Journal of Developing Drugs
ISSN: 2329-6631
Sharma and Garg, J Develop Drugs 2018, 7:2
Review Article
Open Access

# A Comprehensive Review on Aphthous Stomatitis, its Types, Management and Treatment Available

**Sharma D**[1,2*] **and Garg R**[3]

[1]*Ph.D. Research Scholar, I K Gujral Punjab Technical University, Jalandhar, Punjab, India*

[2]*Assistant Professor, Department of Pharmaceutics, Rayat Bahra Institute of Pharmacy, Hoshiarpur, Punjab, India*

[3]*Associate Professor, Department of Pharmaceutics, ASBASJSM College of Pharmacy, Bela, Ropar, Punjab, India*

[*]**Corresponding author:** Deepak Sharma, Ph.D. Research Scholar, IKG Punjab Technical University, Jalandhar, Punjab, India, Tel: 919988907446; E-mail: deepakpharmacist89@yahoo.com

**Rec date:** August 27, 2018; **Acc date:** September 24, 2018; **Pub date:** October 01, 2018



## Abstract

The word "Aphthous" originated from the Greek word "aphtha", the meaning of which is ulcer Aphthous Stomatitis is one of most common ulcerative disease associated mainly with the oral mucosa characterized by the extremely painful, recurring solitary, multiple ulcers in the upper throat and oral cavity. The disease is known by lay public and professionals by several other names such as cold sores, canker sores, recurrent aphthous stomatitis (RAS) and recurrent aphthous ulcers (RAU). These are quite painful; may lead to difficulty in eating, speaking and swallowing thus may negatively affects the life standard of patient's. Aphthous stomatitis is divided into three varieties: minor aphthae, major aphthae and herpetiform. The precise etiopathogenesis of aphthous stomatitis is not entirely disclosed. The factors responsible for aphthous ulcers are genetic predisposition, mechanical injury, microelement and vitamin B12 deficiencies, increased oxidative stress, food allergies, microbial factors, anxiety, hormonal defects, and systemic diseases. In spite of much clinical and research observation, the root causes continue to exist was imperfectly understood. The ulcers are unavoidable, and therapy is symptomatic. The goals of therapy are 3-fold: (a) control the ulcer pain, (b) stimulate healing of ulcer and (c) prevent recurrence. There are several treatment options both local and systemic for management of aphthous stomatitis. No single treatment has been found to be consistently effectual in all patients with RAU, it may be necessary to try several types of medications for optimum response and prevention of recurrence. The present review article aims to summarize the type etiopathogenesis, management and treatment options for RAS.

**Keywords:** Aphthous stomatitis; Etiopathogenesis; Topical and systemic therapy; Symptomatic treatment

## Introduction

The word "Aphthous" originated from the Greek word "aphtha", the meaning of which is ulcer. Aphthous stomatitis is one of most common ulcerative disease associated mainly with the oral mucosa characterized by the extremely painful, recurring solitary, multiple ulcers in the upper throat and oral cavity. These types of ulcers are usually small, multiple, ovoid or round with circumscribed margins which are having gray or yellow floors and are encompassed by erythematous haloe [1,2]. It was delineated in 400 B.C by Hippocrates; the disease is known by lay public and professionals by several other names such as cold sores, canker sores, recurrent aphthous stomatitis (RAS), and recurrent aphthous ulcers (RAU). This is the most prevailing oral ulcerative disorder affecting up to 10-20% of our inhabitants and recurrence rate of 3 months in 50% of population [3]. These are quite painful that leads to difficulty in eating, speaking and swallowing that's why it negatively affects the patient's quality of life [4]. Aphthous stomatitis is divided into three varieties: minor aphthae, major aphthae and herpetiform. Minor aphthae also called as Miculiz's aphthae, is one of the most common variant that constitute 75-85% of all RAS cases. These types of ulcers have size usually less than 1 cm (10 mm) and heal without leaving scarring within 10 to 14 days. This type is commonly found in the non-keratinized mucosal surfaces like buccal mucosa, labial mucosa, and mouth floor as shown in Figure 1. Major aphthae also called as Sutton's disease; usually exceeds 1 cm (10 mm) cause deeper ulceration thus leave scar. It constitutes only 10-15% of RAS cases. These ulcers may remain about 10-20 days and may take months also. The usual sites are throat, lips and soft palate as shown in Figure 2. The Herpetiform is least common variant of RAS that constitutes only 07-10% of RAS cases. Ulcer size is very small measuring 2-3 mm in diameter; numerous in numbers (around 100 ulcers at once) can fuse together producing large irregular lesions that last for 7-10 days without leaving scars as shown in Figure 3 [5-7].

