

# Therapeutic Management of Recurrent Aphthous Stomatitis: A Review of the Growing Knowledge.

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## ABSTRACT

Recurrent aphthous stomatitis (RAS) is one of the common clinical oral diseases that produces painful ulcerations in the oral cavity. It is also called canker sore or mouth ulcer. Although, the clinical features and characteristics of this disease are easily defined, the etiology and the pathophysiology remain 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.

**Keywords:** Aphthous Stomatitis, Canker sore, Mouth ulcer, Treatment modalities.

## INTRODUCTION

Recurrent aphthous stomatitis (RAS) or Recurrent aphthous ulcer (RAU), frequently referred to as 'canker' sores, is among the most common oral ulcerative and vesiculobullous condition encountered in children and adults.<sup>[1-3]</sup> The classic presentation of RAS is recurrent, self-limiting ulcers that mainly affect non-keratinized oral mucosa. The ulcers heal spontaneously within 7-14 days. The etiology appears to be multifactorial with numerous causative and precipitating factors.<sup>[3]</sup> Based on size and number of aphthae the disease can be divided into three different clinical variations: minor recurrent aphthous stomatitis (MiRAS), major recurrent aphthous stomatitis (MaRAS) and herpetiform ulcers. Minor aphthous accounts for approximately 70-90% of recurrent aphthous stomatitis patients presenting the most common form of aphthous ulceration.<sup>[4]</sup> So far, there is no specific treatment for these lesions and the management strategies depend mainly on the severity of the disease.

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In most situations topical therapy can be successful, but sometimes systemic therapy is mandatory for people who are presenting major ulcers or large number of minor ulcers with associated syndromes.

This article reviews the main different types of (RAS) therapies with brief explanation of the etiology, pathophysiology and clinical features of the disease.

**Table 1: Factors proposed as possible causative agents of RAS.**

Host Factors:	Environmental factors:
<ul style="list-style-type: none"> <li>• Genetic factors</li> <li>• Food allergy</li> <li>• Vitamin deficiency</li> <li>• Immune dysregulations</li> <li>• Physical or emotional stress</li> </ul>	<ul style="list-style-type: none"> <li>• Microtrauma.</li> <li>• Local trauma</li> <li>• Chemical injury or physical trauma.</li> <li>• Infections</li> <li>• Smoking</li> </ul>

### Etiology

Although Several factors proposed as possible causative agents of RAS [Table 1]<sup>[5]</sup>, RAS remains a common oral mucosal disorder in most communities of the world, its precise etiology remains unclear. No precise trigger has ever been demonstrated, and there is no conclusive evidence for a genetic predisposition to RAS in most patients. Currently, RAS is recognized as an immunologically mediated, inflammatory oral condition rather than an infectious disease.<sup>[6]</sup>

### Clinical Features

Aphthous ulcers have been categorized into three groups: minor, major and herpetiform. Table 2 lists the categories of aphthous ulcers and their respective features.<sup>[7-10]</sup> Minor aphthae [Figure 1] are by far the most common presentation of RAS, representing 80-85% of cases.<sup>[7-10]</sup> Ulcers are up to 1 cm in size, shallow and generally last 10-14 days.

**Table 2: Categories of Aphthous ulcer.**

	Features at presentation			
	Size (mm)	No. of ulcers in an outbreak	Duration (days)	Scarring
Minor ulcers	5-10	Few	10-14	No
Major ulcers	>10	Few	14+	Yes
Herpetiform ulcers	<5	Many (5-100)	10-14	No

They occur on the labial or buccal mucosa, soft palate, tongue or floor of the mouth.<sup>[7-10]</sup> There may be a prodromal burning or stinging sensation prior to appearance of the lesions. Scar formation does not occur with healing of minor aphthae.<sup>[7-10]</sup> Major aphthae [Figure 2] are rare, representing approximately 10-15% of RAS cases. They are defined by ulcers larger than 1 cm, are generally deeper and have a longer duration than minor aphthae. Major aphthae may form a scar with healing.<sup>[7-10]</sup> Major aphthae can be seen with human immunodeficiency virus (HIV) infection [Figure 3]<sup>[11]</sup>, and HIV testing should be considered when major aphthae are present.<sup>[12]</sup> The herpetiform presentation [Figure 4] is also rare, representing 10% or less of all RAS cases, and is defined by outbreaks of numerous, small, vesicular lesions. Vesicles may coalesce into larger ulcers. Duration of outbreaks is similar to minor aphthae, and generally no scar is formed.<sup>[7,9,10]</sup>



