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CLINICAL PRACTICE GUIDELINES FOR MANAGEMENT OF RECURRENT APHTHOUS STOMATITIS

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ABSTRACT:
Recurrent aphthous stomatitis (RAS) is one of the most commonly seen oral mucosal disease which is characterized by presence of multiple recurrent, round or ovoid ulcers known as aphthae or canker sores, which have circumscribed margins, erythematous haloes, and yellow or grey floors. The fundamental goals of treatment are to shorten the duration of ulcer, provide relief from pain & increase disease-free periods while the secondary goals would be to lessen the frequency & severity of recurrences. Even though several treatment modalities have been recommended, only a few are evidence based and can be considered for the optimal management of RAS. The objective of this study was to propose and review treatment protocol to be followed for the optimal management of RAS. We reviewed several evidence-based studies and through this review we recommend topical interventions as the first-line of treatment since they are associated with low risk of systemic side effects. Due to limitations in the number of evidence-based studies, larger evidence-based clinical trials and

literature reviews are needed to further improve the optimal protocol for the effective management of RAS.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a common oral mucosal condition in which ulcers occur repeatedly in the oral cavity, presenting as painful round, shallow ulcers with well-defined erythematous margin and yellowish-gray pseudomembranous center[1]. It usually affects non-keratinized and movable mucosa and is rarely seen on gingiva and palate. The onset of the lesion is usually in childhood or adolescence. The prevalence of RAS in children may be greater than adults with a slight female predisposition has been observed[2]. 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[3].

Even though RAS is one of the most common oral ulcerative conditions of adults and children recognized throughout the world, it is also one of the least understood oral diseases and is among the most depressing problems faced by affected patients and clinicians alike. Hence the fundamental goals of treatment in RAS are to reduce the duration of ulcer, provide relief from pain and increase disease-free periods while the secondary goals would be to lessen the frequency and reduce the severity of recurrences. The aim of this study was to review and propose a treatment protocol to be followed for the optimal management of RAS

Our recent research portfolio slides numerous articles in reputed journals [4–8]. Based on this experience we planned to pursue “Clinical practice guideline for management of RAS”

AETIOLOGY

An impressive array of factors has been implicated in the aetiology of RAS, although it is likely that many of them influence the nature of the disease rather than cause it. The exact aetiology of RAS lesions is still unknown, but several local, systemic, immunologic, genetic, psychological, endocrine, allergic, nutritional and microbial factors have been proposed as causative agents. The presence of certain types of Human Leukocyte Antigens ((HLA-A2, A11, B12 and DR2) in some patients suggests the genetic predisposition [9]. In some patients ulcers appear to exacerbate during school or university examination times due to stress. Sometimes trauma from biting the mucosa or from dental appliances may lead to aphthae in people. Haematinic deficiency may be relevant in a minority. In up to 20% of patients, deficiencies of iron, folic acid (folate) or vitamin B are found and the correction of deficiency may relieve the ulceration. Allergies to food occasionally predisposes to RAS and there is a high incidence of atopy [9,10.11]. In addition, lesions that are clinically consistent with RAS have been found in association with some systemic or multisystem illnesses such as Behçet’s syndrome, clinical neutropenia and inflammatory bowel disease(Celiac disease). RAS is thus best defined as recurrent oral ulceration in the absence of known systemic factors[12].

CLINICAL FEATURES:

Patients with RAS present with painful, shallow, round ulcers which have a pseudomembranous center surrounded by an erythematous margin. A burning sensation is usually present for about 2 to 48 hours before the appearance of the ulcer. An intense pain is present at the ulcer site and the pain gradually recedes as healing occurs. The most commonly affected sites are non keratinizing epithelial surfaces like buccal mucosa, labial mucosa and tongue and last approximately for about 10 to 14 days without scar formation. The three clinical forms of RAS include minor aphthous ulcers, major aphthous ulcers and herpetiform ulcers.