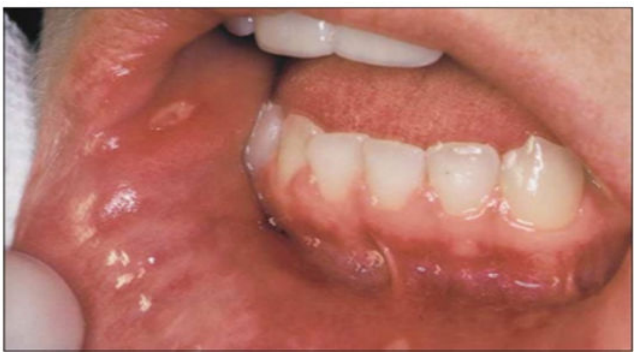

**Figure 1:** Minor Aphthous stomatitis.

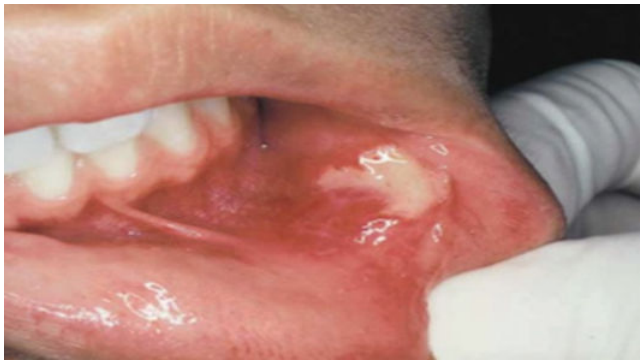

**Figure 2:** Major Aphthous stomatitis.

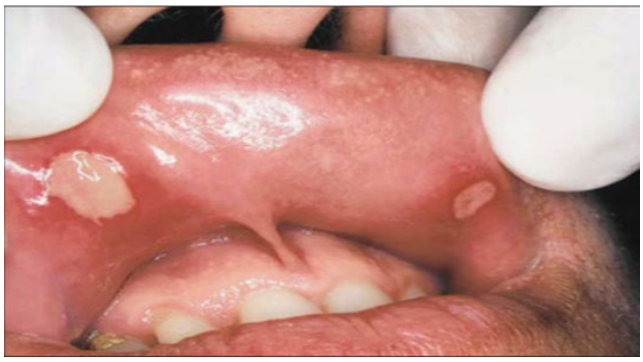

**Figure 3:** Herpetiform Aphthous stomatitis.

## Etiopathogenesis

The precise etiopathogenesis of aphthous stomatitis is not fully disclosed. The potential factors responsible for aphthous ulcers are genetic predisposition, mechanical injury, microelement and vitamin B12 deficiencies, increased oxidative stress, food allergies, microbial factors, anxiety, hormonal defects, systemic diseases (e.g., ulcerative colitis, celiac disease, AIDS, Crohn's disease) [8]. Each of them was described below:

**Genetic predisposition:** For the development of aphthous stomatitis genetic predisposition is responsible for about 40% of patients that have family history and these persons develop ulcers in earlier age which are of severe in nature [9].

**Mechanical injury:** Mechanical injury because of local anesthetic injections, dental treatments, sharp tooth and injury due to tooth brush may susceptible to the occurrence of recurrent aphthous ulceration [10]. Lack of adequate saliva to lubricate and protect the oral mucosa from injury and antigenic exposure may rise to the development of RAS [11].

**Microelement and vitamin B12 deficiencies:** Deficiencies of vitamin B12, folic acid, and iron may contribute to development of RAS. Lack of these microelements is two times more usual in these persons as compared to controls. Contradictory detections in different investigations linking the relationship of hematinic deficiency and RAS have been elaborated because of alter genetic backgrounds and dietary habits of the study population [12].