**Figure 1: Minor recurrent aphthous ulceration. The lesion is discrete, crateriform, uniform in outline and less than 1 cm in diameter.**



**Figure 2: Major recurrent aphthous ulceration. The lesion is greater than 1 cm in diameter and involves deeper tissue layers.**



**Figure 3: Intraoral aphthous stomatitis in a patient with Acquired Immunodeficiency syndrome. A, Major aphthous lesion in the left soft palate. B, Ulcerations of the uvula in the same patient.**



**Figure 4: Herpetiform recurrent aphthous ulceration. Lesions are nonvesicular and 2-3 mm in diameter.**

### PATHOPHYSIOLOGY

The pathophysiology of aphthous ulcers is poorly understood. Histologically, aphthae contain a mononuclear infiltrate with a fibrin coating.<sup>[13]</sup> Patients with recurrent aphthae may have alteration of local cell-mediated immunity. Systemic T- and B-cell responses have also been reported as altered in patients with recurrent aphthae.<sup>[14]</sup> The complex interactions of various etiological factors together can trigger ulcer formation. Etiological factors can be classified into predisposing factors and precipitating / triggering factors. The factors like human leukocyte antigen (HLA) associations, immune dysregulation, nutritional deficiency, personality type A are the predisposing factors. Microtrauma, infections, stress could be the initiating or triggering factor for ulcer formation. Those individuals who are susceptible when exposed to the triggering factors for certain duration tend to develop ulcers. Based on the intensity and duration of the triggering factors, ulcer starts growing till the factors are removed. Pain suffered by the patients is directly proportional to the

size of the ulcer and severity of the triggering factors. For example the serum cortisol level : which is a biomarker of the stress was increased in the subjects with RAS and the increase was directly proportional to the ulcer size.[15]

Guidelines for management of patients

The successful management of RAU depends on a careful patient work-up and correct diagnosis including any features peculiar to a patient's presentation. It also requires patient understanding of the nature of the disease. A patient who leaves the consultation without an understanding of the nature of the condition and that it represents a specific disease like any other disease will not regard the condition as anything other than a mouth ulcer. This is a self-defeating position. The diagnosis and management of RAU requires consultation time and review time and preferably not slotted against "more important" issues such as a dental restoration. A sequence for the diagnostic process used by the authors is:

#### 1. General medical history

written pro-forma , include medications history, review with the patient , signed by both patient and clinician.

#### 2. History of the ulcerative disease

age at onset, duration of condition, frequency of recurrence , remission periods , exacerbating factors/events/medications, food intolerance (dairy, wheat, nuts, tomatoes, chocolate) , role of trauma, association with stress/anxiety, familial history.

3. **Clinical features of lesions** – historical single or multiple average size, margins – irregular (traumatic), linear (Crohn's disease) , vesicular or non-vesicular , duration of individual lesions , tissue morbidity , level of functional morbidity and restriction , rate of onset (erythema multiforme).

#### 4. Extra oral features

ocular or genital lesions (Behcets Disease, Reiter's Syndrome) , skin lesions (erythema multiforme), GIT symptoms (inflammatory bowel disease), haematological abnormality/deficiency pyrexia, pharyngitis (PFAPA Syndrome), chondritis (MAGIC Syndrome).

#### 5. Previous assessments

Medical, specialist, haematology, serology, histopathology ,microbiology.

#### 6. Previous treatments

proprietary medications , prescription medications , clinical efficacy.

#### 7. Clinical examination

general integrity of the oral mucosa , cicatrix from previous lesions, evidence of parafunctional habits, current lesion(s), salivary function, eyes and skin, lymph nodes, pyrexia.