Minor aphthous ulcers are the most common form of childhood RAS, often causing minimal symptoms, presenting as small round or ovoid ulcers, measuring 2–4 mm in diameter in groups of only a few ulcers (1–6) at a time. The lesion usually heals in 7–10 days, leaves little or no evidence of scarring and recurs at intervals of 1–4 months [13].

Major aphthous ulcers also known as Sutton's ulcers or periadenitis mucosa necroticarecurrens (PMNR) usually have its onset after puberty and are often chronic in nature. They are usually round or ovoid in shape, measuring about 1 cm in diameter or even larger. They are seen on any region of the oral mucosa including the keratinized dorsum of the tongue or palate. It occurs in groups of only a few ulcers (1–6) at one time and heals slowly over 10–40 days with scarring[1].

Herpetiform ulcers are found in a slightly older age group than the other RAS are often extremely painful. They are seen mainly in females. They begin with vesiculation, which passes rapidly into multiple minute pinhead-sized discrete ulcers. increase in size and coalesce to leave large, round, ragged ulcers. The lesion can involve any site in the oral cavity, including the keratinized mucosa and heal in 10 days or longer[14].

DIAGNOSIS

Diagnosis of RAS is based on the patient’s history and clinical features, as no specific tests are available. A positive family history, associated medical conditions, medications, occurrence of similar lesions in the past, duration and frequency of ulcers may be suggestive of RAS. An inspection of the site, size, number, shape, edge and base of ulcers will help in the clinical diagnosis. Estimation of full blood count, hemoglobin, C-reactive protein, erythrocyte sedimentation rate (ESR), white cell count and differential count, red cell indices, ferritin levels (or other iron studies), red cell folate assay, vitamin B12 level, calcium measurements (low in coeliac disease), anti endomysial (positive in coeliac disease) and anti-gliadin auto antibodies may provide a clue about the cause of RAS.[15]

MANAGEMENT

Topical therapy may be sufficient for occasional episodes of minor ulcers while systemic interventions are used in patients who are unresponsive to topical agents or have severe disease[10,16,17]

TOPICAL THERAPY

For occasional minor episodes topical therapy is the first line of treatment. When a recurrent episode consisting of a relatively less number of aphthous lesions that are either small or large, closely apposed to one another, and distributed on the labial or vestibular mucosa or the anterior portion of the tongue, first-line therapeutic management should involve regimens based on conservative topical therapy. [1819]

Among the options available are any of the over-the-counter nonsteroidal agents, such as Orabase, with or without topical analgesic (usually benzocaine) that may be applied primarily for symptomatic relief or nonsteroidal antiinflammatory preparations, such as amlexanox 5% paste. Applied directly to active lesions, amlexanox promotes pain reduction by inhibiting release of histamine and leukotrienes. Studies have found that aphthous ulcers treated with amlexanox resolve in less time (by 1 day) than their untreated counterparts [18]. Chlorhexidine 0.2% mouth rinse; 1% gel was also found to be effective in the frequency, duration and severity of ulcer.[20]

Topical corticosteroid gels, creams, or ointments that are selectively prescribed and judiciously applied to active lesions constitute an effective conservative modality for managing RAS. Clinicians should reassure their patients that the use of these topical agents strictly as prescribed for limited periods of time is not likely to produce untoward effects and is safe.[2122]

Over the course of several days, starting as early as possible from the onset of the outbreak, a thin film of the corticosteroid agent should be applied three to five times daily and at bedtime after gentle drying of the affected area reduces the duration of ulcers, so that the lesion heal within several days, rather than prolonging for a week or more, as is typical of untreated lesions.[18]

For aphthous ulcers which are difficult to reach with a finger, mostly ulcers present in the posterior oral regions or are so numerous and widely distributed as to render the direct application of creams or ointments is practically impossible, corticosteroid rinses are an excellent alternative for topical therapeutic[23]. Rinsing over a period of several days with betamethasone syrup 0.5 mg/5 mL, dexamethasone elixir 0.5 mg/5 mL, fastens the healing of the ulcers and reduces the discomfort.1 teaspoonful of the liquid is held and swished in the mouth for 2 to 3 minutes and then expectorated. The rinse regimen is followed by avoidance of food and drink for 30 to 60 minutes afterward three times daily.[19]

