Recurrent Aphthous Ulcers: An In-depth Review

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ABSTRACT

Recurrent aphthous ulcers are common painful mucosal conditions affecting the oral cavity. Despite their high prevalence, etiopathogenesis remains unclear. So as a result, the available treatments still remaining unsatisfactory with the ability to reduce the severity, healing time and the frequency of recurrence of ulceration with no permanent and definitive treatment. The healing time ranges usually from seven to fourteen days. This review discusses the different treatment modalities and updates that are available to the moment and according to the severity of the ulceration, the clinician can decide to go with topical, physical or systemic treatments which give the clinician broad and detailed picture to deal with RAS in an appropriate way. This review article summarizes the clinical presentation, diagnostic criteria, and recent trends in the management of recurrent apthous stomatitis.

Keywords: Diagnostic criteria; immunomodulators; recurrent apthousatomatitis.

INTRODUCTION

Oral ulcerations have plagued the mankind since antiquity. Particularly troublesome, though by no means most serious, are those which are called as "Recurrent Aphthous Stomatitis (RAS)" or aphthae or by other numerous synonyms, which are of unknown etiology. The term "aphthous" is derived from a Greek word "aphtha" which means ulceration. The diagnosis is entirely based on history and clinical criteria and no laboratory procedures exist to confirm the diagnosis. There is no curative therapy to prevent the recurrence of ulcers, and all available treatment modalities can only reduce the frequency or severity of the lesions. Although RAS may be a marker of an underlying systemic illness such as Coeliac Disease, Inflammatory Bowel Disease, Crohn's disease and Ulcerative Colitis or may be present as one of the features of Behçet's disease (International Study Group for Behcet's Disease 1990), in most cases no additional body systems are affected, and patients remain otherwise well.[1]

DEFINITION AND CLASSIFICATION

As given in literature, Aphthous ulcers can be defined as -

Graykowski et al (1966)[2] and Natah SS et al (1998)[3] defined RAS as - An inflammatory condition of unknown etiology characterized by painful, recurrent (single or multiple) ulcerations of the oral mucosa.

Scully in 2003[4] defined RAS as 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.

A mucosal ulcer with a regular outline, usually less then 1cm in diameter, having a yellowish or grayish-white necrotic centre surrounded by a narrow erythematous zone and with a pronounced tendency to recur (Natah et al 2004).[5]

As per Dorland's Medical Dictionary 32nd Edition[6]

Table 1: Types of aphthous ulcers.

	MINOR RAS (Mikulicz's ulcer)	MAJOR RAS (Suttons Disease)	HERPETIFORM RAS
Size	<1CM	>1CM	<4MM
Duration	10-14 days	>2weeks	10-14 days
Scarring	No	Yes	No
Percent of All RAS	>80	10-15	5-10

- An aphthous ulcer also known as a canker sore, is a type of mouth ulcer that presents as a painful open sore inside the mouth or upper throat characterized by a break in the mucous membrane.

The varied clinical presentations and the occurrence of some in mucocutaneous-ocular syndromes led to a classification proposed by Donatsky (1976)[7] –

1. Stomatitis aphthosa recurrens, which is similar to Mikuliz's aphthae, described by Mikulicz and Kummel in 1898.
2. Stomatitis aphthosa recurrens cicatricicans, which is similar to periadenitis mucosa necrotica recurrens, described by Sutton in 1911.
3. Stomatitis aphthosa recurrens herpetiformis, which is similar to herpetiform ulcers, described by Cooke (19617).
4. Mucocutaneous-ocular syndromes with aphthous-like stomatitis.

In 1977, De Meyer et al8 gave a classification of RAS on the basis of size of the ulcer as major ulcer (<1cm) and minor ulcer (>1cm). According to Sircus et al (19579) and Natah (20045) three distinct forms of RAS can be distinguished clinically: minor and major aphthae and herpetiform ulcers:

PREDISPOSING FACTORS

Age and Sex: The prevalence of RAS detected during oral examination was found to be about 1% in children of developed countries (Kleinman 1994),[10] but 40% of children (aged 15 years or less) may have a history of RAS, with ulceration beginning before 5 years of age and the frequency of affected patients rising with age (Miller M.F 1980).[11] A decreased prevalence has been noted in males, though not females, over the age of 50 in the Scottish population (Sircus et al 1957)[9] whereas Axéll (1976)[12] found a decrease in prevalence with age in both sexes in the Swedish population.