#### 8. Laboratory investigations

full blood examination (FBE) iron studies (serum iron, ferritin, TIBC, transferrin saturation), serum and red blood cell folate , serum vitamin B12, other mucosal conditions, e.g., lichen planus, may require

alternative blood screens. The authors employ a routine haematological screen covering full blood examination (FBE), iron studies, folate and vitamin B12 for all patients presenting with RAU. Only a small number of patients show a specific anaemia or other haematological deficiency but their exclusion is an important part of the complete patient work-up. The authors have also noted that 10–20 per cent of patients with RAU show a tendency toward a sideropenia and this requires attention. The eyes, skin and other mucosal surfaces are also examined either directly or by questioning as a routine. This is a required part of the work-up of all mucosal disease patients and in many conditions can be surprisingly informative. Similarly, folate levels are an indicator of intestinal absorption function but patients are also questioned concerning any abdominal symptoms and particularly those without an identified cause.<sup>[16]</sup>

#### Management and Treatment

The primary goals of therapy of RAS are relief of pain, reduction of ulcer duration, and the restoration of normal oral function. Secondary goals include reduction in the frequency and severity of recurrence and maintenance of remission. The best treatment must control the ulcers for the longest period with minimal side effects. The treatment approach is 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 in RAS, it is important to rule out predisposing factors and treat any such factors, where possible, before introducing more specific therapy.<sup>[12,17]</sup> The forms of therapy range from topical application to systemic administration of drugs, and even the newer technologies of ultrasound have been tried. The treatment to be initiated practically depends on the severity of the ulcers and whether its associated with any systemic illness.<sup>[18]</sup>

#### **Topical Therapy**

Topical agents are the first choice of management for RAU. They are cheap, effective, safe and available usually.

#### **Local Anaesthetics and Analgesics:**

2% Lidocaine is proven to be effective in relieving pain associated with recurrent aphthous ulcer (RAS), but combination of adrenaline (1:8000) further increases the period of pain relief which allow the patient enough time to take the meals. Patient is instructed to apply 2 to 3 drops of it directly onto the ulcer surface and ask to keep mouth open.<sup>[12]</sup> Lidocaine as a 2% containing gel (Gelicaine 2% gel, Xylocaine 2% gel), or as a spray (Xylocaine pump spray), polidocanol as a paste (Solcoseryl adhesive dental paste), and benzocaine in the form of lozenges (Anaesthesin lozenges) can be used.<sup>[19,20]</sup>

#### **Antiseptic Therapies:**

Chlorhexidine gluconate

Chlorhexidine gluconate aqueous mouth rinse may be of some benefit in the management of RAS. Studies show that it reduces the duration of ulcers but cannot prevent the recurrence of ulcers. It is generally used as 0.2% w/w (weight for weight) mouth rinse but the 0.1% w/w mouthwash or 1% gel can also be beneficial.<sup>[21]</sup>

#### Listerine

Studies showed that regular use of Listerine as mouth rinse for 6 months reduces incidence of recurrent aphthous ulcer, decrease the duration and recurrence of RAS.<sup>[22]</sup>

#### Topical Antimicrobials:

A more effective measure in the relief of symptoms caused by secondary infection is the application of topical antibiotics. A mouthwash containing tetracycline (dissolve soluble tetracycline capsule 250 mg in 5–10 ml water and rinse) or chlortetracycline is often highly effective in reducing the pain caused by severe ulceration.<sup>[2]</sup>

Other antibiotics such as aureomycin (containing 3% chlortetracycline), doxymycin, minocycline (0.2% aqueous solution), penicillin G (50 mg penicillin G potassium troches) have been proven to be effective in managing these ulcers. Also preparations containing chlorhexidine (0.2% w/w mouth rinse or a 1% gel) are also helpful in relieving symptoms.<sup>[20]</sup>

#### Topical Anti-Inflammatory Agents:

##### Amlexanox:

Topical paste of 5% Amlexanox having anti-allergic and anti-inflammatory activities has been proved to be clinically safe and efficient in several clinical studies for managing RAS.<sup>[23-25]</sup>

##### Sucralfate

Topical sucralfate is effective in treating RAS ulcerations when administered at 5ml, 4 times/day. Sucralfate exerts a soothing effect on the lesions by adhering to mucous membrane tissues and forming a protective barrier on the affected site. This drug is commonly used to treat peptic ulcers.<sup>[26]</sup>

