

# Management of Recurrent Aphthous Ulcers: An Update

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Received date: 02 Oct 2015; Accepted date: 15 Dec 2015; Published date: 20 Dec 2015.

Citation: Aljbab AA, Almuhaiza M, Patil SR, Alanezi K (2015) Management of Recurrent Aphthous Ulcers: An Update. *Int J Dent Oral Health* 2(2): doi <http://dx.doi.org/10.16966/2378-7090.164>

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## Abstract

Recurrent aphthous stomatitis (RAS) is a common clinical condition producing painful ulcerations in oral cavity. The diagnosis of RAS is based on well-defined clinical characteristics but the precise etiology and pathogenesis of RAS remain unclear. The number of treatment modalities for RAS are ever increasing but the treatment of RAS still remains unsatisfactory, as most therapies only reduce the severity of the ulceration and do not stop recurrence. The present article provides a detailed review and update of the various treatment modalities presently available for RAS.

**Keywords:** Aphthous stomatitis; Diagnosis; Management

## Introduction

Recurrent aphthous stomatitis (RAS) is a common oral condition affecting 20% of population. RAS is an ulcerative disease that most often occurs in an otherwise healthy individual, and presents as a painful lesion of the buccal, labial mucosa and tongue. One responsibility of clinician managing oral disease is to distinguish systemic disease from localized RAS [1].

## Etiology

Several factors proposed as possible causative agents of RAS include local factors, such as trauma in individuals who are genetically susceptible to RAS, microbial factors, nutritional factors, psychological stress, and allergy to dietary constituents [2]. Extensive research has focused predominantly on immunologic factors, but a definitive etiology of RAS has not been conclusively established [3].

## Pathophysiology

The pathophysiology of aphthous ulcers is poorly understood. Histologically, aphthae contain a mononuclear infiltrate with a fibrin coating [4]. 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 [5].

## Clinical Features

The onset of RAS usually is during childhood, with a tendency of ulcer to diminish with age. The clinical features of RAS consist of recurrent bouts of one or several rounded, shallow, painful oral ulcers at intervals of a few days to a few months. RAS has 3 main presentations, minor, major, or herpetic form ulcers.

Aphthous minor (also called Mikulicz's aphthae or mild aphthous ulcers) are the most common and account for 80% - 95% of all RAS lesions. They are white ulcerative lesions that may be single or multiple and round or oval. 2 to 8 crops of lesions occur per year, lasting 7 to 14 days and then heal without scars. Aphthous major, accounts for 10 - 15% of RAS cases and is characterized by larger lesions with 1-2 lesions occurring at

time. These are more common in the immune deficient population, and are associated with severe pain, lasting 6 or more weeks. Herpetiform ulcers are the least common variety and account for only 5 - 10 % of cases they appear on non - keratinized and keratinized mucosa unlike aphthae minor and major are limited to non keratinized mucosa [6-8].

## Management

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 [2,3].

## General Measures

The patient with RAS, which is possible secondary to systemic disease, requires to be referred for detail evaluation and suitable therapy. Individuals with RAS possible related to food stuffs may occasionally benefit from dietary alteration and hematonic replacement can be of value in patients with hematonic deficiencies of unknown cause. Certain foods should be avoided as they appear to trigger eruption of new aphthae and prolong course of the lesions (e.g. foods that are hard, acidic, and alcoholic or carbonated beverages). In addition, because surfactants and detergents can cause irritation, dental care products containing sodium lauryl sulphate should be avoided [9].

## Local Anesthetic

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 [2].

## Antiseptic Anti-Inflammatory 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 [10].

### 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 [11].

### Tetracycline and minocycline

Tetracycline has antibacterial effect and also known to reduce collagen breakdown. It can be used in the form of mouth rinse which can be prepared by dissolving 250 mg capsules into 180mL of water and asking the patient to swish and spit four times per day for 4 to 5 days [12]. Minocycline is considered being superior to tetracycline because of its additional immunomodulatory effects. 100mg tablets can be dissolved in 180 ml of water and patient is asked to rinse twice daily for 4 to 5 days. In both cases patient should be instructed to avoid food or drink for at least 30 minutes [13].