Another method of application of topical steroids to active lesions (particularly major aphthous ulcers or other types of aphthae located primarily in

intertriginous-like regions of the oral mucosa, such as the upper or lower buccal or labial vestibules or the sublingual vestibule) involves the use of a gauze sponge either soaked in corticosteroid rinse preparation or on which a small amount of corticosteroid cream or ointment has been applied for delivery, by laying the gauze sponge directly onto the lesion or lesions and resting it in that place for 15 to 20 minutes two or three times daily during waking hours, the concentrated contact method for delivery of the medication requires fewer applications and promotes more expeditious healing of ulcers[21]

SYSTEMIC THERAPY

The systemic therapies are aimed to reduce the frequency of recurrences and to minimise the duration of ulcers. Therefore systemic immunomodulatory medications have been tried for the treatment and management of severe and recurring RAS, including systemic prednisolone, dapsone, azathioprine, pentoxifylline, colchicine and thalidomide. These may produce remission or reduction in symptoms but also have side effects. Therefore, the treatment choices should be considered by the severity of the RAS and the potential adverse effect of medications [24252627282930]

Therapeutic regimen of prednisone 40 mg taken in the morning for 5 days, followed by 20 mg every other day for an additional week has been found to be effective[19]. Azathioprine is an immunosuppressive drug which belongs to the chemical class of purine analogues is used in treatment of auto-immune disease. Azathioprine taken 25-100 mg/day was found to be an effective therapy in the management of oral ulceration in Behcets[29]

Colchicine is an anti-inflammatory agent which limits leukocyte activity by binding to beta-Tubulin, a cellular microtubule protein and therefore inhibiting protein polymerization [31]. Although colchicine is generally well tolerated, the most frequent gastrointestinal adverse events include nausea, diarrhoea, vomiting and abdominal pain. Colchicine at 0.5 mg/day over 3 months showed a significant improvement of ulcers in patients. [323334]

Thalidomide, a potent immunosuppressive medication, was found to be effective for treating patients with severe RAS and can be considered when other treatments have failed. Complete remission in 85–90 % of patients with severe RAS has been reported using thalidomide 50-100 mg a day for a range of periods from 3–6 months [3035] .Because of thalidomide's recognized potential for profound side effects, it must be reserved only for patients whose aphthous ulcers have been so unrelenting and sufficiently symptomatic as to significantly compromise quality of life and who, after exhaustive efforts, also have failed to respond to other, more conservative therapeutic measures. Use of this systemic agent requires strict adherence to guidelines for patient selection. Patients who take thalidomide must be monitored frequently to intercept and prevent its potential toxic effects. [36]

Pentoxifylline an anti inflammatory drug taken at dosage of 400 mg/day taken thrice have been found to reduce ulcer pain, size, number reduced and ulcer free period increased when taken for a duration of 2 months minimum. [27]

Dapsone has been found to reportedly reduce ulcer recurrences in complex aphthosis with a daily dose of 50–125 mg. The exact mechanism is thought to be due to its anti neutrophilic action. However, dapsone should not be administered to patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency and regular monitoring for haemolyticanaemia and methemoglobinemia is essential [373835].

Based on the available literature a clinical practice guideline is formulated for the management of recurrent aphthous stomatitis (figure 1). However no single treatment protocol has been identified to be efficient and there was inadequate evidence to approve or disregard any particular intervention. Therefore, the best systemic intervention for RAS still remains a matter of debate.

