

## Recurrent aphthous stomatitis: An overview

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### Abstract

For many years, a common and painful oral mucosal ulcer termed as “Recurrent Aphthous Stomatitis” remains a mystery affecting the oral cavity as a whole. Its etiopathogenesis is still unclear though its prevalence is high. Researchers, dental practitioners have been trying to reveal its underlying secrets that have been creating a major drawback in the treatment strategy but in the end it remains the same. In this article, we have tried to describe briefly about the etiology and clinical features of recurrent aphthous stomatitis along with the diagnosis and management options by searching out the literatures available until now.

**Keywords:** Recurrent aphthous stomatitis, Etiology, Diagnosis, Management.

### Introduction and Epidemiology

Hippocrates (460–370 BC) who has been known as the “Father of Medicine” first used the term ‘aphthai’ which means ‘ulcer’ to express the ulceration of the mouth. Hence, the term ‘Aphthous’ is derived from the Greek word ‘aphtha’.<sup>1</sup> In 1888, von Mikulicz and Kummel gave first valid clinical description of the recurrent aphthous stomatitis (RAS).<sup>2</sup> Recurrent aphthous ulcer or stomatitis (RAS) appears to be the most common disease of the oral mucosa. It can affect children to young and old aged person because of its recurrent nature. Children and women are the main victim of RAS.<sup>3,4</sup> 10 to 19 years old people are more commonly affected than any other ages and of total general population, 5-25% general peoples are frequently affected. These ulcers are small, round shaped. The centre of the ulcer is shallow and necrotic, margins are raised and surrounding of the ulcer margins is erythematous. Health history of the patient, clinical examination can be useful for the diagnosis. Local factors, systemic factors, genetic factors, immunopathogenic factors have been associated with RAS. Analgesic, antimicrobial and immune system enhancing drugs have been used but specific management is not found yet. As there are advancements in dental research field, we can assume that disease origin, diagnosis, prevention and treatment of RAS will be revealed some day very soon.

**Etiology:** There are various etiological factors associated with RAS.<sup>5</sup>

- Hormone Related Factors:** In females, menstrual cycle, pregnancy, dysmenorrhea<sup>6</sup> plays an important role in formation of RAS ulceration. Sex steroids may increase/decrease RAS.<sup>7</sup> In pregnancy period especially in first trimester, RAS tend to be increased.<sup>8</sup>
- Traumatic Injuries:** Accidental tooth-brushing trauma, trauma during local anesthetic injection

application for dental treatment, instrumental trauma during dental treatment, trauma due to unfitting dentures, sharp cusp tip or irregularities of the broken cusp of the teeth can cause RAS.<sup>9,10</sup>

- Drug Related Factors:** Some drugs like sodium hypochloride, phenobarbital, phenindione, phenylacetic acid, propionic acid, diclofenac may cause ulcers like RAS.<sup>11,12</sup>
- Food Hypersensitivity Related Factors:** It is assumed that gluten containing wheat flour, cereals, cheese, chocolate, peanuts, almonds, strawberries, tomatoes, coffee may have association with RAS formation.<sup>13,14</sup>
- Nutritional Deficiency Factors:** Iron deficiency anaemia and nutritional deficiency like vitamin B<sub>1</sub>, B<sub>2</sub>, and/or B<sub>6</sub> may cause ulcers associated with RAS.<sup>15,16</sup>
- Stressful Lifestyle:** Daily life stresses, especially psychological stress beyond limit due to mental trauma and/or, nervous breakdown may cause RAS.<sup>17</sup>
- Tobacco Smoking:** The smokers have less frequently developed RAS ulcers than non-smokers due to hyperkeratinization of the oral mucosa which is less susceptible to ulceration. It is found that a smoker when stops smoking develops ulcers.<sup>18-20</sup>
- Genetical/Hereditary Factors:** RAS may occur in members of the same family and the predilection is high. Moreover, RAS may occur in any individual without family history of RAS.<sup>21,22</sup>
- Other Factors:**
  - Sodium Lauryl Sulfate containing toothpaste.
  - Inflammatory bowel diseases, e.g. Crohn’s disease, ulcerative colitis.
  - Para functional habits, e.g. Lip/Cheek biting trauma.

- d. Microorganisms, e.g. Streptococcus sanguis, Streptococcus mitis, Helicobacter pylori, Human cytomegalo virus, Epstein-barr virus.

