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## Recurrent Aphthous Stomatitis: A Review.

Sarumathi T<sup>1\*</sup>, Saravanakumar B<sup>2</sup>, Amudhan A<sup>1</sup>, Hemalatha VT<sup>1</sup>, and Aarthinisha V<sup>1</sup>.

<sup>1</sup>Department of Oral Medicine & Radiology, Sree Balaji Dental College & Hospital, Bharath University, Chennai, Tamil Nadu, India.

<sup>2</sup>Department of Oral & Maxillofacial Surgery, Sree Balaji Dental College & Hospital, Bharath University, Chennai, Tamil Nadu, India.

### ABSTRACT

Recurrent aphthous stomatitis (RAS; recurrent aphthous ulcers; canker sores) belongs to the group of chronic, inflammatory, ulcerative diseases of the oral mucosa. The diagnosis of RAS is based on well-defined clinical characteristics but the precise etiology and pathogenesis of RAS remain unclear. This review article provides the associated etiologic factors, diagnostic criteria and treatment of RAS.

**Keywords:** Recurrent aphthous stomatitis, Canker sores, Ulcers.

*\*Corresponding author*

## INTRODUCTION

Tissue defects rank among the most frequent lesions of the oral mucosa. The morphological similarity of the defects of different origins, however, creates a major diagnostic problem [1]. Recurrent aphthous stomatitis is a common oral mucosal disorder that, despite detailed investigation, has an unknown cause and poor effective management in general and specialty dental practice [2].

Recurrent aphthous ulcer (RAS) seems to be as old as humanity itself. The Father of Medicine, Hippocrates (460 to 370 BC) is credited with the first use of the term “aphthai” in relation to focal painful inflammation of the oral mucosa, although valid clinical description of RAS only appeared in 1898 in a paper published by Mikulicz and Kummel [3].

### Epidemiology

Epidemiologic studies have shown that the prevalence of RAS is influenced by the population studied, diagnostic criteria, and environmental factors. RAS seems to be infrequent in Bedouin Arabs and is more common in Western countries [4,5]. Approximately 20% of the general population is affected by RAS, but incidence varies from 5% to 50% depending on the ethnic, and socioeconomic groups studied [6].

Activities of daily living affect the prevalence of RAS. RAS prevalence was higher (male, 48.3%; female, 57.2%) among professional-school students than in the same subjects 12 years later when they had become practicing professionals [2].

The onset of RAS seems to peak between the ages of 10 and 19 years before becoming less frequent with advancing age and does not seem to depend on geographic influences, age, gender, or race [7].

RAS beginning or worsening well into adult life should increase suspicion that the oral ulcers are being caused by an underlying medical disorder such as hematologic, immunologic, or connective tissue disease or Behcet's syndrome [2].

### Etiologic factors associated with recurrent aphthous stomatitis [8]

#### Environmental factors

- Stress / psychological imbalance
- Trauma
- Tobacco
- Dysregulated saliva composition

#### Microbiological agents

- Bacterial
- Viral

#### RAS and Hormonal changes Nutritional

- Gluten sensitive enteropathy
- Iron, folic acid, zinc deficiencies
- Vitamin B1, B2, B6 and B12 deficiencies

#### Genetic

- Ethnicity
- HLA haplotypes

#### Allergic / immunologic

- Local T- lymphocytes cytotoxicity
- Abnormal; CD4: CD8 ratio
- Dysregulated cytokine levels
- Microbe induced hypersensitivity
- Sodium lauryl sulfate sensitivity

- Food sensitivity
- Drugs and RAS

#### Systemic diseases associated with RAS [9]

- Behcets disease
- MAGIC syndrome
- Marshalls syndrome
- Sweet's syndrome
- Crohns diseases
- Ulcerative colitis
- Cyclic neutropenia
- HIV infection

#### Clinical Manifestations

Recurrent aphthous stomatitis comprises recurrent bouts of one or several rounded, shallow, painful ulcers at intervals of a few months to a few days. All forms of RAS are painful recurrent ulcers. Patients occasionally have prodromal symptoms of tingling or burning before the appearance of the lesions [10,11].