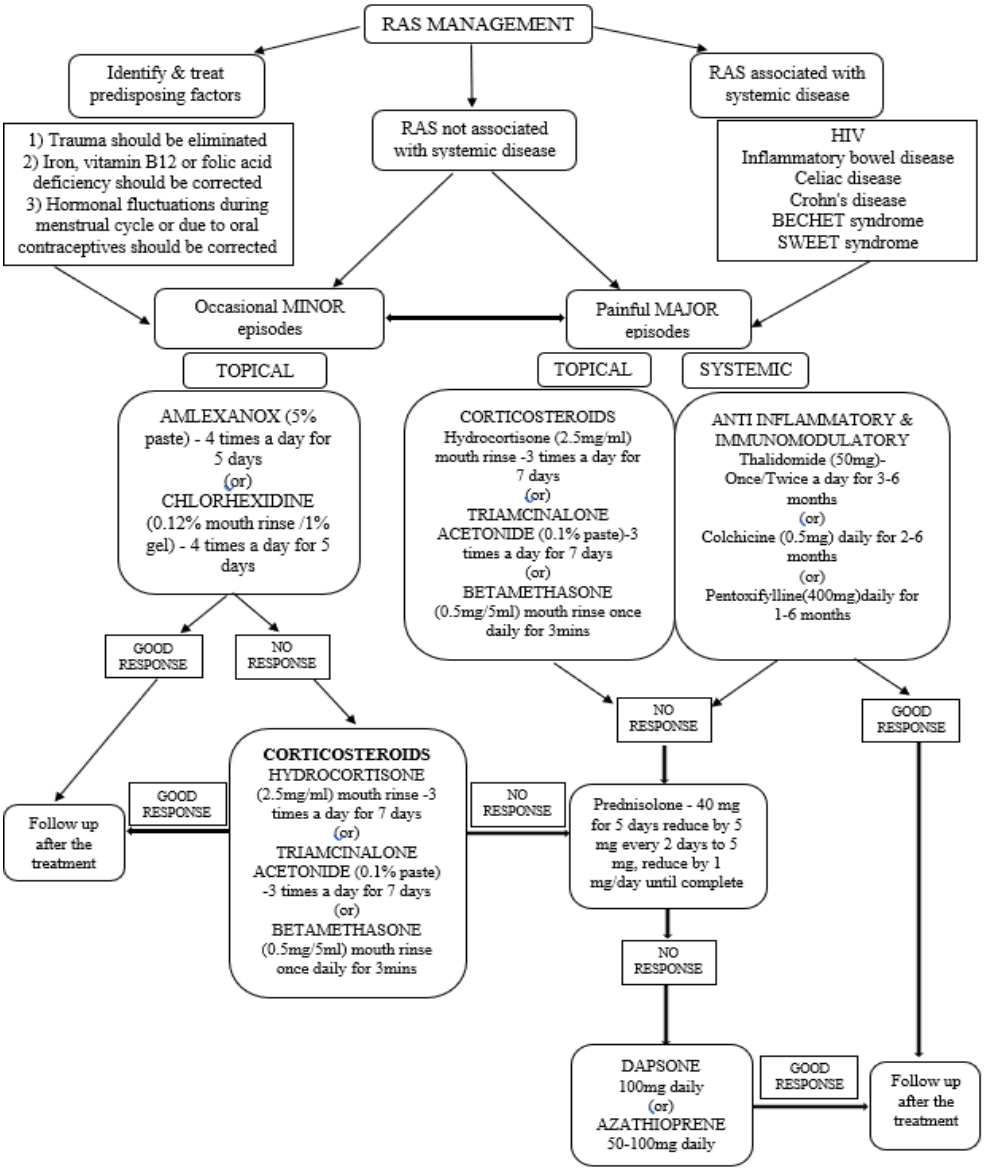

FIGURE 1 RAS Management

CONCLUSION

The fundamental goal of therapy in RAS should primarily aim to provide symptomatic relief and reduce the frequency of recurrence. Topical interventions are considered as the first-line of treatment since they are associated with low risk of systemic side effects. Elimination of the predisposing factors is of prime importance in the management of RAS. A variety of treatments for RAS are abound in oral medicine but a definitive treatment protocol for RAS still remains inconclusive. This might be due to the lack of large clinical trials and a difference in response between patients.

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CONFLICT OF INTEREST

There was no potential conflict of interest as declared by the authors.

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