**Stress:** Stress and psychological imbalance have been linked with recurrent aphthous ulcers. Patient often manifest increased stress with inception of aphthous ulcers and several studies have reported higher occurrence. Fergusson et al. suggested that antidepressant therapy reduces the incidence of ulcers. Several mechanisms can be postulated for a cause and effect relationship between trait anxiety and recurrent aphthous stomatitis. There could be an as yet unknown biochemical effect or trait anxiety that could lead to parafunctional habits including lip and cheek biting and physical trauma which might initiate the ulcerative process in susceptible individual [13,14].

**Food allergies:** Food such as chocolate, coffee, almonds, cereals, peanuts, strawberries, tomatoes, cheese and wheat flour containing gluten may be responsible for aphthous ulcers [15].

**Microbial factors:** There is limited consistent confirmation to assist the presumption that RAS constitutes an infectious disease. In particular from investigations to examine whether there might be an association between previously suspect L-forms of streptococci and RAS or the adenoviruses, herpes simplex virus (HSV), varicella- zoster virus or cytomegalovirus and RAS, the accessible proof indicates that none of these micro-organisms appears to be directly responsible for RAS in spite of continued speculation about their feasible role. One should record that an antiviral agent, acyclovir provide no valuable outcome in preventing or reducing episodic outburst of the condition, which set out to weaken logic in favor of a possible viral causation for RAS. From irregular unscientific cases in which patients outline a noticeable reconcilable time related association between their aphthous outbursts and an immediately antecedent reactivated (recurrent) HSV infection, it is tempting to postulate that in a narrow subset of individuals who get RAS, the herpes virus may serve as an antigenic 'trigger' that initiates the cascade of immunologic events that result in ulceration. In a limited subset of RAS patients, it is possible that this is actually the case. Presumably, such patients would benefit from appropriate therapeutic and prophylactic antiviral therapy, coupled with treatments specifically aimed at lessening the severity and frequency of the RAS episodes by modulating their supposedly heightened immune responses to the viral 'trigger'. Such therapeutic strategies probably would be best carried out in consultation with an infectious disease specialist. It must be emphasized, however, that regarding most aphthous patients, any suggestion of a causative nexus between RAS and HSV seems to represent unsubstantiated conjecture rather than proven fact [16].

**Tobacco smoking:** Nonsmokers persons usually are more prone to RAS and there is a lower occurrence and extremity of RAS among heavy smokers as compared to moderate smokers. Few patients report an onset of RAS after cessation of smoking, while others report control on smoking re-initiation. The usage of smokeless tobacco is linked with a remarkably lower universality of RAS. The tables containing Nicotine also seems to manage the frequency of RAS [17].

**Immunopathogenesis:** RAS with primary immunologic abnormalities result into altered immunoregulatory balances. For example, there are rise in antibody dependent cell cytotoxicity and higher levels of serum immunoglobulins in patients with RAS Lymphocytes from patients with serious RAS demonstrate growing numbers of T-helper/inducer cells, decreased numbers of T-suppressor/inducer cells, and depressed responses to mitogens. Activated T-lymphocytes aggregate in the periphery of RAS lesions

confirming the hypothesis that RAS represents an activated cell mediated immune response. Immunohistochemical studies of lymphocyte subsets in aphthous ulcers of HIV-seronegative patients and HIV-seropositive patients have yielded similar findings, which strongly indicate that these ulcers represent a cell-mediated immunologic dysfunction in which infiltrating T-lymphocytes play a primary role. It seems likely that in genetically predisposed persons, antibody-dependent cellular cytotoxicity mad local immune complex-related reactions are involved in the immunopathogenesis of RAS, but the precipitating factors are unknown. Unfortunately, to date no consistent theory of immunopathogenesis has been accepted. This information will be useful in the future so that more effective treatment and preventive modalities can be identified [18].