### Classifications and Clinical Features

There are three variations in RAS according to clinical presentations:<sup>23</sup>

1. Minor recurrent aphthous stomatitis,
2. Major recurrent aphthous stomatitis, and
3. Herpetiform ulceration.

#### 1. Minor RAS or, Mikulicz's Aphthae or, mild aphthous ulcers:

- a. Among others types, it is the most common type of aphthous ulceration (85% of patients involved).<sup>24</sup>
- b. These are superficial ulcers, round to elongated shaped, 4-5 mm in diameter, 1 to 5 in numbers.<sup>22,25,26</sup>
- c. These may appear in labial and buccal mucosa, the floor of the mouth and the ventral or lateral surface of the tongue (usually in non-keratinized mucosa of the oral cavity) (Fig. 1).<sup>27</sup>
- d. These ulcers heal within 2 weeks and do not scar.<sup>21,28</sup>



**Fig. 1: Minor Aphthous Ulceration**

#### 2. Major RAS or, Sutton's Disease or, Periapical Mucosa Necrotica Recurrens:

- a. It is the less common type of recurrent aphthous ulceration (of all RAS patients 10-15% are involved). HIV (human immunodeficiency virus) infected patients are the worst sufferer of this type of RAS.
- b. These lesions are round shaped, >10 mm in diameter.
- c. These lesions may occur in lips, tongue, soft palate, and the palatal fauces (Fig. 2) causing pain and difficulties in swallowing.
- d. These can produce scars due to deep sitting ulceration and can last for weeks to months.<sup>22,25</sup>



**Fig. 2: Major aphthous ulceration**

#### 3. Herpetiform Ulceration:

- a. Among total RAS cases, only 5-10% is Herpetiform ulcers.<sup>24</sup> Females are affected mostly and it occurs in late age.<sup>27</sup>
- b. Herpetiform ulcers are small, grey in color, have no marked border, usually 1-2 mm in diameter, appear in clusters and multiple ulcers (5 to 100 in numbers) can be present at the same time (Fig. 3). Individual ulcers can merge with each other to form larger cluster. Clusters appear to be erythematous and can cover a large area making eating, drinking and speaking very painful and difficult.
- c. These ulcers may appear in non-keratinized oral mucosa especially ventral surface and lateral margins of the tongue, floor of the mouth.<sup>26</sup>
- d. This type of cluster forming ulcers can take up to 7-14 days to heal but it can vary depending upon period of intervals between recurrences. These ulcers do not leave scars after healing.



**Fig. 3: Herpetiform ulceration**

Other clinical features, e.g. fever, lymph node enlargement, GIT upset, mucosal lesion other than non-keratinized mucosa of the oral cavity is uncommon in RAS. If these clinical features arise, other diseases such as IBD, HIV or any other autoimmune diseases should be taken in consideration.<sup>29,30</sup>

**Immunopathogenesis:** It's still unclear about the documentation of immunological connection in pathogenesis of RAS. But it was reported earlier that

both cell-mediated and humoral immune response is involved. Macrophages and mast cells produce T-cells and Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) which results in inflammation of the tissue. Inflammation can be initiated by TNF- $\alpha$  affecting either adhesion capacity of endothelial cell or chemotactic activity of the neutrophils. At the beginning of the ulcer lymphocytic infiltration occurs in the epithelium commencing a series of events, e.g. vacuole formation in keratin cells, papule in the mucosa and inflammation of the vascular tissue surrounding the papule. The papule then bursts and produces ulceration of the mucosa. The ulcer is covered by membranous tissue consists of plasma cells, neutrophils, lymphocytes. During the remission period, epithelium tends to regenerate. Interleukins, e.g. IL-2, IL-10, NK-cells, CD1+ Langerhans cells, CD4+, CD8+, Endothelial intercellular adhesion molecule-1 (ICAM-1), Lymphocyte function antigen-3 (LFA-3), Immunoglobulins, e.g. IgG, IgM, IgA, factor XIIIa+ dendrocytes, dendritic cells are involved in RAS formation.<sup>31-39</sup>

**Diagnosis and Differential Diagnosis of Recurrent Aphthous Stomatitis (RAS):** There is no accurate diagnostic tool to rule out RAS from other mucosal lesions which are the manifestation of systemic disorders except family history and/or, clinical history. Diagnostic design is made to see if other disorders coincide with RAS. A complete blood count, haemoglobin percentage, haematinic level estimation, ESR should be done to see any vitamin or iron deficiency is present. To diagnose autoimmune disorders anti gliadin, anti endomysial antibody, C-reactive protein test is done. Clinical examination, e.g. inspection and palpation of the ulcer is necessary. During inspection number, site, size and shape of the ulcer along with appearance of the surrounding tissue is taken care of. During palpation, base of the ulcer is examined to see if it's soft or, firm; edges are irregular or, not and free or, fixed to underlying structure or not. Lymph node is palpated to examine enlargement.

