

Review Article

Non-Pharmacological Management of Recurrent Aphthous Stomatitis- A narrative review

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ABSTRACT

Recurrent aphthous stomatitis (RAS) is a very common oral mucosal lesion characterized by frequent, painful ulcerations with undiscerned etiopathology with several theories proposed like it being a bacterial infection, immunological abnormality, genetic predisposition, nutritional deficiency with trauma, stress and allergies being trigger factors. The treatment mainly focuses on symptomatic relief and keeping the intervals of remission protracted. Topical corticosteroids, analgesics, systemic antibiotics, and immunosuppressant drugs are the commonly used medications. Non-pharmacological measures like laser, photodynamic therapy (PDT), and cryotherapy can also be used which have proven to cause analgesia, reduce ulcer dimensions and accelerate healing, PDT being the novel approach requiring single session application and giving symptomatic relief to patients within hours. Meanwhile, stress management and dietary modifications also help in keeping the ulcers at bay. Therefore, along with conventional management, these emerging therapeutic options can be explored and employed to provide synergistic treatment to the patients of RAS.

Key words: Recurrent aphthous stomatitis, photodynamic therapy, Dietary antioxidant index, cryotherapy

Recurrent aphthous stomatitis (RAS) generally known as Canker Sores are recurrent painful, solitary or multiple ulcerations lasting from days to months, seen in the non-keratinized oral mucosa with the prevalence ranging from 1.4% to 21.4%[1,2]. These eruptions pose a significant challenge to the patients and the healthcare professionals due to their uncertain etiology. RAS appears usually in childhood or adolescence, developing as an individual entity or as part of systemic conditions [3]. Different systemic conditions associated with RAS are Behçet syndrome, cyclic neutropenia, PFAPA syndrome (periodic fever, aphthae, pharyngitis, and cervical adenitis), MAGIC syndrome (major aphthous and generalized inflamed cartilage), and HIV (Human Immunodeficiency Virus) infection [3, 4].

Etiology

There has been substantial research to discern the etiology and pathophysiology of RAS but none of them have been able to precisely elucidate the very much ubiquitous mucosal lesion. It has been proposed to be multi-factorial. Various etiological factors that have been put forward in the causation of these ulcers include Immunological abnormalities, Genetic history, Streptococcal bacterial infection, Nutritional deficiencies

(Iron, Vitamin B12, and folic acid) with trigger factors like stress, trauma, allergies, and hormonal fluctuations [4, 5]. Research supporting each etiological possibility is elaborated in Table 1 [2, 4, 5].

Clinical presentation and diagnosis

RAS present as multiple, small, round, or ovoid ulcers, with well-circumscribed margins, surrounded by erythematous halos, and having yellow/gray floors [2]. Clinically, RAS is categorized mainly into 3 forms, namely minor, major, and herpetiform. The minor form is the most common comprising 70-85% of all RAS lesions. They are circular to ovoid shaped with a diameter of less than 10mm, resolving within 10-14 days without or with minimal scarring [6]. Major forms are larger than 1cm in diameter, with higher healing time and they almost always leave behind a scar. Herpetiform type superficially resembling herpes simplex virus infection (although there's no association between the two lesions) is rare with pin-point ulcers with a size of 0.1-0.2cm and in large numbers [7].

A multitude of other lesions like herpetic stomatitis, pemphigus, pemphigoid, and erosive lichen planus serve as differential diagnoses for RAS [4]. Although clinically they may look similar, close inspection along with histological examination sets the former lesions apart as they have distinct microscopic features like intra-nuclear inclusions in herpetic

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lesions, intraepithelial blister with acantholysis in pemphigus, subepithelial blister in pemphigoid, Civatte bodies in erosive lichen planus, immunofluorescence aiding in further differentiation. Therefore RAS is considered as a diagnosis of exclusion after thoroughly scrutinizing other mentioned definable mucosal lesions since the histopathology of it as well is non-specific, exhibiting a fibropurulent exudate, microbial colonies, and inflammatory cell infiltrate with granulation tissue [4].

Table 1: Etiopathology of Recurrent Aphthous Stomatitis

Sl. No	Etiological / Precipitating factor	Proposed explanation
1.	Immunological abnormality	Diffusion of bacterial toxins, and food act as haptens, initiating an immune response. These react with epithelial cell surface antigens resulting in cell-mediated inflammation involving T-cells and Tumour Necrosis Factor- α .
2.	Bacterial infection	L-form streptococci infection stimulates the formation of antibodies and causes cytolysis. S. oralis, S. mitis and S. oralis, have been suspected to provoke the development of RAS.
3.	Genetic predisposition	HLA-B51 is implicated in the occurrence of RAS. Individuals with a positive family history develop ulcers at the early ages.
4.	Iron, vitamin B12, or folic acid deficiency.	When nutritional deficiencies were addressed, oral mucosa showed a reduction of ulcers.
5.	Trauma	Local trauma is inculcated in nearly 75% of cases possibly by initiating an immune response.
6.	Stress	Transient elevation in the salivary cortisol levels stimulates the immunologic response
7.	Hormonal fluctuations	Due to increased progesterone levels, there is an exacerbation of ulcers in the post-ovulation phase. Pregnant women showed remissions for a long time until parturition.
8.	Allergy	Patients with histories of hay fever, and food,

or drug allergies are more prone to RAS. The outbreak of ulcers following the use of certain foods or drugs proves that allergy is a precipitating factor

