REVIEW ARTICLE

Recurrent Aphthous Stomatitis: Therapeutic Management from Topicals to Systemics

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ABSTRACT:
Recurrent Aphthous Stomatitis (RAS) is a pathologic condition characterized by multiple, recurring, painful, small, round or ovoid oral mucosal ulcers with circumscribed margins, peripheral erythematous halos, and yellow or grayish bases, appearing first in childhood or adolescence.[1,2] Multiple therapeutic regimens and drugs have been advocated for the treatment of RAS. Various multivitamins, adhesive pastes, local antiseptics, analgesics, local and systemic antibiotics, topical non-steroidal anti-inflammatory drugs, topical corticosteroids, and even topical & systemic immunomodulators, immunosuppressants are the treatment options given to patients with RAS. The best treatment is that, which will control ulcers for the longest period with minimal adverse side effects. In evaluating treatment regimens, it is important to remember that RAU heal spontaneously, and that the frequency of recurrence, lesion duration, and degree of discomfort vary over time for a particular person and among different persons. In this article an attempt has been made to discuss the various management strategies and practical treatment modalities for recurrent aphthous stomatitis including the recent ones.
Key words: Aphthous Stomatitis, recurrence, management modalities.

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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.[1-3] It is one of the most painful oral mucosal inflammatory ulcerative condition and cause pain on eating, swallowing and speaking.[4] 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.[3] There is growing evidence that there may be a genetic and immunopathogenic basis for recurrent aphthous ulceration.[4]

Epidemiological studies have indicated that the prevalence of this condition is between 5% and 25% in the general population. In children, RAS is most common form of oral ulceration and the peak age of onset is between 10-19 years. 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.[6]

Lesions consistent with or identical to RAS are encountered in association with systemic or multisystemic illness of an immunopathic nature. These include idiopathic inflammatory bowel disease, Behcet's syndrome, magic syndrome, cyclic neutropenia, Sweet syndrome, Marshall Syndrome and vitamin B_{12} deficiency.[7]

Diagnosis of RAS is almost invariably established on the basis of the patient's clinical history and presentation of the lesions.[1] There is no specific treatment for RAS. Management strategies should be

determined by disease severity, especially in terms of pain, duration, the patient's medical history, the frequency of flare-ups and the patient's ability to tolerate the medication. Most cases can be managed with topical therapy, but systemic therapy is available for patients with major RAS or those who experience large number of minor ulcers and syndrome associated ulcers.

THERAPEUTIC LADDER FOR MANAGEMENT OF RAS:

The treatment of RAS becomes a frustrating experience for the clinician, as it is extremely difficult to determine the exact cause of the lesion. Hence, the main aim of the clinician is directed towards alleviation of the symptoms and reduction in the severity and duration of the ulcers rather than to address basic issues of susceptibility and prevention.[8] 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 weather its associated with any systemic illness. (Table1)

TOPICAL THERAPY

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

Local Anaesthetics and Analgesics:

Locally acting symptomatic preparations can relieve symptoms and decrease the duration of the ulcer attack. Several pastes and gels can be used to coat the surface of the ulcers and form a protective barrier against secondary infection and mechanical irritation. 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.[9,10]

Over The Counter (OTC) Preparations:

Several prescriptions and over the counter preparations topical agents are available like 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.[11]

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. The drugs most commonly adopted for local oral application in RAS are hydrocortisone hemisuccinate as 2.5 mg pellets and triamcinolone acetonide in a adhesive paste containing 0.1% of the steroid.[5] The corticosteroids vary in their degree of potency and may be given as mouth rinses, ointments, creams or in adhesive vehicles.[10] In severe minor ulcers unresponsive to these preparations and in major type ulcers it may be necessary to use a more potent steroid preparation such as a betamethasone sodium phosphate rinse (dissolve 0.5 mg in 5 mL of water and rinse for 2–3 min), or a high-potency topical corticosteroid, such as clobetasol 0.05% in orabase (1 : 1) or fluocinonide 0.05% in orabase (1 : 1).[2,12] 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.[8]

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.[2]

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. Topical preparations containing chlorhexidine (0.2% w/w mouth rinse or a 1% gel) are also helpful in relieving symptoms.[10]

Topical Anti-Inflammatory Agents:

a) 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.[13,14]

b) Sucralfate: A recent study on Italian patients suggested that 20% sucralfate is beneficial in

reducing the symptoms of RAS (Campisi et al, 1997).

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.[8]

Physical Therapies
Suggested physical therapies include surgical removal, debridement or laser ablation of ulcers, low intensity ultrasound, chemical cautery and the use of physical barriers such as cyanoacrylate adhesives.