Family and Heredity: Predisposition for the development of apthous ulcer is strongly suggested as about 40% of genetic patients have a family history and these individuals develop ulcers earlier and are of more severe nature. Various associations with HLA antigens and RAS have been reported. These associations vary with specific racial and ethnic origins.[9]

RAS and Hormonal changes: Sircus et al (1957)[9] reported a complete remission during pregnancy but with exacerbations occurring in the puerperium. Sircus and co-workers (1957) had reported that almost no men developed RAS after the age of 50, whereas 10% of women had their first episode between 50-59 yrs. However, the association between RAS and menopause has not been established (McCartan and Sullivan, 1992).[11]

Food Hypersensitivity: Scully and Porter (2008)[13] correlated the onset of ulcers with exposure to certain foods, such as cow's milk, gluten, chocolate, nuts, cheese, azo dyes, flavoring agents and preservatives but Eversole and co-workers (1982) did not find any significant association of RAS with 3 specific food items (tomatoes, strawberries and walnuts). Some studies have noted an increased prevalence of atopy among RAS patients.

Drugs: Certain drugs have been associated with development of RAU; these include angiotensin converting enzyme inhibitor captopril, gold salts, nicorandil, phenindione, phenobarbital, and sodium hypochloride. NSAIDS such as propionic acid, diclofenac, and piroxicam may also cause oral ulceration similar to RAS.[3]

Hematinic Deficiency: Deficiencies of iron, vitamin B12 and folic acid predispose development of RAS. Deficiencies of these hematinics are twice more common in these individuals than

controls. Contrary findings in various studies relating the association of hematinic deficiency and RAS have been explained as due to varying genetic backgrounds and dietary habits of the study population.[14]

Gluten sensitive enteropathy/celiac disease, inflammatory bowel disease: It is characterized by severe malnutrition, anemia, abdominal pain, diarrhea, aphthous oral ulcers, glossitis and stomatitis. RAS may be the sole manifestation of the disease. The use of gluten-free diet in the improvement of RAS is considered uncertain. It has been suggested that evaluation for celiac disease may be appropriate for RAS patients, Inflammatory bowel diseases such as Crohn's disease and ulcerative colitis may present with apthous-like ulceration.[9,13]

Environmental Factors

Stress: Stress has been emphasized as a causative factor in RAU. It has been proposed that stress may induce trauma to oral soft tissues by parafunctional habits such as lip or cheek biting and this trauma may predispose to ulceration. A more recent study shows lack of direct correlation between levels of stress and severity of RAS episodes and suggests that psychological stress may act as a triggering or modifying factor rather than etiological factor in susceptible RAS patients.[9,15]

Local Trauma: As per studies done by Wray et al (1991) a subset of patients with RAS is predisposed to develop aphthae at sites of local trauma such as anesthetic injections, tooth-brushing, and dental treatment. How this local trauma can trigger aphthous ulceration in these patients is still unknown (Axell 1985).[12]

Tobacco and Nicotine: Several studies reveal negative association between cigarette smoking, smokeless tobacco and RAS. Possible explanations given include increased mucosal keratinization; which serves as a mechanical and protective barrier against trauma and microbes. Nicotine is considered to be the protective factor as it stimulates the production of adrenal steroids by its action on the hypothalamic adrenal axis and reduces production of tumor necrosis factor alpha (TNF-α) and interleukins 1 and 6 (IL-1 and IL-6). Nicotine replacement therapy has been suggested as treatment for patients who develop RAU on cessation of smoking.[15]

Sodium Lauryl Sulfate (SLS) - Containing Toothpaste: An increased frequency in the occurrence of RAS has been reported on using sodium lauryl sulfate (SLS)-containing tooth paste with some reduction in ulceration on use of SLS-free tooth paste. However, because of the widespread use of SLS-containing dentifrice, it has been proposed that this may not truly predispose to RAS.[15]