**Hormonal defects:** It appears from different and sometimes conflicting studies that a minor subset of women with RAU have cyclical oral ulceration related to the onset of menstruation or the luteal phase of the menstrual cycle. Complete remission during pregnancy has been reported with exacerbation occurring in the puerperium. Although 10% of women have been reported to have had their first episode of RAU between the ages of 50-59 and more recent work has not uncovered an association between RAU and the menopause [19].

**Drugs:** Drugs such as non-steroidal anti-inflammatory drugs (NSAIDs e.g., Diclofeanac phenylacetic acid and proprionic acid) can cause oral ulcers identical to those of RAU, accompanied with genital ulceration or only oral ulcers in the case of piroxicam. A relationship between beta-blockers and aphthous ulcers was also proposed. These types of ulcers commonly occur as an adverse side effect and fade away when the usage of drug is discontinued [19].

**Systemic diseases:** Behcet's disease (BD) is a multisystemic, chronic, relapsing vasculitis that affects nearly all organs and systems. It is associated with multiple oral, genital ulcers, arthritis, hematemesis, melena and epigastric pain as predominant manifestations. Seung-Ho described that RAS and BD had similar presenting symptoms like oral lesions and abdominal pain. There were no clinical, endoscopical, histopathological or serological difference between patients with intestinal BD, RAS and healthy volunteers in anti-neutrophil cytoplasmic antibodies [20]. Celiac disease (CD) is caused by gluten sensitivity of the small intestines. According to Selim the CD prevalence (40%) in patients with RAS is higher than in the normal population. It is also described that RAS may be the presenting sign of the disease and may be used as a marker for the CD [21]. The intraoral involvement in Crohn's disease is observed in approximately 9% of cases and oral inflammation precedes intestinal symptoms in about 60% of these patients. Hence it is important to consider the differential diagnosis of Crohn's disease in subjects with intestinal symptoms and RAS [22].

## Management and treatment of aphthous stomatitis

In spite of much clinical and research observation, the root causes continue to exist was imperfectly understood. The ulcers are unavoidable and therapy is symptomatic. Various local and systemic factors are correlated with these conditions and there is evidence that a genetic and immunopathogenic form a basis for recurrent aphthous ulceration. There is no specific treatment for RAS, and management strategies depend on the symptoms, duration, and severity [18]. There is abundance of therapies for recurrent aphthous ulcers. The goals of therapy are 3-fold: (a) control the ulcer pain, (b) stimulate healing of ulcer and (c) prevent recurrence. For the determination of appropriate treatment, the medical history of patient, pain severity, outburst/frequency and medication tolerance ability of patient is some of factors have to be considered to start the treatment. It is very important that all the susceptible factors should be treated or ruled out before starting specific treatment for RAS. As there is no single treatment is available which is uniformly effective in RAS, it is important to explore a spectrum of therapies to validate a definitive treatment strategy [23]. The First choice for aphthous stomatitis treatment is the topical agents because they are cheap, effective and safe. The problem with topical agents is obtaining effective drug delivery, because substances applied to mucosal surfaces are inevitably rubbed or rinsed away. Topical management of aphthous stomatitis may not be enough for the constantly recurring and severe ulcerations. In those cases, systemic medications are employed. The first line therapy options consists of antiseptics and anti-inflammatory drugs/analgesics and second line therapy options include systemic immunomodulator, systemic antibiotic and systemic corticosteroids as shown in Table 1[24, 25].

| First Line Therapy | |
|---|---|
| Topical Antiseptic | Chlorhexidine Gluconate, Triclosan |
| Topical/ Systemic Anti-inflammatory/ Analgesic | Benzydamine Hydrochloride, Diclofenac |
| Topical Anesthetic | Lidocaine, Benzocaine |
| Topical antibiotic | Chlortetracycline, Doxycycline |
| Topical corticosteroids | Hydrocortisone hemisuccinate, Triamcinolone acetonide, Betamethasone valerate, Beclometasone dipropionate, Budesonide, Clobetasol |
| **Second Line Therapy** | |
| Systemic Immunomodulator | Levamisole, Colchicine, Hydrocortisone and Triamcinolone, Thalidomide, Dapsone, Pentoxphylline, 5-Amino salicylic acid, Azathioprine, Prostaglandin E2 |
| Systemic Antibiotic | Penicillin G Potassium |
| Systemic Corticosteroids | Prednisone |

**Table 1:** Therapeutic Options for Aphthous stomatitis.

## First Line Therapy

### Topical therapy

When there is recurrent incidence of aphthous ulcers are occurred in limited number that are either minor or major, closely opposed to one another and scattered on readily available oral surfaces such as the labial or vestibular mucosa or the anterior portion of the tongue, first-line therapeutic management based on conservative topical therapy should be involve [26].