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. In these cases, systemic medications are employed.

Immune Enhancement:
Levamisole was proposed as a possible treatment for RAS by virtue of its wide immune-stimulatory effects. Levamisole in a dosage of 150 mg/day on three successive days per week, against oral and genital aphthae, with or without combination with steroids (15 mg prednisolone), has been reported to be beneficial.[2,10,15]

Immune and Inflammatory Suppression:
The agents that suppress or modulate the immune system are the most effective for management of RAU.
a) Systemic Corticosteroids: Severe cases of major RAS may require systemic corticosteroids. Systemic prednisone therapy should be started at 1.0 mg/kg per day as a single dose in patients with severe ulceration and should be tapered after 1 to 2 weeks.[4]
Steven D.Vincent, concluded in his study that a dose of 40-60 mg of prednisone, administered each morning one hour after arising for five consecutive days is usually therapeutic and seldom results in appreciable adverse effects.

b) 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 aphthosis 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.[10,15]

C) Chlorambucil and Cyclophosphamide (Alkylating agents):
Therapy with alkylating agents such as chlorambucil and cyclophosphamide should be reserved for severe cases of aphthosis. 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.

D) Dapsone: Dapsone in a dose of 100–150 mg/day can be used for oral and genital aphthae. Haemolysis, methaemoglobulinemia and agranulocytosis are serious side-effects that may occur.[16,17]

E) Colchicine:
Colchicine with anti-inflammatory activity may be of clinical benefit in severe cases of RAS and Behcet's disease.Therefore, a therapeutic trial at least over 4 to 6 weeks in a dose of 1 to 2 mg/day orally is recommended, which is followed by long-term therapy according to tolerability and clinical response.

Pentoxifylline (PTX):
Results of limited open studies by Pizarro et al, 1995, 1996; Wahba-Yahav in 1995**,** suggested that the anti-TNF-a agent pentoxifylline in a dosage of 400 mg three times daily for one month, significantly reduced the number of ulcers for up to 9 months and there were no major side effects while receiving the therapy.[2,16]

Thalidomide:
The therapy with thalidomide (anti-TNF-a 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.[12]

Biologics:
a) 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.[15] 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).

b) Efalizumab and Adalimumab other biological agents which are highly efficient and completely prevented the development of aphthae.[18]

c) Etanercept: Etanercept (Enbrel) is a recombinant TNF-soluble receptor can be used 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.[19]

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 aphthae.[15]

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.[15] Pregnancy, lactation, severe bone marrow depression, liver function abnormalities, peptic ulcers and renal insufficiency are the main contraindications for both azathiprine and methotrexate.

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.

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.[12] Intermediate doses (6×106 IU thrice a week) or high doses (9× 106 IU thrice a week) are principally more effective than low doses (3×106 IU thrice a week).

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. The successful management of RAU is variable but, in most cases, a useful strategy can be tailored to the individual patient. (Table2)

According to a review on the recurrent aphthous presentation and management by V.Vucicevic Boras and NW Savage in 2007, the management of MiAU can be successfully divided into three phases[20]:

1. Symptomatic and supportive (Phase I): The symptomatic and supportive treatment is self explanatory and focuses on the current level of patient morbidity. This phase is defined by the prescription of generally proprietary preparation that obvious and major concerns of the patient: (a) antiseptic/anaesthetic preparations; (b) adequate analgesia; (c) maintenance of fluid balance; (d) adequate dietary intake.

2. Specific treatment (Phase II): Specific treatment of MiAU requires a recognition and acceptance of the immunopathogenesis of RAU, irrespective of the exacerbating factor(s) of a specific episode. The aim is to prevent epithelial destruction and the most effective strategy to date is the use of topical corticosteroids. The specific agent employed will depend upon the number, size and duration of lesions but, for most patients, a betamethasone preparation will be effective.

3. Preventive treatment (Phase III): Preventive treatment is a consideration for patients who with exacerbations of their condition. It focuses on the prodromal stage, and attempts to intercept ulcer development again by the use of topical immunosuppressants and particularly corticosteroids. Clinical experience shows that many RAU patients will enter a phase of complete clinical remission following the medium term use of a corticosteroid mouth rinse on a daily basis initially and then on a minimal maintenance dose over one to two months.

CONCLUSION:

No single treatment has been found to be uniformly effective in all patients with RAU, it may be necessary to try several types of medications for optimum response and prevention of recurrence. Patient education about the chronic nature of the disease and a careful patient work-up is required along with close monitoring of patient compliance.