Management

The treatment for RAS is usually empirical and symptomatic, with the main objectives of alleviating pain, reducing exacerbation, and accelerating the healing time with minimal scarring [8]. Conventional treatments corresponding to the etiological hypotheses include antimicrobials like 5% tetracycline mouthwash (four times for 5-7 days), 50mg Penicillin G troches (four times a day for 4 days), 0.2% chlorhexidine mouth rinse, and 5% triclosan mouth rinse [2]. Anti-inflammatory agents and topical steroids are used to relieve pain, hasten healing, and reduce inflammation. These include 1.5% cortisone acetate ointment, hydrocortisone acetate lozenges, 2% benzydamine hydrochloride ointment, and 5% amlexanox oral paste [2, 4]. Immunomodulators including thalidomide (200mg daily for 4 weeks), pentoxifylline (400 mg thrice daily for 1 month), levamisole, colchicine, and others are used in extreme conditions only as they have several adverse effects [2, 5, 9]. Additionally, drugs like Zinc and Vitamin supplements are administered citing nutritional deficiency to be the cause [9, 10].

Taking into account the adverse effects of conventional medications like opportunistic mycotic infections, immunosuppression, and antibiotic resistance, it is of paramount importance to explore alternative measures to improve the quality of life of RAS-affected patients while providing symptomatic aid.

Emerging non-pharmacological therapeutics

A) Laser therapy

Controlled levels of laser in a particular wavelength have a role in local metabolic processes in the oral mucosa via various physicochemical activities, hence bearing excellent anti-inflammatory, analgesic, and pro-repair outcomes without any thermal damage to the mucosae [1]. Different types of lasers used are carbon dioxide laser, crystal laser, diode laser, and low-level laser therapy (LLLT). LLLT has gained popularity in recent times [11, 12].

There are several upsides to using a laser over conventional topical/systemic interventions. The treatment period is shortened, efficiency is superior along with excellent analgesic properties and reduced defect healing time [1]. Analgesia is made possible due to the alteration of the electrical activity in the nerve cells, thus reducing pain which is the main difficulty faced by RAS patients [13].

A randomized controlled trial deduced that LLLT can relieve RAS pain. The study included 40 patients receiving

LLLT with a wavelength of 809 nm, power of 60 mW for a duration of 80 seconds per session; three sessions with a 1-day interval with the control group undergoing the same procedure without the laser power. Patients who received laser found it easier to eat, and brush their teeth with considerable reduction in pain when compared to the placebo patients [14]. Several other studies have shown the efficacy of laser as well [15, 16].

In recent times, Ghali HG et al in 2022 compared 3 groups of patients (n=21; divided equally), one group receiving LLLT, one group treated using Anginovag (steroid) spray medication while the third group was managed conservatively with motivation and follow-up. The LLLT was applied by using Gallium–Aluminum–Arsenide diode laser. A power of 0.5W and wavelength of 940 nm for 3 minutes. The ulcer was exposed to laser light for 45 seconds, then released for 15 seconds, and repeated twice for a total time of 180 seconds on each visit, with a gap of 3 days between each visit. The results showed that LLLT caused a reduction in pain intensity, thereby reducing morbidity. There was also reduction in the diameter as well as the healing period of the ulcer when compared with Anginovag spray medication and the control group [17].

All the above studies show beyond doubt that laser therapy can be considered as a valuable course of action especially in

severe cases with frequent exacerbations.

B) Photodynamic therapy

Photodynamic therapy (PDT) works on the principle of photochemical reaction between the visible length of a specific wavelength and power range, a photosensitizing agent, and the target lesion in question [18]. PDT has been used in treating periodontal, endodontic lesions, dental caries, and lesions caused by fungal infections and has recently been implemented in the management of RAS. A case report in 2017 using PDT showed remarkable improvement in the size of the lesion, shortened healing time, and relief of pain after a few hours of therapy [19].

A clinical study involving 30 patients of RAS employed PDT with a single session application, measuring the dimension of ulcer size, healing pattern as well as pain intensity using Visual Analog Scale (VAS) on 3rd, 5th, and 7th days post-therapy and found significant results with respect to all three aspects mentioned above between control group and the group receiving PDT [20]. PDT for the management of aphthous has been employed only in the above two mentioned instances, details of which are described in Table 2. Although more studies are required in this aspect, perhaps it can be accepted that PDT can serve as a novel treatment alternative.