**Topical gels, creams and pastes:** Different gels and pastes can be employed to cover the ulcer surface to form a defensive obstacle against secondary infection and further mechanical irritation. The first option of the treatment of RAS is the topical agents. A little amount of cream or gel should be applied by patient after rinsing and stay away from drinking or eating for 30 min. It should be followed by 3 to 4 times a day [27]. It is good to employ various types of adhesive bases in association with drug that prevents the topical medications to wash away from the target region. The inflammatory process that occurred with the development of aphthae may limit by topical corticosteroids. Al-Namah et al. have concluded that the novel dexamucobase was found to be equally effective in treating oral aphthous ulceration, with some advantages, as the widely used preparation Kenalog in Orabase [28]. Meng et al. have indicated that amlexanox oral adhesive pellicles are as effective and safe as amlexanox oral adhesive tablets in the treatment of minor RAS for this Chinese cohort. However, pellicles seem to be more comfortable to use when compared with the dosage form of tablets. Therefore in clinical practice, amlexanox oral adhesive pellicles may be a better choice for RAS patients [29].

**Topical anesthetic:** Lidocaine in 2% is found to be beneficial in alleviate pain related with recurrent aphthous ulcer (RAS), but mixture of adrenaline (1:8000) further enhances the pain relief period that permit the patient more time to take the meals. Patient is directed to apply 2 to 3 drops of it onto the surface of ulcer and ask to keep open the mouth [30].

**Topical antimicrobials:** In the RAS management, the aqueous mouth rinse containing Chlorhexidine gluconate provides some beneficial effects. Investigations reflect that it decreases the ulcers duration but the recurrence of ulcers cannot prevent by it. 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 [31].

**Topical antibiotics:** The antibacterial effect of tetracycline is also known to decrease the breakdown of collagen. This can be employed in mouth rinse form prepared by dissolving the capsule of 250 mg into 180 ml of water and direct the patient to swish and spit four times a day for 4 to 5 days. Tetracycline is considered inferior to minocycline due to additional immunomodulatory effects of minocycline. It can be used by dissolving the 100 mg tablets in 180 ml of water and direct the patient to rinse two times daily for 4 to 5 days. In both cases patient should be directed to stay away from food or drink for at least 30 minutes [32].

**Topical corticosteroids:** These are the backbone for the treatment of RAS. Different types of topical corticosteroids are employed that alleviate the symptoms of RAS with no suppression of adrenal. Some of currently available agents are designed in new drug delivery system in form of protective film that is designed to attach firmly to the wet moving mucous there by forming a protective film over the ulcer area leads to rapid healing and faster relief of pain. It has applied in paste form 2-3 times in a day. These steroids may develop local candidiasis on long term use. Other topical corticosteroids include: Clobetasol Propionate 0.05%, Triamcinolone acetonide, Fluocinionide 0.05% [33,34].

**Topical anti-inflammatory agents:** 5% Amlexanonx in paste form possesses anti-inflammatory and anti-allergic property has been found to be efficient and clinically safe in many clinical investigations for RAS management [35]. In the treatment of RAS ulcerations, topical sucralfate when given at 5 ml, 4 times in a day found to be very effective. It forms a protective barrier on the affected area by adhering to mucous membrane tissues, there by exerts a soothing effect on the lesions. It is commonly employed for treatment of peptic ulcers [36].

**Topical analgesic/anti-inflammatory spray and rinses:** Topical analgesic sprays or rinses such as Benzydamine hydrochloride can be utilized to alleviate discomfort in aphthous stomatitis due to its analgesic, anti-inflammatory, antimicrobial and anesthetic activity [37].