Aphthous Ulcer and Micro-organisms

Bacteria: Oral streptococci were previously suggested as important in the pathogenesis of RAS, either as direct pathogens or as an antigenic stimulus culminating in the genesis of antibodies that may conceivably cross-react with keratinocyte antigenic determinants. In 1963, Bar lie et al isolated S. oralis (previously known as S. sanguis 2A) from an aphthous ulcer but later analysis disclosed that this organism was actually a strain of S. mitis (Natah et al 2004).[5] Helicobacter pylori have been detected in lesional tissue of ill-defined oral ulcers, but the frequency of serum IgG antibodies to H. pylori is not increased in RAS. It has been reported to be present in high density in dental plaque.[15]

Viral aspect of RAS: Various viruses have been implicated in the etiopathogenesis of recurrent apthous stomatitis. There have been several suggestive, but as yet there exists inconclusive evidence toward a viral etiology. Characteristics of aphthous ulcers which are indicative of infectious etiology include recurrent ulceration, lymphocytic infiltration, perivascular cuffing, presence of auto-antibodies, inclusion bodies in case of herpetiform ulcers and similarity of RAS to viral ulcerative diseases in animals (Hooks 2006).[16]

Mycoplasma and RAS: A controlled cultural and serological investigation of Mycoplasmas in recurrent oral ulceration was undertaken by Gordon et al (1967).[17] No evidence for an etiological relationship between oral Mycoplasmas and this condition was obtained. Mycoplasmas, principally M. orale, were frequently recovered from the oral cavities of individuals with natural teeth, but rarely from edentulous subjects.

SYSTEMIC DISEASES ASSOCIATED WITH RAS

The various systemic diseases and syndromes associated with RAS are summarized as follows:

Table 2: Systemic diseases and syndromes associated with RAS.

DISEASE	PRESENTATION
BEHCETS SYNDROME	RAS; Ocular: Uveitis, conjunctivitis, retinitis; Genital: Scrotal or Penile ulcers, Vaginal or vulval ulcer, perianal, Epididymo-orchitis; Dermatological: Papule, pustule, erythema nodosum, cutaneous pathergy; Arthralgia and Neuralgia
MAGIC SYNDROME	Variant of Behcets with Inflammed cartilage
PFAPA	Periodic fever, Aphthae, Pharyngitis, and cervical adenitis. Seen in young children
SWEET SYNDROME	Fever, increased PMN in peripheral blood, skin lesions, Erythematous plaque, nodule, vesicle, pustule, dense dermal neutrophilic infilterate.
CYCLIC NEUTROPENIA	Cyclic reduction in circulating neutrophils, oral ulcerations, cutaneous abscess and upper respiratory tract infection, lymphadenopathy
HIV	Aphthous like ulceration

CLINICAL FEATURES OF RAS

Stanley (1972)19 have divided the symptoms of RAS into 4 stages:

Table 3: Summarizing clinical features of RAS

STAGE	TIMING	SYMPTOMS
PRELIMINARY	First 24hrs	Beginning of parathesia
PREULCERATIVE	18-72 hrs	Increasing Pain
ULCERATIVE	Days to weeks	Diminishing Pain
HEALING	Days to weeks	Painless

Histopathology of RAS

The microscopic picture of aphthous ulcer is non-specific, and diagnosis must be based on history and careful clinical examination. The mucous membrane of aphthous ulcer shows superficial tissue necrosis with a fibrinopurulent membrane covering the ulcerated area. The necrosis is covered by tissue debris and neutrophils. Epithelium is infiltrated by lymphocytes and few neutrophils. Intense inflammatory cell infiltration, predominantly neutrophils present immediately below the ulcer, mononuclear lymphocytes are seen in adjacent areas. Minor salivary glands commonly present in areas of aphthae exhibit focal periductal and perialveolar fibrosis and chronic inflammation (Scully C 2008).13 The various phases in the development of RAS are:

PREULCERATIVE PHASE (T- helper cells): There is lymphocytic infilterate in the epithelium followed by papular swelling (keratinocyte vacuolation) followed by vasculitis present as erythematous halo.