Table1: Treatment modalities for RAS

TOPICAL THERAPY:	**SYSTEMIC THERAPY:**
i) LOCAL ANAESTHETICS	i) IMMUNE ENHANCEMENT:
ii) OVER THE COUNTER (OTC) PREPARATIONS	ii) IMMUNE AND INFLAMMATORY SUPPRESSION:
iii) TOPICAL CORTICOSTEROIDS	iii) ANTIBIOTICS
iv) TOPICAL ANTIMICROBIALS	iv) ANTIMETABOLITES
v) TOPICAL ANTI-INFLAMMATORY AGENTS	v) DIET SUPPLEMENTATION
vi) IMMUNOMODULATORY AGENT	vi) OTHER TREATMENTS
vii) PHYSICAL TREATMENT	

Table 2: Recommendations for Recurrent Aphthous Stomatitis

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

REFERENCES:

1. V Cugadasan. Management of Recurrent ulcers of the mouth- current concepts. Singapore Medical Journal, 1987; vol 28, No.1, Feb.
2. S Jurge, R Kuffer, C Scully, SR Porter. Recurrent Apthous Stomatitis. Oral Diseases 2006;12:1-21.
3. SundayO.Akintoye, Martin S. Greenberg. Recurrent Apthous Stomatitis. Dent Clin N Am 2005;49:31-47
4. S.S.Natah, Y.T.kontiinen, N.S.Enattah, N.Ashammakhi, R.Hayrine Immonen. Recurrent apthous ulcers today: a review of the growing knowledge. Int. J. Oral and Maxillofac. Surg. 2004; 33:221-234.
5. Robert A. Lindemann, George R. Riviere, J. Philip Sapp. Serum antibody response to indigenous oral mucosal antigens and selected laboratory-maintained bacteria in Recurrent Apthous ulcerations. Oral Surg Oral Med Oral Pathol 1985;59:585-589.
6. Ilia Volkov, Inna Rudoy, Gabriel Sardal, Sody Naimer. Effectivenss of Vitamin B 12 in treating Recurrent Apthous Stomatitis: A randomized, Double-blind, Placebo-Controlled Trial. J Am Board Med 2009;22:9-16.
7. Lewis R. Eversole, Thomas P. Shopper, David W. Chambers. Effects of suspected foodstuff challenging agents in the etiology of recurrent apthous stomatitis. Oral Surgery 1985;54(1):33-38.
8. Crispian scully, Meir Gorsky, Francina Lozada-Nur. Aphthous Ulcerations. Dermatologic Therapy 2002;15:185-205.
9. E.A.Field, R.B.Allan. Review Article- oral ulcerations- aetiopathogensis, clincal diagnosis and management in the gastrointestinal clinic. Aliment Pharmacol Ther 2003;18:949-962.
10. A.Ross Kerr, Catherine A. Drexel, Andrew I. Spielman. The efficacy and safety of 50 mg pencillin G potassium troches for recurrent apthous ulcers. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;96:685-694
11. Steven D. Vincent, Gilbert E. Lilly. Clincal, historic, and therapeutic features of apthous stomatitis. Oral Surg Oral Med Oral Pathol Oral Radiol 1992;74:79-86.
12. Crispian scully, Stephen Porter. Oral Mucosal Diseases: Recurrent Apthous Stomatitis. British Journal Of Oral and maxillofacial Surgery 2008;46:198-206
13. Khandwala A, Richard G. Van Inwegen, Michael C. Alfano. 5% Amlexanox oral paste, a new treatement for recurrent minor apthous stomatitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997;83;222-230.

14. Murray B, McGuinness N, Paul Biagioni. A Comparative study of the efficacy of Aphtheal in the management of recurrent minor aphthous ulceration. J of Oral Pathology and Medicine 2005;34(7):413-419.
15. A. Altenburg, C. C. Zouboulis. Current Concepts in the Treatment of Recurrent Aphthous Stomatitis. Skin Therapy Letter 2008;13(7):1-10.
16. .Porter SR, Scully C, Perdersen A. Recurrent Apthous Stomatitis.Cric Rev oral Biol Med 1998;9(3):306-321.
17. Ship JA, Arbor A. Recurrent Apthous Stomatitis- An update. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81:141-147.
18. H Zribi, B Crickx, V Descamps. Prevention of recurrent aphthous stomatitis by efalizumab (Raptiva®), Journal of European Academy of Dermatology and Venereology. Vol21, issue9:1286-1287.
19. Robinson ND. Recalcitrant, Recurrent aphthous stomatitis treated with Etanercept. Arch Dermatol, 2003;139:1259-1261.
20. Boras VV, Savage NW. Recurrent apthous ulcerative disease: Presentation and Management. Australian dental Journal 2007;52(1):10-15

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