**Topical hyaluronic acid:** Topical application of Hyaluronic acid in form of 0.2% gel is found to be beneficial in RAS treatment. The main function of hyaluronic acid is activation and moderation of angiogenesis, promoting re-epithelization via proliferation of basal keratinocytes and reducing collagen disposition and scarring [38].

## Second Line Therapy

### Systemic therapy

The outbreaks of RAS are normally resolved with topical treatments, though in some cases these measures prove insufficient because of the severity of the lesions or for unknown reasons. This is when second line therapy with systemic drug substances are utilized as given following:

**Levamisole:** Due to its vast immumostimulatory effects, it was recommended as a possible treatment for RAS. By giving a dose of 10-15 mg/day for a period of 2-3 months helps in alleviate the pain, frequency, number and duration of ulcer. Due to its hazardous effects like dyspepsia, nausea, agranulocytosis and hyperemia, the use of this drug is limited [39].

**Thalidomide:** This is one of the few drugs that are extensively efficacious in the management of RAS. It retards the synthesis of tumor necrosis factor alpha and neutrophil function and also aids in the healing of aphthae, disappearance of pain and delay or disappearance of recurrence. When it is given in standard dosing levels of 100-300 mg/day or 50 mg/day, a dose dependent effect originates in 7-10 weeks following the treatment. Due to its widely known adverse reaction like teratogenicity and irreversible polyneuropathy, the therapy should be given only in case of severe ulceration and confined to patient with ulceration relating to HIV [40].

**Pentoxifylline:** Pentoxifylline is a drug that retards the synthesis of tumor necrosis factor alpha, chemotaxis and neutrophil function. When administered at a dosage of 400 mg three times a day, it alleviate the level of pain, reduce the ulcer size and number during episodes of RAS. Due to its lesser adverse effects and escalating results it is regarded as primary systemic medication for RAS treatment [41].

**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 [42].

**Zinc sulphate:** Systemic zinc treatment causes an improvement or remission in patients with RAS. It is given systemically, a total of 660 mg of zinc sulphate per day in divided doses [43].

**Azathioprine:** Azathioprine has been effective in decrease the incidence, severity and frequency of severe oral and genital aphthae when it is administered alone or in combination with other immunosuppressants in a dosage of 1 to 2 mg/kg/day (50-150 mg/day) [34].

**Methotrexate:** Methotrexate, an a analogue of folic acid found to be very beneficial in severe oro-genital aphthosis when administered in a dosage of 3-6 mg/kg or 7.5 to 20 mg weekly. After intake of methotrexate the intermittent administration of folic acid should be given [34].

**Prednisone:** It can be utilized in association with topical mouth rinses and gels. Systemic treatment of prednisone should be started at dose of 1.0 mg/kg a day as a single dose in the patients with severe RAU and it should be reduce after 1 to 2 weeks because on long term exposure drug carries the risk of several adverse effects such as hyperglycemia, moon faces, depression, lipodystrophy and hypothalamic-pituitary-adrenal axis suppression. That's why it should be used for a shorter period of time. In order to provide the effective treatment, it can be given along with other immunosuppressive agent, azathioprine to reduce the dosage of prednisone [19].

**Vitamin B12:** When researchers treated the patients suffering from RAS with a dosage of 1000 μg of vitamin B12, they concluded after 5 to 6 months of treatment that number of ulcers, duration of outbreaks and level of pain were remarkably reduced. During the treatment of around six months, "no aphthous ulcers status" was obtained by 74.1% of 31 interventional group participants concluded that treatment of RAS with vitamin B12 seems to be effective, cheap and lower risk in treating patients with RAS irrespective of their initial level of serum vitamin B12 [44].

**Dapsone:** It is an extensively employed drug for the treatment of leprosy in long term and some dermatologic conditions have been tried with limited success in the management of major aphthae. It is administered orally in a dosage of 100 mg in divided doses and it can also be increased at the rate of 50 mg/day per week to a maximum of 300 mg/day. Due to its toxic nature it can precipitate hemolytic anemia, therefore strict patient monitoring for methemoglobinemia, hemolysis, agranulocytosis and anemia is required [45].