ULCERATIVE PHASE (T-suppressor cells): A fibrinous membrane covers the ulcer which is infiltrated by lymphocytes neutrophils and plasma cells.

HEALING PHASE (T- helper cells): There is epithelial regeneration.

DIAGNOSIS OF RAS

Diagnosis of RAS is based on history, clinical manifestations, and histopathology. Other causes of recurrent oral ulceration must be ruled out. Systemic diseases which present with recurrent oral ulcerations must be ruled out. Natah et al (2004)5 proposed that a diagnosis of idiopathic RAS and secondary RAS (associated with systemic disease) can be established when four major and one minor criterion are fulfilled.

Table 4: Major and minor criteria for the diagnosis of RAS.

CRITERIA	DESCRIPTION
MAJOR CRITERIA	
Clinical appearance	Single or multiple round/oval ulcers shallow regular margins, yellow gray base surrounded by erythematous margins. Ulcers are never preceded by vesicles. Less than 1cm in diameter
Recurrence	Atleast three attacks of RAS within past 3 years, ulcers do not appear in the same focal site
Mechanical Hyperalgesia	Painful lesions, exacerbated by movement of ulcer affected area
Self limitation of condition	Ulcers heal spontaneously without sequelae with or without treatment
MINOR CRITERIA	
Family history of RAS	Positive family history of RAU present
Age of onset	First attack of RAU below 40 yrs
Location	Non-keratinized mucosa
Duration	From few days to weeks
Pattern of occurrence	Irregular
Histopathological examination	Non-specific inflammation
Presence of precipitating factors	Attacks triggered by hormonal changes, exposure to certain foods, drugs, inter-current infections, stress and local trauma
Presence of hematinic deficiency	Especially ferritin, folate, iron, vitamin B and zinc
Negative association and smoking	RAS patient is a non-smoker or develops RAS on cessation of smoking
Therapeutic trial with glucocorticosteroid	Positive response to treatment with topical or systemic corticosteroid

MANAGEMENT OF RECURRENT APHTHOUS STOMATITIS

Most patients with RAS need no treatment because of the mild nature of the disease. Some manage with maintenance of good oral hygiene, the right kind of toothpaste (without irritating sodium lauryl sulfate, e.g. Biotene and occasional palliative therapy for pain. Patients who experience multiple episodes of RAS each month and/or present with symptoms of severe pain and difficulty in eating should, however, be considered for drug therapy. To help determine management strategies, Crispian Scully (2003)4 divided RAS in three clinical presentations (Table 5): Type A, Type B and Type C.

Table 5: Management of RAS.

Type	Features	Treatment
Type A	RAS episodes lasting for only a few days, occurring only a few times a year.	1. 1.Medication may not be indicated 2. 2.Topical anesthetics for pain relief
Type B	Frequent and painful RAS lasting between three and ten days The patient might have changed the diet and oral hygiene habits due to because of pain.	1. 1.Medication needed in this type of RAS 2. 2.Treated by topical or systemic corticosteroids
Type C	Painful, chronic courses of RAS in which by the time one ulcer heals, another develops.	Best treated by topical and systemic corticosteroids, azathioprine or other immunosuppresant's such as Dapsone, pentoxifylline and sometimes thalidomide

The following tables illustrates the topical and systemic treatment modalities:[3,13,14]

Table 6: Topical and systemic agents used in the treatment of RAS.

