precipitating factor can be identified—for example, oral hygiene, stress, trauma or diet—alternatives or remedies should be discussed with the patient. It is imperative to identify patients who experience prodromal symptoms, such as tingling or swelling, because the patient can

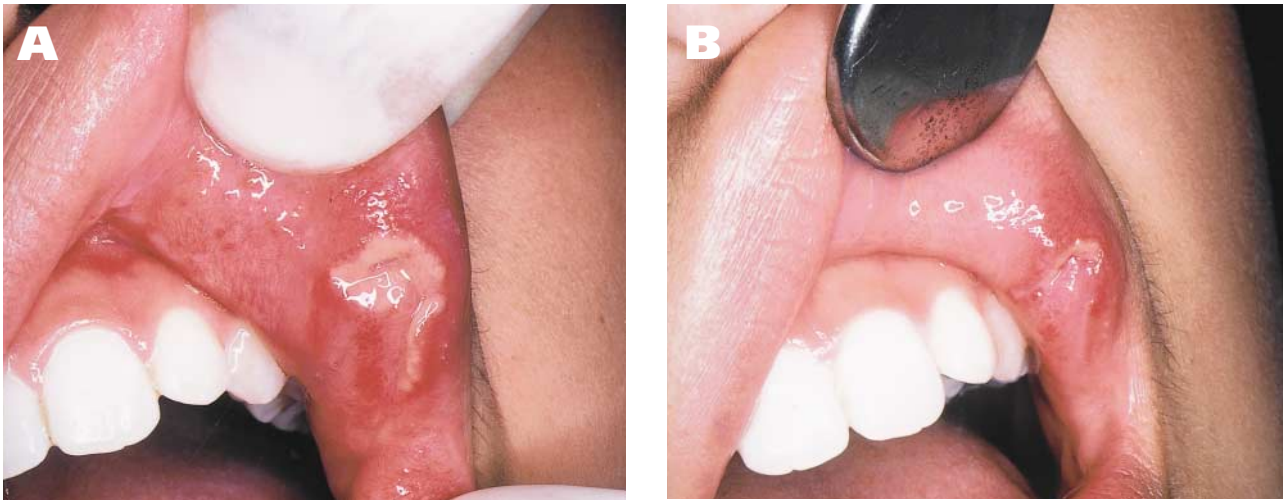

Figure 5. The case of a 14-year-old patient with recurrent aphthous stomatitis. A. Baseline photo. Note the erythema around the base of the ulcer. B. The patient after one week of treatment with clobetasol ointment in adhesive paste.

use corticosteroids (if they are indicated for him or her) at the prodromal stage to abort the attacks.

Treatment often includes the use of a chlorhexidine mouthwash (without alcohol base), and a short course of topical corticosteroids as soon as the ulcers appear. Because of the consistent recurrent pattern, these patients may need a maintenance treatment protocol.

Alternative regimens include dexamethasone 0.05 milligrams/5 mL (rinse and spit three times per day) or a high-potency topical corticosteroid such as clobetasol ointment 0.05 percent in Orabase (1:1) (Colgate Oral Pharmaceuticals, Canton, Mass.) or fluocinonide ointment 0.05 percent in Orabase (1:1) if the ulcer(s) recur on the same site, used three times daily (Figure 5). If corticosteroids are used, patients should be monitored for yeast superinfection.[49] In patients with poor oral hygiene, professional help from a dental hygienist should be considered once ulcers heal.

In patients with recalcitrant RAS, a short course of systemic corticosteroid therapy may be required, never exceeding more than 50 mg per day (preferably in the morning) for five days. This course of treatment is best left to a physician or oral medicine specialist.

Type C. Type C RAS involves painful, chronic courses of RAS in which by the time one ulcer heals, another develops.

These patients are best treated by an oral medicine specialist, who often will use potent topical corticosteroids (such as betamethasone, beclomethasone, clobetasol, fluticasone or fluocinonide), systemic corticosteroids, azathioprine or other immunosuppressants such as dapsone, pentoxifylline and sometimes thalidomide.[50] Table 2 shows the potential adverse effects of these agents.

In addition, oral medicine specialists may administer intralesional injections of a corticosteroid such as betamethasone, dexamathasone or triamcinolone to enhance or boost the local response, thus allowing for shorter systemic treatment. In patients with poor oral hygiene,

TABLE 2

RAS* THERAPY: COMMON ADVERSE EFFECTS OF DRUGS TO BE USED SYSTEMICALLY ONLY BY ORAL MEDICINE SPECIALISTS.

DRUG	POSSIBLE ADVERSE EFFECT(S)
Colchicine	Painful gastrointestinal symptoms, diarrhea, male infertility
Dapsone	Methemoglobinemia
Levamisole	Decreased white blood cell count
Pentoxifylline	Nausea
Thalidomide	Teratogenicity, polyneuropathy, mood change

* RAS: Recurrent aphthous stomatitis.

professional help from a dental hygienist should be considered.