#### Topical Corticosteroids:

Topical steroids are reserved for cases that show inadequate success from the combination of local anaesthetics and anti-inflammatory agents. Corticosteroids by their anti-inflammatory action modify, in a minor way, the progress of the ulceration at all stages.<sup>[18]</sup> The drugs most commonly adopted for local oral application in RAS are hydrocortisone hemisuccinate as 2.5 mg pellets and triamcinolone acetonide in an adhesive paste containing 0.1% of the steroid.<sup>[27]</sup> Spectrum of different topical corticosteroids may be used; all can reduce symptoms with no adrenal suppression. Few agents are currently available in new drug delivery system, which is designed to stick firmly to the wet, moving mucous, forming a protective film over the

ulcer, leading to faster pain relief and rapid healing. The paste is to be applied 2-3 times a day. Long term use of these steroids may develop local candidiasis. Other topical corticosteroids include: Triamcinolone acetonide, Clobetasol Propionate 0.05%, Fluocinonide 0.05%.<sup>[28,29]</sup> The combination of a local anaesthetic during daytime (e.g. Dynexan A gel) and triamcinolone adhesive paste at night has been proved to be very effective. Crispian Scully stated that most patients of RAS can be managed satisfactorily with the topical steroids. These when used for short period, have a very safe profile and should be the first line of treatment for recurrent aphthous stomatitis.<sup>[30]</sup> Also recently Betnesol mouthwash is being used. It is a betamethasone sodium phosphate tablet 500 mcg dissolved in 10 ml of water and used as a mouthwash for 3 min then discarded. It is administered four times a day (QID) in the presence of ulcers and twice a day (BID) in between ulcer attacks.<sup>[31]</sup> A 3-month study by Tappuni et al.<sup>[32]</sup> compared betnesol mouthwash (four times a day) with betnesol mouthwash plus colchicine tablets 0.5 mg a day. Using an ulcer severity scoring (USS) system, the authors showed significant improvement in USS of most patients in the betnesol group, as well as in the combined treatment of colchicine plus betnesol.

#### Intralesional corticosteroids:

Local submucosal injections may substantially reduce pain and inflammation. Intralesional injection of triamcinolone acetonide 0.1 – 0.5 ml /lesion can be injected into submucosal tissue directly beneath ulcer. Dose and distribution can be increased for large lesions. Pre-medication with topical anaesthetic may reduce discomfort.<sup>[29]</sup>

#### Over The Counter (OTC) Preparations:

Several prescriptions and over the counter preparations topical agents are available like Saltwater Solution and Sodium Bicarbonate [33], 7% Tannic acid in denatured alcohol (Zilactin), Camphor and phenol in 90% alcohol (Cold Sore Lotion), Copper sulphate, iodine, potassium iodide and 1.5% alcohol (ORA-5), 10% Benzyl alcohol and antimicrobial mouth rinse as Listerine.<sup>[34]</sup>

#### Herbal Treatments:

Several topical herbal treatments have shown efficacy as alternative therapies including aloe vera gel.<sup>[35]</sup> berberine gelatin<sup>[36]</sup>, Yunnan baiyao<sup>[37]</sup>, Myrtus communis<sup>[38]</sup> and citrus oil with magnesium salts<sup>[39]</sup> All of these topical herbal therapies have been used for the treatment of minor RAS only.

#### Immunomodulatory Agents:

Topical non-corticosteroid based immunomodulatory agents, which have been suggested to be of some benefit in the management of RAS include Azelastine, human alpha-2-interferon in cream, topical cyclosporin, topical 5-

aminosalicylic acid and prostaglandin E2 (PGE2) gel.<sup>[30]</sup>

### Physical Therapy

Suggested physical therapies include surgical removal, debridement or laser ablation of ulcers, low intensity ultrasound, chemical cautery.<sup>[18]</sup>

#### Laser therapy

Laser therapy is perhaps one of the most intriguing treatments. Studies have shown that laser therapy of most apthae immediately relieves pain, speeds healing, and reduces recurrence. Limitations include expensiveness and specialized training that is required to operate them. Patients who have severe disease or frequent recurrence may benefit from referral to a laser treatment center or specialist.<sup>[40]</sup>

#### Silver nitrate

Controversy continues to surround the application of silver nitrate. The therapy promotes changing the lesion to a burn. Some studies revealed decreased severity of pain. However, none have demonstrated shortened healing time. Additional and large studies are needed before this therapy can be recommended on a routine basis.<sup>[12]</sup>