CATEGORY	AGENT	THERAPEUTIC EFFECT
Antimicrobials	Chlorhexidine	Increase number of ulcer free days
	Triclosan	Reduces number and relieves pain
	Tetracycline	Shortens ulcerative phase, reduces healing time and pain
	Penicillin G	Reduce symptoms and fastens healing
	Steroids	Reduce number of ulcers and pain
Immunomodulators	Thalidomide	Reduce number of ulcer
	Pentoxifylline	Reduce number of ulcers, decrease in size of ulcer, increase ulcer free days, reduce pain and promote healing
	Colchicine	
	Levamisole	
	Dapsone and Cemetidine	Adverse drug reactions reported with each of the mentioned drugs
Topical analgesic/ anti-inflammatory	Benzdymine Amelxanox	Reduction in ulcer pain and accelerated ulcer healing
Barrier	Topical Hyaluronic acid	Local tissue hydration and anti-oxidant effect ,Ulcer protectant
	Adhesive Cyanoacrylate	
Physical Therapy	Surgical removal, Laser ablation, Chemical cautery, Low density ultra-sound	Soothing effect by adhering to mucosal tissue

CONCLUSION

Recurrent apthous stomatitis is a very common, recurrent painful ulceration occurring in the oral cavity. The etiopathogenesis of this disease is yet unclear. Treatment strategies must be directed toward providing symptomatic relief by reducing pain, increasing the duration of ulcer-free periods, and accelerating ulcer healing.

REFERENCES

1. Criteria for diagnosis of Behcet's disease. International Study Group for Behçet's disease. Lancet. 1990 May 5;335(8697):1078-80.
2. Graykowski EA, Barile MF, Lee WB, Stanley HR Jr. Recurrent aphthous stomatitis: Clinical, therapeutic, and histopathologic, and hypersensitivity aspects. JAMA. 1966 May 16;196(7):637-44.
3. Natah SS, Haynnen Immonen R, Hietanen J, Malmström M, Konttinen YT. Quantitative assessment of mast cells in recurrent aphthous ulcers (RAU). J Oral Pathol Med. 1998 Mar;27(3):124-9.
4. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. J Am Dent Assoc. 2003 Feb;134(2):200-7.
5. Natah SS1, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Häyrinen-Immonen R. Recurrent aphthous ulcers today: a review of the growing knowledge. Int J Oral Maxillofac Surg. 2004 Apr;33(3):221-34
6. Dorland 2011. Dorland Illustrated Medical Dictionary. United States of America ;Contexo Media's Dorland Healthcare Information.
7. Donatsky O. A leukocyte migration study on the cell-mediated immunity against adult human oral mucosa and streptococcal antigens in patients with recurrent aphthous stomatitis. Acta Pathol Microbiol Scand (C). 1976 June;84(3):227-34.
8. Meyer JD, Degraeve M, Clarysse J, De Loose F, Peremans W. Levamisole in aphthous stomatitis: evaluation of three regimens. Br Med J. 1977 Mar 12;1(6062):671-4.
9. Sircus W, Church R, Kelleher J. Recurrent aphthous ulceration of the mouth. Q J Med. 1957;16: 235-49.
10. Kleinman DV, Swango PA, Pindborg JJ. Epidemiology of oral mucosal lesions in United States School children. Community Dent Oral Epidemiol. 1994;22:243-53.
11. Miller MF, Garfunkel AA, Ram CA, Ship II. The inheritance of recurrent aphthous stomatitis. Observations on susceptibility. Oral Surg Oral Med Oral Pathol. 1980:49(5): 409-12.
12. Axéll T. A prevalence study of oral mucosal lesions in an adult Swedish population. Odontol Revy Suppl. 1976:36:1-103.
13. Scully C, Porter S. Oral Mucosal Disesase: Recurrent Aphthous Stomatitis. Br J Oral Maxillofac Surg. 2008;46(3):198-206.
14. Porter SR, Scully C, Flint S. Hematologic status in recurrent aphthous stomatitis compared with other oral disease. Oral Surg Oral Med Oral Pathol. 1988;66:41-4.
15. Preeti L, Mangesh, Rajkumar A. Recurrent Apthous Stomatitis. J Oral Maxillofac Pathol. 2011 Sep;15(3):252-6.
16. Hooks JJ. Possibility of a viral etiology in recurrent aphthous ulcers and Behçet's syndrome. J Oral Pathol. 1978;7(6):353-64.
17. Gordon AM, Dick HM, Mason DK, Manderson W, Crichton WB. Mycoplasmas and recurrent oral ulceration. J Clin Pathol. 1967;20(6):865-9.
18. Stanley HR. Aphthous lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1972; 33:407-16.