CONCLUSION

RAS is a common oral disorder of uncertain etiopathogenesis for which symptomatic therapy only is available. Its ethiopathogenesis remains unknown, and there are no diagnostic tests available. Diagnosis, therefore, is made on clinical grounds alone. Several factors—such as trauma, diet and stress—are known to trigger the disease. The most important role of the HCP is to identify underlying precipitating factors and try to eliminate them. Furthermore, it is essential to educate the patient regarding the nature of this condition, especially the fact that RAS is not a contagious condition, as often is thought, and that it is not caused by the herpes simplex virus.

Given its painful presentation and inflammatory nature, RAS responds quite well to the use of topical or systemic anti-inflammatory drugs, particularly corticosteroids. Since the advent of high-potency topical steroids, most patients with RAS can be managed this way. However, early intervention is the key. Topical steroids, when used for a short period, have a very safe profile and should be the first line of treatment for recurrent oral stomatitis. ■

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1. Miller MF, Ship II. A retrospective study of the prevalence and incidence of recurrent aphthous ulcers in a professional population, 1958-1971. Oral Surg Oral Med Oral Pathol 1977;43(4):532-7.
2. Rogers RS 3rd. Recurrent aphthous stomatitis: clinical characteristics and associated systemic disorders. Semin Cutan Med Surg 1997;16:278-83.
3. Eversole LR. Immunopathology of oral mucosal ulcerative, desquamative, and bullous diseases: selective review of the literature. Oral Surg Oral Med Oral Pathol 1994;77:555-71.
4. Scully C, Porter S. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. J Oral Pathol Med 1989;18(1):21-7.
5. Shohat-Zabarski R, Kalderon S, Klein T, Weinberger A. Close association of HLA-B51 in persons with recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol 1992;74:455-8.
6. Ship II. Epidemiologic aspects of recurrent aphthous ulcerations. Oral Surg Oral Med Oral Pathol 1972;33:400-6.
7. Ship II. Inheritance of aphthous ulcers of the mouth. J Dent Res 1965;44:837-44.
8. Natah SS, Hayrinen-Immonen R, Hietanen J, Malmstrom M, Konttinen YT. Immunolocalization of tumor necrosis factor–alpha expressing cells in recurrent aphthous ulcer lesions (RAU). J Oral Pathol Med 2000;29(1):19-25.
9. Sampaio EP, Sarno EN, Galilly R, Cohn ZA, Kaplan G. Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. J Exp Med 1991;173:699-703.
10. Sun A, Chu CT, Liu BY, Wang JT, Leu JS, Chiang CP. Expression of interleukin-2 receptor by activated peripheral blood lymphocytes upregulated by the plasma level of interleukin-2 in patients with recurrent aphthous ulcers. Proc Natl Sci Counc Repub China B 2000;24(3):116-22.
11. Buno IJ, Huff JC, Weston WL, Cook DT, Brice SL. Elevated levels of interferon gamma, tumor necrosis factor alpha, interleukins 2, 4, and 5, but not interleukin 10, are present in recurrent aphthous stomatitis. Arch Dermatol 1998;134:827-31.
12. Sun A, Chu CT, Wu YC, Yuan JH. Mechanisms of depressed natural killer cell activity in recurrent aphthous ulcers. Clin Immunol Immunopathol 1991;60(1):83-92.
13. Pedersen A. Psychologic stress and recurrent aphthous ulceration. J Oral Pathol Med 1989;18(2):119-22.
14. Hay KD, Reade PC. The use of an elimination diet in the treatment of recurrent aphthous ulceration of the oral cavity. Oral Surg Oral Med Oral Pathol 1984;57:504-7.
15. Eversole LR, Shopper TP, Chambers DW. Effects of suspected foodstuff challenging agents in the etiology of recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol 1982;54(1):33-8.
16. Nolan A, Lamey PJ, Milligan KA, Forsyth A. Recurrent aphthous ulceration and food sensitivity. J Oral Pathol Med 1991;20:473-5.
17. Ferguson MM, McKay Hart D, Lindsay R, Stephen KW. Progestin therapy for menstrual related aphthae. Int J Oral Surg 1978;7:463-70.
18. Tuzun B, Wolf R, Tuzun Y, Serdaroglu S. Recurrent aphthous stomatitis and smoking. Int J Dermatol 2000;39:358-60.
19. Axell T, Henricsson V. Association between recurrent aphthous ulcers and tobacco habits. Scand J Dent Res 1985;93:239-42.
20. Dorsey C. More observations on relief of aphthous stomatitis on resumption of cigarette smoking. Calif Med 1964;101:377-8.
21. Grady D, Ernster VL, Stillman L, Greenspan J. Smokeless tobacco use prevents aphthous stomatitis. Oral Surg Oral Med Oral Pathol 1992;74:463-5.
22. Bittoun R. Recurrent aphthous ulcers and nicotine. Med J Aust 1991;154:471-2.
23. Shotts RH, Scully C, Avery CM, Porter SR. Nicorandil-induced severe oral ulceration: a newly recognized drug reaction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87:706-7.
24. Cribier B, Marquart-Elbaz C, Lipsker D, Alt M, Grosshans E. Chronic buccal ulceration induced by nicorandil. Br J Dermatol 1998;138:372-3.
25. Healy CM, Thornhill MH. An association between recurrent orogenital ulceration and non-steroidal anti-inflammatory drugs. J Oral Pathol Med 1995;24(1):46-8.
26. Boulinguez S, Cornee-Leplat I, Bouyssou-Gauthier ML, Bedane C, Bonnetblanc JM. Analysis of the literature about drug-induced aphthous ulcers. Ann Dermatol Venereol 2000;127(2):155-8.
27. Muzyka BC, Glick M. Major aphthous ulcers in patients with HIV disease. Oral Surg Oral Med Oral Pathol 1994;77(2):116-20.
28. MacPhail LA, Greenspan D, Feigal DW, Lennette ET, Greenspan JS. Recurrent aphthous ulcers in association with HIV infection: description of ulcer types and analysis of T-lymphocyte subsets. Oral Surg Oral Med Oral Pathol 1991;71:678-83.
29. Porter SR, Scully C. Orofacial manifestations in primary immunodeficiencies: common variable immunodeficiencies. J Oral Pathol Med 1993;22(4):157-8.
30. Flint SR, Sugerman P, Scully C, Smith JG, Smith MA. The myelodysplastic syndromes: case report and review. Oral Surg Oral Med Oral Pathol 1990;70:579-83.
31. Vanderhoof JA, Rich KC,Stiehm ER, Ament ME. Esophageal ulcers in immunodeficiency with elevated levels of IgM and neutropenia. Am J Dis Child 1977;131:551-2.
32. Wright DG, Dale DC, Fauci AS, Wolff SM. Human cyclic neutropenia: clinical review and long-term follow-up of patients. Medicine (Baltimore) 1981;60(1):1-13.
33. Olson JA, Feinberg I, Silverman S Jr., Abrams D, Greenspan JS. Serum vitamin B12, folate, and iron levels in recurrent aphthous ulcer-