### Ultrasound therapy

Twice-daily application of low intensity medical ultrasound may have a modest beneficial effect on RAUs. However as laser treatment, ultrasound is neither cost effective nor for practical use by the common practitioner.<sup>[41]</sup>

### Excision

One of the more controversial therapies involves removing biopsy specimens from lesions as a therapeutic modality, when the traumatic lesions are less painful and heal faster than aphthous ulcers. Limited data support this practice, and it cannot be recommended.<sup>[32]</sup>

### Systemic Therapy

For the severe and constantly recurring ulcerations, may be associated with systemic disease or syndrome, topical management of RAU may not be enough.<sup>[18]</sup> In these cases, systemic medications are employed. The main goals of systemic therapies are to reduce the frequency of recurrences and to minimise the duration of ulcers.<sup>[42]</sup>

#### Immune and Inflammatory Suppression:

##### Systemic steroids

Systemic corticosteroids are used as rescue treatment in patients with acute exacerbation. Oral prednisolone or its equivalent, 10–30mg/day for up to 1 month can be administered during an outbreak. To avoid adrenal suppression prednisolone can be given in high dose for short course therapy or burst therapy in which 40 to 60 mg given to patient as single morning dose for not more than 10 to 12 days.<sup>[29]</sup>

##### Dapsone

It is an antioxidant which exerts its effects primarily through suppression of inflammatory cell migration. Dapsone is an effective second-line steroid-sparing drug in the systemic treatment of RAS<sup>[43]</sup> a dose of 100–150 mg/day can be used for oral and genital apthae. Haemolysis, methaemoglobinemia and agranulocytosis are serious side-effects that may occur.<sup>[44,45]</sup>

##### Chlorambucil and Cyclophosphamide (Alkylating agents):

Therapy with alkylating agents such as chlorambucil and cyclophosphamide should be reserved for severe cases of apthosis. In general, chlorambucil (leukeran) is given initially in a dose of 6 to 8 mg/day. With a maintenance dose of 2 mg/day, the complete absence of lesions with chlorambucil as a monotherapy can be achieved.<sup>[18]</sup>

##### Cyclosporine (Calcineurin inhibitors):

Cyclosporine therapy in a dose of 3 to 6 mg/kg/day was found to be effective in about 50% of patients with recurrent apthosis either as a monotherapy or in combination with steroids to achieve a higher anti-inflammatory effect. Its use is absolutely contraindicated in nursing women. Pregnancy and renal insufficiency are considered relative contraindications.<sup>[20,29]</sup>

##### Colchicine

Colchicine is an anti-inflammatory agent that limits leukocyte activity by binding to beta-Tubulin, a cellular microtubular protein, and therefore inhibiting protein polymerization.<sup>[46]</sup> Although colchicine is generally well tolerated, the most frequent gastrointestinal adverse events include nausea, diarrhoea, vomiting and abdominal pain. Colchicine at 1.5 mg/day over 3 months showed a significant improvement of ulcers in over two thirds of patients.<sup>[47-49]</sup>

##### Azathioprine (Imuran)

Azathioprine as a monotherapy or in combination with other immunosuppressants, administered in a dosage of 1 to 2 mg/kg/day (50–150 mg/day), has been shown to reduce the incidence, frequency and severity of severe oro-genital apthae.<sup>[29]</sup> Pregnancy, lactation, severe bone marrow depression, liver function abnormalities, peptic ulcers and renal insufficiency are the main contraindications .

##### Thalidomide:

Thalidomide inhibits the production of various cytokines as a result of its effects on T lymphocytes, monocytes, and polymorphonuclear cells and selectively inhibits the production of TNF. Due to its potentially serious teratogenic and neurologic adverse effects thalidomide was initially used only in HIV-positive patients with recurrent ulcers.