There are three different forms of presentation of ulcers in ROA: minor, major, and herpetiform [12,13].

#### Minor type (Mikulicz's aphthae)

The most frequent type of aphthae affecting about 80% of RAS patients [14].

According to Robert E. Marx and Diane Stern [15] the lesions emerge in four stages

- **Prodromal stage** – the individual will experience a tingling or burning pain in a clinically normal appearing site.
- **Preulcerative stage** - red oval papules appear and the pain intensifies
- **Ulcerative stage** - the classic ulcer appears; it will measure between 3 and 10 mm and may last 7 to 14 days
- **Healing stage** - granulation tissue followed by epithelial migration incurs healing without scar.

#### Major type

#### Synonyms

Sutton's aphthae, periadenitis mucosae necroticans, stomatitis neurological chronica.

Major recurrent aphthous stomatitis (MaRAS) is a rare, severe form of RAS. According to the review of this disease by Hjorting – Hansen and Siemssen, there is no predilection for occurrence in any particular age group, although females are affected more frequently than males [16]. The ulcers of Major RAS persist for up to 6 weeks and often heal with scarring. The depth of the involvement is also responsible for the chronicity and scarring of these ulcers. Major RAS usually has its onset after puberty and is chronic, persisting for up to 20 or more years [17]. They are frequently found in patients infected with human immunodeficiency virus perhaps because of the amplification of local immune imbalance secondary to HIV disease.

Extreme pain, fever, associated edema, jaw trismus, and lymphadenitis are characteristic. Because Major RAS often involves underlying mucous glands, at one time major aphthae were thought to be associated with salivary glands hence the term periadenitis mucosae necroticans recursens.

#### Herpetiforme type (Cook's aphthae)

The third and least common variety of RAS is herpetiform (HU), characterized by multiple recurrent crops of small, painful ulcers that are widespread and may be distributed throughout the oral cavity. They were first described by Cooke in 1960 [18]. It occurs in less than 10% of patients with RAS. As many as 100

ulcers may be present at a given time, each measuring 2- 3 mm in diameter, although they tend to fuse and producing large irregular ulcers. HU may have a predisposition for women and have a later age of onset than other types of RAS [17, 19] or may represent a spectrum of oral disorders manifesting as recurring ulcers [17]. They last for 7 to 30 days and have the potential to scar.

Minor RAU (MiAU) has a tendency to appear on the movable, lining, and non-keratinized mucosae, predominately buccal and lip mucosa, ventral tongue, soft palate, and in the vestibule. Major RAU (MaAU) is seen on the soft palate and fauces, tongue, and buccal and labial mucosae while herpetiform aphthous ulceration (HAU) involve the anterior part of the mouth, tip lateral and ventral tongue, and the floor of the mouth but rarely appear on the lips [11].

**Major criteria for recognizing and diagnosing the condition as RAS minor**

Major criteria	Description
External appearance	Single or multiple round / oval shaped ulcers, never preceded by vesicles. The ulcers are shallow and have regular margins and a yellow grey base surrounded by thin erythematous halos. Variable in size, but less than 1cm in diameter.
Recurrence	At least three attacks of RAS within the past 3 years and the recurrences do not affect the same focal site.
Mechanical hyperalgesia	The lesion is painful and the pain is exacerbated by movement of the area affected by the ulcer.
Self – limitation of the condition	The ulcer heals spontaneously without sequelae either with or without treatment.

**Minor criteria for recognizing and diagnosing RAS minor**

Minor criteria	Description
Family history of RAS	A positive family history of RAS is present.
Age at onset	The first RAS attack started before the age of 40 years
Location of ulcers	Occur on non-keratinized oral mucosa
Duration of the lesion	Each bout of ulceration lasts from a few days to two weeks
Pattern of recurrence	Irregular
Histological examination	Shows non-specific inflammation
Presence of a precipitating factor	The attacks are triggered by hormonal changes, exposure to certain foods or drugs, intercurrent infections, stress and local trauma.
Presence of haematinic deficiencies	Laboratory investigations reveal an accompanying haematinic deficiency. In particular, ferritin, folate, iron, vitamin B and zinc
Negative association with smoking	RAS patients is a non-smoker or develops the ulcer after stopping smoking
Therapeutic trial with glucocorticoids	Positive response to treatment with local or systemic steroids.