ation. Oral Surg Oral Med Oral Pathol 1982;54:517-20.
34. Wray D, Ferguson MM, Mason DK, Hutcheon RI, Lee FD. Recurrent aphthae: treatment with vitamin B12, folic acid and iron. Br Med J 1975;2:490-3.
35. Porter S, Flint S, Scully C, Keith O. Recurrent aphthous stomatitis: the efficacy of replacement therapy in patients with underlying hematinic deficiencies. Ann Dent 1992;51:14-6.
36. Ferguson MM, Wray D, Carmichael HA, et al. Coeliac disease associated with recurrent aphthae. Gut 1980;21:223-6.
37. Wray D. Gluten-sensitive recurrent aphthous stomatitis. Dig Dis Sci 1981;26:737-40.
38. Hunter IP, Ferguson MM, Scully C, Galloway AR, Main AN, Russell RI. Effect of dietary gluten elimination in patients with recurrent minor aphthous stomatitis and no detectable gluten enteropathy. Oral Surg Oral Med Oral Pathol 1993;75:595-8.
39. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease: a prospective study of 792 patients. J Clin Gastroenterol 1996;23(1):29-34.
40. Schwartz T, Langevitz P, Zemer D, Gazit E, Pras M, Livnen A. Behcet's disease in familial mediterranean fever: characterization of the association between the two diseases. Semin Arthritis Rheum 2000;29:286-95.
41. Marshall GS, Edwards KM, Butler J, Lawton AR. Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr 1987;110(1):43-6.
42. Notani K, Kobayashi S, Kondoh K, Shindoh M, Ferguson MM, Fukuda H. A case of Sweet's syndrome (acute febrile neutrophilic dermatosis) with palatal ulceration. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;89:477-9.
43. Paydas S, Sahin B, Zorludemir S. Sweet's syndrome accompanying leukemia: seven cases and review of the literature. Leuk Res 2000;24(1):83-6.
44. Porter SR, Kingsmill V, Scully C. Audit of diagnosis and investigations in patients with recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol 1993;76:449-52.
45. Woo SB, Sonis ST. Recurrent aphthous ulcers: a review of diagnosis and treatment. JADA 1996;127:1202-13.
46. MacPhail L. Topical and systemic therapy for recurrent aphthous stomatitis. Semin Cutan Med Surg 1997;16:301-7.
47. Ship JA. Recurrent aphthous stomatitis: an update. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81(2):141-7.
48. Porter SR, Scully C. Aphthous ulcers: recurrent. Clin Evidence 2002;3:606-12.
49. Lozada-Nur F, Miranda C, Maliksi R. Double-blind clinical trial of 0.05% clobetasol propionate ointment in orabase and 0.05% fluocinonide ointment in orabase in the treatment of patients with oral vesiculoerosive diseases. Oral Surg Oral Med Oral Pathol 1994;77:598-604.
50. Eisen D, Lynch DP. Selecting topical and systemic agents for recurrent aphthous stomatitis. Cutis 2001;68:201-6.