Table 2: Studies describing the management of RAS using Photodynamic Therapy

Study and year	Type of study	No. of patients	Photo sensitizing agent used	Light source used	Wave length	Dose	Pain relief	Healing time
Casu., et al (2017) [19]	Case Report	1	Toluidine blue	LED light	630nm	10 cycles,30 seconds each	Pain relief after few hours of the appointment	Completely healed in one week
Eroglu., et al (2024) [20]	Randomized controlled clinical study	30	Indocyanine green	Gallium Aluminum Arsenide diode laser	810nm	Single application, 40 seconds	Pain relief more in the test group (p=0.001)	Complete healing in 78.6% patients in a week

C) Cryotherapy

Cryotherapy has long been used both in the management of acute and chronic types of pain. Cold, when applied to painful regions slows down the release of neurotransmitters that cause pain and inflammation. Tissue cooling also alters the conduction velocity as well as the synaptic activity of the surface nerves, which in turn reduces the pain sensory input thus providing an anesthetic action on the pain fibers [21]. Therefore, localized cryogenic applications can be used to reduce pain and inflammation, thereby contributing to symptomatic relief [22]. Another proposed mechanism of action for analgesia is that cryotherapy reduces inflammation, causing subsequent vasoconstriction and reduction in edema as well as pain-causing mediators like bradykinin, 5-hydroxytryptamine (5-HT), and substance P which leads to blockage of arachidonic acid’s release resulting in inhibition

of the formation of prostaglandins and leukotrienes, thus producing pain relief [23].

A prospective randomized controlled trial in 2006 with 20 subjects was conducted to determine if cryotherapy can reduce the pain of patients with a minor form of RAS. One of the two discrete ulcers in each of the patients was treated with cryotherapy, and the other was given cellulose-containing hydrogel, serving as a control. A cryoprobe of a target temperate of -20⁰ C, with a freezing time of 10-15 seconds was used. Although, there were no statistical differences found between the cryotherapy-treated ulcers and the control in terms of pain severity and the change in size of the ulcer, a trend toward less pain in the aphthous stomatitis receiving cryotherapy was noted [24]. More studies with larger sample sizes and variables are recommended to showcase the efficacy of cryotherapy.

The advantages of cryotherapy over conventional modalities are that it is simple to use, and cost-effective with a very low incidence of secondary infection as in the case of topical corticosteroids which may cause opportunistic infections [21, 22].

D) Stress Management

Stress is one of the eminent trigger factors for aphthous ulcers. Several trials have been conducted proving psychological stress to be higher in RAS patients [25, 26]. A study by Hullung et al in 2012 involving 168 RAS patients was followed up for over a year. Stressful events were quantified using the Recent Life Changes Questionnaire (RLCQ). The results showed that stressful life events were significantly associated with the onset of RAS ($p < 0.001$), but, not with the duration of the RAS episodes [27].

In 2023, Nurdiana et al aimed to determine the role of stress in RAS using a Perceived Stress Scale questionnaire along with serum cortisol level testing. Although, no significant results were obtained, it cannot be denied that stress indeed is an important precipitating factor, if not an etiological factor for the onset of RAS [28]. Techniques for stress reduction, including cognitive-behavioural therapy, mindfulness, psychotherapy, and biofeedback, will definitely be of use in the comprehensive management of ulcers [29, 30].

E) Dietary modifications

There are studies indicating that specific food substances trigger RAS occurrence and avoiding the same is beneficial in keeping the ulcers at bay, particularly if the patient has observed a flare-up post intake of such substances [31].

A study conducted by Xu et al in 2021 found that the consumption of fruits and water was negatively associated with RAS, therefore proving the complementary role of certain food in management [31]. The role of disrupted oxidative balance increases free radicals and oxidative stress in the body which in turn is a strong implicit in the development of RAS is already established [32]. In light of this, a recent study examined the relationship between RAS and Dietary antioxidant index (DAI) indicating that diet with increased DAI score is inversely proportional to the occurrence of RAS, proving that antioxidant diet helps in reducing episodes of the latter [33].

As a whole, individuals with RAS must avoid acidic and spicy food as well as alcoholic and carbonated beverages for increased periods of remission [29].

Table 3: Comparison of various non-pharmacological therapeutics

	Merits	De-merits
Laser therapy	Significant pain relief Reduced healing time	Prolonged irradiation Multiple appointments Expensive
Photodynamic therapy	Remarkable healing, analgesia	Photosensitizer toxicity Poor tissue penetration

	Single appointment	with shorter wavelengths Expensive
Cryotherapy	Cost-effective Low incidence of secondary infection	Possible scarring Potential nerve damage
Stress management	Reduces incidence of RAS Promotes overall well-being	Subjective
Dietary modifications	Reduce frequency and severity of lesion Increased remission period	Abstaining from particular food items at all times is unfeasible

CONCLUSION

There has been a potential shift in the management of RAS lesions after recognition of the adverse effects of long-term or frequent use of corticosteroids, immunomodulators which cause opportunistic infections, drug resistance, or other unfavourable outcomes. Non-pharmacological therapeutics should be given preference for the sake of the patient's welfare and used as adjuvant if not alternative to the conventional treatment choices.

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