**Diagnostic criteria**

Due to the absence of a definitive aetiology or diagnostic test for RAS, the identification of RAS in clinical practice usually, relies on the combination of history, clinical features and histopathology. A set of diagnostic criteria for Minor RAS which are meant to distinguish the condition from other diseases, and to be practical, all based on working knowledge of aphthous ulcers and clinical experience have been reviewed by S.S Natah et al. The diagnosis of primary RAS minor (idiopathic) or secondary RAS minor (that occurs in

association with systemic diseases) can be made if the condition fulfills the four major criteria (which are necessary to establish the diagnosis of Minor RAS) plus at least one of the minor (supportive) criteria [20].

## Treatment

### Goals of treatment

Treatment of RAS has 4 major goals:

- Ulcer management (to promote healing and reduce duration),
- Pain management (to reduce morbidity and enhance function),
- Nutritional management (to ensure adequate food and fluid intake), and
- Disease control (to prevent recurrence or reduce frequency).

The relative importance and priority of each goal depends on the severity of the condition.

According to Crispian Scully et al [21] 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. If a precipitating factor(s) is identified, the HCP should try eliminating it first.

**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 use corticosteroids 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) or fluocinonide ointment 0.05 percent in Orabase (1:1) if the ulcer(s) recur on the same site, used three times daily.

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.

**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. In addition, oral medicine specialists may administer intralesional injections of a corticosteroid such as betamethasone, dexamethasone or triamcinolone to enhance or boost the local response, thus allowing for shorter systemic treatment. In patients with poor oral hygiene, professional help from a dental hygienist should be considered.

## Management/Treatment [22]

### Non-pharmacological therapy

Oral hygiene, trauma prevention, avoidance of certain foods/drinks, use of straws, relaxation techniques

**Pharmacological therapy for minor to major recurrent aphthous stomatitis:**

Type of treatment	Preparations	Particularly suitable for
Over-the-counter conservative treatment	Liquid antacids or 3% hydrogen peroxide/water solution, 1:1 as a gargle	Minor recurrent aphthous ulcer

Type of treatment	Preparations	Particularly suitable for
Covering agents/topical analgesics/anesthetics/numbing agents/anti-inflammatory	<ol style="list-style-type: none"> <li>1. Orabase, Benzylamine hydrochloride (HCL) mouthwash</li> <li>2. Diphenhydramine EMLA, or mixed 1:1 with Kaopectate or aluminum hydroxide, or Maalox</li> <li>3. Viscous lidocaine 1:1 with Benadryl plus</li> <li>4. Aphthasol 5%(amlexanox) paste, apply over canker sore, forms a film which protects canker sore and delivers medication, four times daily (QID), after meals and at bedtime (HS).</li> </ol>	<p>Single, sporadic, infrequent minor or major ulcers.</p> <p>Accelerate resolution of pain and healing, have not been shown to reduce the rate of occurrence</p>

Type of treatment	Preparations	Particularly suitable for
Antiseptic mouthwashes	<ol style="list-style-type: none"> <li>1. Benzylamine hydrochloride (Difflam), at least three times daily (TID)</li> <li>2. Chlorhexadine gluconate (Peridex/Corsodyl) at least TID</li> <li>3. Carboxymethylcellulose paste (Orabase)</li> </ol>	Antibacterial mouthwashes. Primarily for reduction of pain and with wide range of oral sites not accessible to covering pastes, also speed up healing