Differential diagnosis is made upon the clinical presentation of other diseases manifest similarities with RAS. If keratinized attached oral mucosa, e.g. hard palate and/or, gingiva is affected along with fever, Herpes Simplex Virus infection can be taken in consideration because RAS appears in movable oral mucosa and fever is uncommon.<sup>40</sup> Lichen planus also have ulcerative lesions in some instances but less painful than RAS and can be differentiated by its appearance on both movable and attached oral mucosa where RAS is confined to movable oral mucosa.<sup>41</sup> Other mucosal ulcerations, e.g. vesiculo-bullous lesions, erythema multiforme, varicella zoster virus infections have their own characteristic presentations different than RAS depending upon ulcer distribution sites, fever, malaise, papule/macule formation external to oral cavity, tendency to rupture etc.<sup>42-45</sup>

**Management of Recurrent Aphthous Stomatitis:** As there is no definitive underlying cause found for the origination of RAS, the basic protocols for the management is pain relief, maintenance of normal function and reduction of ulcer duration and recurrence. The following management methods are found to be helpful but have few proven evidences:

**Lifestyle Modification:**<sup>46</sup>

- A. Vitamin Supplements:** Vitamin B complex deficiency can be supplemented by vitamin B complex tablets, capsules, syrups available.
- B. Iron Deficiency Supplements:** Iron deficiency anaemia can be treated by iron, folic acid, zinc containing capsules available.
- C. Dietary Changes:** Food allergens suspected to produce RAS can be avoided by removing them from daily food menu. Artificial coloring and flavoring agents should be avoided. Varieties of freshly prepared diet should be added and oily, spicy food can be avoided.
- D. Maintenance of Good Oral Hygiene:** Brushing twice daily after breakfast and before going to bed at night followed by regular mouth rinsing with mouthwash can keep up good oral environment reducing the opportunity to build up opportunistic microorganisms colonization thus limiting the recurrence of ulceration.
- E. Use of Sodium Lauryl Sulfate (SLS) free Toothpaste:** As SLS seems to be a potent component of RAS formation found in toothpastes, use of SLS free toothpaste can be a solve for reduction of RAS episodes.
- F. Safety during Dental Treatment and Appliance Correction:** Accidental trauma from dental instruments can be avoided by dentists, chronic irritation from ill fitting dental appliances can be corrected, overhanging filling or, sharp cusps can be grinded judiciously which are causing RAS.
- G. Aloe Vera:** Topical application on the ulceration in gel form and/or, as a mouth rinse seems to be quite helpful in RAS.

**Topical Therapy:**

- A. Topical Anaesthetics :** Topical anesthetics, e.g., 1% lidocaine cream, 2% lidocaine gel/spray used alone or, in combination with adrenaline (1:8000), benzocaine lozenges, polidocanol paste, spray combining tetracaine 0.5% and polidocanol 0.1%, Diclofenac 3% gel combining with 2.5% hyaluronic acid directly applied on the ulcer can relief the pain and prolong the remission period making the patient comfortable to eat and drink.<sup>47-49</sup>
- B. Mouthwashes:**
  - i. Chlorhexidine Gluconate:** 0.2% Chlorhexidine gluconate as an aqueous mouth rinse, 0.1% Chlorhexidine gluconate as mouthwash, 1%