### Topical corticosteroids

These are the main stay of RAS treatment. 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% [14,15].

### 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 [15].

### 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 [16].

### Systemic corticosteroid therapy

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 [15].

### Dapsone

Dapsone, also known as diaminodiphenyl sulfone (DDS), is a commonly used sulfone antibiotic in combination with rifampicin and clofazimine for the management of leprosy [17]. Dapsone has been

reported to reduce the oral lesions in patients with RASs like lesions. Dose being 100mg/day, rapid relapses can occur after discontinuation of treatment [18].

### Colchicine

Colchicine has anti-inflammatory activity and inhibits cell mediated response. Studies show that 1.5 mg per day for 2 months can produce a significant reduction in pain course and frequency of ulcers. Relapse is common following discontinuation. Physicians must ensure that appropriate contraceptive methods are practiced by patients before initiating the treatment [18].

### Thalidomide

It is one of the few drugs that have been effective in the management of RAS. This drug inhibits the production of tumor necrosis factor alpha and neutrophil function. The effects include disappearance of pain, healing of apthae and disappearance or delay of recurrence. Under standard (100-300mg/day) or low (50mg/day) dosing levels of thalidomide a dose dependent effect emerges in 7-10 weeks following treatment. Because of the well known adverse effects of drug such as teratogenicity and irreversible polyneuropathy, the therapy should be considered in patients of severe ulceration, and to be restricted to person with HIV- related ulceration [19].

### Levamisole

Levamisole was proposed as a possible treatment for RAS by virtue of its wide immunostimulatory effects. 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 [20].

### 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 [2].

### 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 [21].

### 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 [22].

### 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 [15].

## Recent Treatment Modalities

### Amlexanox 5%

The first U.S. FDA approved treatment for mouth ulcers. It decreases

healing time and has faster re-epithelization and pain resolution. The effects are seen within 3 days. The drug is to be applied 4 times a day till lesion resolve [23].

### 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 [24].

### Pentoxifylline (PTX)

PTX inhibits tumor necrosis factor alpha production, neutrophil function and chemotaxis. 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 [25].

### 5 – Aminosalicilyacid

Application of 5 aminosalicilyc acid 5% cream, TDS for 14 days should reduce discomfort and pain with short healing time [15].

### Prostaglandin E2

Application of this drug (PGE2) as a gel dose of 0.3mg BD should reduce new ulcerated lesions with no change in speed of healing and pain relief [26].

### 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 [27].

### Lactic acid 5% mouthwash

It has been use 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 [15].

### Aloevera

It seems that aloevera 2% oral gel is not only effective in decreasing the recurrent aphthous stomatitis patients pain score and wound size but also decreases the aphthous wound healing period. It should be applied on the lesions three-times a day for at least ten days [28].

### Myrtle communis

Myrtle is a perennial herb used in some cultures as treatment for mouth ulcers. The subjects were treated with myrtle oral paste in two consecutive episodes. The paste was applied by subjects themselves four times a day for 6 days [29].

Lozenges containing *Lactobacillus brevis* CD2, administered 4 times daily for a total period of 7 days, including in the case of reduced symptoms. Patient should melt the lozenge in the mouth slowly and away from food intake. Each lozenge was composed of the following: lyophilized bacteria of *Lactobacillus brevis* CD2, at least 1 billion live bacteria per lozenge. Excipients: mannitol, aspartame, fructose, talc, silicon dioxide, magnesium stearate, and banana flavor lozenge containing *Lactobacillus brevis* [30].

## Conclusion

Treatment of RAS remains to date, empirical and non specific. Various treatment modalities are used, but no therapy is definitive. Topical medication such as antimicrobial mouthwash and corticosteroids can achieve the primary goal to reduce the pain and improve healing time but not improve recurrence and remission rate.

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