However, due to its good results in controlling the recurrence of aphthosis it is now being used in HIV-negative patients with severe form or recalcitrant aphthous ulcers.<sup>[50]</sup> The therapy with thalidomide (anti-TNF- $\alpha$  actions), proved to be effective in low dose of 50 mg/day against major type of RAS and oro-genital ulcers. Usual doses are 100 to 300 mg/day. The therapy is restricted to particular cases due to teratogenicity and adverse effects such as peripheral neuropathy.<sup>[51]</sup>

#### Immune Enhancement:

Levamisole is an immunopotentiating agent that has demonstrated the ability to normalize the CD4+ cell/CD8+ cell ratio and improve symptoms in recurrent aphthous ulcers (RAU) patients. Seven placebo-controlled clinical trials assessed the efficacy and safety of levamisole in patients with RAU. Four of the studies showed a reduction in the frequency and duration of aphthous ulcers during levamisole treatment, with ulcer recurrences decreasing by half in up to 43% of patients.<sup>[52]</sup> Dosage of 10-15-mg/day for 2-3 months can reduce the pain, number, frequency and duration of ulcer. Adverse effects like nausea, hyperemia, dyspepsia and agranulocytosis limits the use of this drug.<sup>[53]</sup>

#### Biologics:

**Infliximab:** Recently, it has been shown by L. P. Robertson that infliximab (Remicade), a chimeric anti-TNF antibody, is very effective in the management of refractory and recurrent oral and genital ulcers. It is usually given in a dose of 5 mg/kg body weight intravenously in different schemes (e.g. 2, 6 and 32 weeks after the first injection).<sup>[18]</sup>

Efalizumab and Adalimumab other biological agents which are highly efficient and completely prevented the development of aphthae.<sup>[18]</sup>

**Etanercept:** Etanercept (Enbrel) is a recombinant TNF-soluble receptor can be used in cases of recalcitrant, recurrent ulceration in a dose of 25mg subcutaneously twice a week. The only adverse effect reported is mild erythema, induration and tenderness at injection site.<sup>[18]</sup>

#### Other Treatments:

**Pentoxifylline (PTX):**

Pentoxifylline is an anti-inflammatory, immunomodulatory, methylxanthine derivative that blocks neutrophil adherence and is indicated for peripheral vascular disease. It also has been used to treat infectious diseases, immunodeficiency, hypercoagulable states, a diverse group of cutaneous diseases, and RAS.<sup>[54]</sup> Dosage of 400mg three times/day showed lower pain levels, decreased ulcer size and reduced number during of RAS episodes. Because of its minimal adverse effects and progressive results this drug may be considered as

primary systemic medication in the treatment of RAS.<sup>[55]</sup>

#### Interferon Alpha

Interferon alpha 2a (Roferon A) and 2b (Intron A) have been successfully used in the treatment of mucocutaneous forms of the disease, resulting in complete or partial remission of oral and genital lesions in majority of the cases.<sup>[30]</sup>

#### Methotrexate:

Methotrexate, a folic acid analogue, in a dose of 7.5 to 20 mg weekly or 3-6mg/kg proved to be very effective in severe oro-genital aphthosis. Intermittent folic acid administration should be given after methotrexate intake.<sup>[29]</sup> Pregnancy, lactation, severe bone marrow depression, liver function abnormalities, peptic ulcers and renal insufficiency are the main contraindications.

#### 5 – Aminosalicylic acid:

Application of 5 aminosalicylic acid 5% cream, TDS for 14 days should reduce discomfort and pain with short healing time.<sup>[29]</sup>

#### Lactic acid 5% mouthwash:

It has been used in treatment of many skin lesions. The mechanism of action related to increase in spontaneous secretion of endothelial growth factor from keratinocyte. The drug used to be prescribed 5 ml, TDS for 15 minutes before meals. Studies show significant reduction in the duration, number and associated pain of aphthous ulcer.<sup>[29]</sup>

#### Irsogladin:

This drug used for treatment of gastritis and peptic ulcer studies shown that irsogladin when administered orally 2 to 4 mg/day, reduce ulcer counts increments and also taking it regularly prevent the recurrent aphthous stomatitis.<sup>[56]</sup>

#### Rebamipide:

It is the first antiulcer drug that increases the endogenous prostaglandins in mucosa and inhibits oxygen derived free radical production. Studies show that that drug administered 100 mg {tablet} TID for seven days reduced aphthae count and decreased pain with excellent recovery by seventh day.<sup>[57]</sup>