<p>Low potency topical steroid pellets and Ointments</p>	<p>1. Triamcinolone 0.1% in carboxymethylcellulose paste (Adcortyl in Orabase) &amp; Triamcinolone acetonide (Kenalog in Orabase), qid to dried areas around ulcers with moistened finger. Allow film to hydrate before allowing contact with uninvolved mucosa, one application last thing at HS (minor AU).</p> <p>2. Hydrocortisone sodium succinate 2.5mg (Corlan) qid during attack, bid between attacks for at least 6 weeks before reducing to use during attacks only (minor AU) (use of steroids is consensus effective treatment from almost all sources).</p>	<p>Anti inflammatory agents. Frequently recurring mild ulcers or major ulcers. Steroids may be used to reduce the frequency of attacks. Most successful with ulcers located in the sulci where pellet can be left to dissolve.</p>
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Type of treatment	Preparations	Particularly suitable for
<p>Aerosols</p>	<p>1. Beclomethasone dipropionate aerosol (Beconase spray) 2 puffs (100 micrograms) spray onto affected mucosa to a max of 8 puffs/day. Reduced risks of adverse effects over Betamethasone mouthwash but slightly less effective. Useful if only one or two ulcers are present (moderately severe).</p>	<p>Most useful when more potent steroid needed and for inaccessible sites (i.e., soft palate or oropharynx).</p>

Type of treatment	Preparations	Particularly suitable for
Steroid mouthwashes	<p>1. Betamethasone sodium phosphate (Betnesol mouthwash/Diprolene) one 0.5mg tablet dissolved in 5 to 10 ml of water used as a mouthwash qid during ulcer attack. Must be held in mouth for a minimum of 3 minutes for maximum effectiveness; spit out after use. Can be used 6 times a day under strict supervision</p> <p>2. Fluocinonide (Lidex), clobetasol (Temovate) same as Betamethasone</p>	Useful with wide range of ulcer sites and of sufficient severity to merit therapeutic treatment. Monitoring for side effects of steroids is essential as some medication always gets swallowed inadvertently.

**Pharmacological therapy for severe aphthous stomatitis**

Type of treatment	Preparations	Particularly suitable for
Systemic drugs	<p>Oral prednisolone 40 mg for 5 days, reduce by 5 mg every 2 days to 5 mg, reduce by 1 mg/day until complete. Monitor severity closely at 15 mg dos; select maintenance dose to maintain remission before ulcers reappear</p> <p>Thalidomide 200 mg qd or bid 3 to 8 weeks for HIV or Behcet's disease severe AU</p> <p>Colchicines 500 micrograms/day or Pentoxifylline 400 mg tid</p> <p>Azathioprine 50 to 100mg daily primarily as a steroid sparing agent during maintenance phase of treatment</p>	Reserved for severe recurrent aphthous ulcers interfering with nutrition.
Tetracycline	<p>Tetracycline 250-mg capsules dissolved in 10 ml of water and used as a mouthwash. Gargle for 3 minutes then spit out</p> <p>Topical tetracycline</p>	<p>Tetracycline 250-mg capsules dissolved in 10 ml of water and used as a mouthwash. Gargle for 3 minutes then spit out</p> <p>Topical tetracycline</p>
Topical immunomodulatory agents	<p>Azelastine, human alpha-2 interferon cream, topical cyclosporine, deglycyrrhizinized licorice, topical 5-aminosalicylic acid (5-ASA), amlexanox 5% paste, and prostaglandin E2 (PGE2) gel.</p>	Suggested to be of some benefit in the management of recurrent aphthous stomatitis may significantly reduce the pain and healing time to RAS ulceration.

**Pharmacologic therapy for children under age 12**

First Line	Benzydamine and local anesthetics Lidocaine gel preps may be applied several times a day in small quantities and before meals to improve eating
In more severe cases	Triamcinolone 0.1% in carboxymethyl cellulose paste can be managed only by older children. Hydrocortisone sodium succinate 2.5mg tablets are safe in children because of their low steroid potency

**Treatment for HIV-associated ulcers**

- Antifungal treatment may be required in conjunction with steroids.
- Biopsy may be indicated to ensure treatable infection (i.e., herpes simplex, cytomegalovirus ).
- A further immunosuppression with new infections may arise.
- Steroids should be used with caution: prednisolone 40 mg for 4 days, reducing by 5 mg every 2 days until 5 mg, then reducing by 1 mg per day to 0 mg provide rapid relief.
- Intralesional injection delivers high doses of steroids directly to the lesion and avoids long-term systemic adverse effects.

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