- Chlorhexidine spray/gel is proven to be helpful for RAS treatment. Chlorhexidine in combination with dexpanthenol spray, solution and tablets is effective, too.<sup>50</sup>
- ii. **Listerine** : Regular use of antimicrobial mouthwash, e.g., Listerine can produce prolong recurrence period of RAS.<sup>51</sup>
  - iii. **Tetracycline and Minocycline Mouthwashes:** Both tetracycline and minocycline is helpful as a mouthwash in RAS treatment. Tetracycline has antibacterial effect and minocycline has immunological regulatory property. 0.25% chlortetracycline containing mouthwash produces healing but 0.2% minocycline containing mouthwash is way too effective than tetracycline mouthwash.<sup>52,53</sup>
- C. Topical Corticosteroids:** Triamcinolone oral paste, Dexamethasone, Phenytoin, 0.05% Clobetasol Propionate produces rapid healing and pain relief from ulceration and treatment of choice in RAS when previous treatment regimens fail. Long term use of these steroids can give rise to candidal infection.<sup>54-56</sup>
- D. Intralesional Corticosteroids:** Use of topical anaesthetic prior to submucosal application of 0.1-0.5 ml of triamcinolone acetonide intralesional injection can reduce inflammation and pain. If the ulcer is large, dose can be increased.<sup>57</sup>
- E. 5% Amlexanox Hydrochloride oral Cream:** 5% Amlexanox Hydrochloride formulation can produce rapid healing by re-epithelialization of the epithelial breaching in ulcerative oral mucosa, thus reproducing epithelial integrity. This formulation is approved by U.S. FDA. 3-4 times application daily can reduce the pain and can make the patient comfortable for normal oral functions.<sup>58</sup>
- Systemic Therapy:**
- A. Colchicine:** As the ulcer in RAS produces pain due to cell mediated immune response, colchicine can be a drug of choice for pain relief due to its anti-inflammatory effect. It has an inhibitory effect on cell mediated immune response. Daily use of 0.5–2 mg of colchicine can help in reducing RAS recurrence episodes but the optimal dose of 1.5 mg daily seems to be accurate for healing. If colchicine alone can't produce significant healing, benzathine penicillin adjuvant therapy is proven to be more outstanding. The use should be continued otherwise discontinuation can bring up the recurrence.<sup>59</sup>
- B. Pentoxifylline:** Another pain producing factor is Tumor necrosis factor alpha (TNF- $\alpha$ ) due to cell mediated immune response. Pentoxifylline is proven to inhibit TNF- $\alpha$  production. 3 times daily use of 300-400 mg of pentoxifylline can reduce the pain and recurrence episodes.<sup>60</sup>
- C. Systemic Corticosteroid Therapy:** Daily dose of oral corticosteroid, e.g., prednisolone 10–30 mg orally can be taken not more than a month or, 40-60 mg single dose in the morning for not more than 2 weeks when the recurrence episode produces hamper in normal oral function and colchicines, pentoxifylline therapy are not satisfactory enough. Systemic corticosteroids should not be given in high dose for a long time because they can cause adrenal suppression.<sup>57</sup>
- D. Other Systemic Agents:** Other systemic medications, e.g., daily dose of antimicrobial drug such as 40 mg of doxycycline, daily dose of 300 mg of zinc sulfate can reduce the ulcer size and produces immense remission period between recurrence.<sup>61,62</sup>
- New Treatment Protocols:** There are new treatment strategies that have been proposed which are still controversial and still remain mysterious (Table 1). These can be applied according to severity and recurrence of RAS. These are as follows:<sup>46,48,60</sup>

**Table 1: New Treatment Strategies for the treatment of RAS**

Natural methods	Home remedies	Topical therapy	Systemic therapy
1. Lactobacillus acidophilus. 2. <u>Herbs-</u> (i) Licorice (DGL) (from Glycyrrhiza glabra). (ii) Chamomile (Matricaria recutita). (iii) Echinacea (E. purpurea, E. angustifolia, E. pallida). (iv) Myrrh (Commiphora molmol). (v) Myrtle Communis.	1. Saltwater Solution and Sodium Bicarbonate. 2. Hydrogen Peroxide Solution. 3. Milk of Magnesia. 4. 500mg L-Lysine. 5. Liquid Antihistamine.	1. Sucralfate. 2. 5-Aminosalicilic Acid 5%. 3. Lactic Acid 5%. 4. Prostaglandin E2.	1. Dapsone. 2. Thalidomide. 3. Levamisole. 4. Rebamipide. 5. Irsogladin. 6. Antimetabolite: Methotrexate. 7. Cyclosporine. 8. Interferon- $\alpha$ . 9. Silver Nitrate. 10. Laser Therapy. 11. Ultrasound therapy. 12. Excision.

## Conclusion

Besides various treatment strategies, effective treatment method still remains unclear because of the mysterious immunopathogenesis and exact cause of origin of RAS. Since the advancement in research field in dentistry is at its peak, more and more controlled studies should be carried out to evaluate the efficacy and safety of various drugs in RAS management because of their cytotoxic effects. First line safe drugs should be developed for the primary management during disease severity. Also, new treatment strategies should be practiced which are still in controversy and mystery yet to be revealed.

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