#### Diet Supplementation

Approximately, 20% of the patients who suffer from RAS have an associated nutritional deficiency which responds to appropriate replacement therapy of iron, vitamin B12 and folic acid.<sup>[18]</sup> One recent study tested the efficacy of vitamin B12 supplement in reduction of aphthous ulcer outbreaks. In a randomized, double-blind, placebo-controlled test, a total of 58 patients were studied to determine the effect of 1,000 mcg of sublingual vitamin B12 on aphthous ulcer outbreaks.<sup>[58]</sup> The authors found that “the duration of outbreaks, the number of ulcers, and the level of pain were reduced significantly (P>0.05) at 5 and 6 months of treatment.” In addition, they found that 74% of the treatment group reached had

no ulcers by the end of their 6-month observation period vs. 32% in the control group. A recently published study assessed the efficacy of dietary omega-3 fatty acid supplementation in educing symptoms of RAS and improving quality of life.<sup>[59]</sup> Although certain vitamin deficiencies have been proposed as playing a role in RAS, a large study that followed 160 patients for 1 year showed no benefit in the use of a daily multivitamin (containing 100% of the recommended daily intake of essential

vitamins) to reduce number of ulcers or frequency of outbreaks when compared to placebo.<sup>[60]</sup> Multivitamin use should not be recommended to be used as an ulcer treatment.

Other systemic therapies include harmones, gammaglobulin therapy, cimetidine, anxiolytic agents, azelastine and certain antioxidants. The efficacy of these treatment modalities have yet to be proven and further studies are required.<sup>[18]</sup>

**Table 3: First, Second and Maintenance Treatment Modalities of RAS.**

	First line treatment	Second line treatment	Maintenance treatment
Minor RAS	For 3 months local steroid mouthwash four times a day when ulcers present, twice daily when not.	Colchicine 500–1000 µg/day for 3 to 6 months	Local steroid mouthwash four times a day when ulcers present
Major RAS	Colchicine 500–1000 µg/day for 6 months. Short course of systemic steroids may precede	Azathioprine 50–100 mg/day	Local steroid mouthwash four times a day when ulcers present
Herpetiform RAS	Tetracycline mouthwashes four times a day when ulcers	Colchicine 500–1000 µg/day for 3–6 months	Tetracycline mouthwashes four times a day in prodrome
RAS in children	Hydrocortisone hemisuccinate pellets 2.5 mg four times daily	Local steroid mouthwash four times a day when ulcers present	Continue for 3 months, twice daily if no ulcers

**Table 4: Treatment Modalities of RAS.**

Topical	Physical	Systemic
<ul style="list-style-type: none"> <li>Local Anaesthetics and Analgesics</li> </ul>	<ul style="list-style-type: none"> <li>Laser therapy</li> </ul>	<ul style="list-style-type: none"> <li>Immune and Inflammatory Suppression :                             <ul style="list-style-type: none"> <li>Systemic steroids</li> <li>Others</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>Antiseptic Therapies</li> </ul>	<ul style="list-style-type: none"> <li>Silver nitrate</li> </ul>	<ul style="list-style-type: none"> <li>Immune Enhancement</li> </ul>
<ul style="list-style-type: none"> <li>Topical Anti-Inflammatory Agents</li> </ul>	<ul style="list-style-type: none"> <li>Ultrasound therapy</li> </ul>	<ul style="list-style-type: none"> <li>Biologics</li> </ul>
<ul style="list-style-type: none"> <li>Topical Corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>Excision</li> </ul>	<ul style="list-style-type: none"> <li>Other Treatments :                             <ul style="list-style-type: none"> <li>Pentoxifylline (PTX)</li> <li>Interferon Alpha</li> <li>Methotrexate</li> <li>5 – Aminosalicilylic acid</li> <li>Lactic acid 5% mouthwash</li> <li>Irsogladin</li> <li>Rebamipide</li> <li>Diet Supplementation</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>Intralesional corticosteroids</li> </ul>		
<ul style="list-style-type: none"> <li>Over The Counter (OTC) Preparations</li> </ul>		
<ul style="list-style-type: none"> <li>Herbal Treatments</li> </ul>		
<ul style="list-style-type: none"> <li>Immunomodulatory Agents</li> </ul>		

## CONCLUSION

Management of recurrent aphthous stomatitis (RAS) remains up to now non specific and empirical. Different therapeutic modalities can be used. Topical, physical and systemic treatments are available. These modalities can reduce pain and improve healing in most cases , but not to improve recurrence rate .So further studied to reach a definitive and permanent treatment are required.

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