**Rebamipide:** It is the first antiulcer drug that is found to enhance the endogenous prostaglandins in mucosa and retards the production of oxygen derived free radical. Investigations revealed that when the drug administered in a dose of 100 mg (tablet) three times a day for seven days decreases the pain and number of aphthae with excellent recovery by seventh day [46].

**Irsogladin:** When the drug is administered orally 2 to 4 mg/day which is used for treatment of peptic ulcer and gastritis, found to be decreasing the ulcer counts and on regularly taken it also prevent the recurrence of aphthous stomatitis [47].

**Cyclosporine A:** At a dosage of 3-6 mg/kg, was found to be efficacious in about 50% of patients suffered from aphthosis. However, abrupt withdrawal of therapy may lead to a rebound phenomenon. Due to the potential for severe side-effects from therapy, clinical and serologic vigilance must be observed [25].

**Adalimumab:** Adalimumab is an anti-TNF- monoclonal antibody that has been used to treat severe, recalcitrant, RAS, but in view of the risk of serious adverse effects, it should be used with extreme caution [48].

**Acyclovir:** Acyclovir (400 mg twice a day for 1 year) was used in a double-blind study in 25 patients with RAS without any benefit in the prevention of ulcers. 64 Alternatively, higher dosages (800 mg twice a day for 8 weeks) of acyclovir were used in one study of eight patients with recurrent RAS, and six patients experienced either total regression of existing ulcers or relief of symptoms within 2 days of therapy [49].

**Montelukast:** In a study carried out by Femiano, in which 20 participants received a daily oral dosage of 10 mg montelukast for 1 month followed by alternate days for the second month. It was concluded that the time in days to resolution of first ulcer was shorter, accompanied with a remarkable reduction in the total count of new lesions over the treatment period of 2-months [50].

**Infliximab:** Recently, it has been shown by LP 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) [34].

**Etanercept:** Etanercept (Enbrel) is a recombinant TNF-soluble receptor can be used cases of recalcitrant, recurrent ulceration in a dose of 25 mg subcutaneously twice a week. The only adverse effect reported is mild erythema, induration and tenderness at injection site [51].

**Clofazimine:** It is an antimicrobial used for the treatment of leprosy is combination with other drugs such as rifampicin and dapsone. In application to severe RAS, and when administered at a dose of 100 mg/day during 6 months, the emergence of new lesions was found to be inhibited by drug during the prescribed period of treatment [52].

**Penicillin G potassium:** Penicillin G potassium in 50 mg tablets administered four times a day during four days reduces the size of the ulcers and lessen the pain [53].

## Research work done on aphthous stomatitis (Mouth ulcers)

A very few research work has been done on aphthous stomatitis which makes it challenging for scientists as well as for the researchers. Some of works done reported are given as follows:

In 2018, Zhang developed and evaluate *in-vitro in-vivo* the bilayered mucoadhesive buccal film containing ornidazole (OD) and dexamethasone sodium phosphate (DEX) in combined form employing solvent casting technique for the treatment of oral ulcers. The prepared films were evaluated systemically for *in-vitro* in order to find the optimized formulation. The rabbit oral ulcer model was investigated to study the therapeutic effectiveness of these films and the *in-vivo* release of OD and DEX in the human oral cavity was also evaluated. It was concluded that the developed film become a local drug delivery device for the treatment of oral ulcers [54].

In 2017, Heng-zhong developed and evaluate the fast disintegrating films containing Lignocaine as a model drug to treat the mouth ulcers. For the evaluation of local anesthetic activity of developed film, tail flick test in rat model was performed. 32 full factorial design was applied to develop oral fast disintegrating films by solvent casting

evaporation technique. Chitosan, Croscarmellose Sodium (CCS) and Dibutyl Phthalate (DBT) were used as polymer, superdisintegrant and plasticizer respectively. The developed films were evaluated for physical appearance, thickness, weight variation, folding endurance, disintegration time, drug content uniformity and *in-vitro* drug release. It was concluded that oral fast disintegrating films of Lignocaine serves as potential drug delivery systems for mouth ulcer management [55].

In 2017, Joshi developed a herbal oral dissolving film for mouth ulcer and throat infection treatment contained herbal plants extract and powders of *Ocimum tenuiflorum* (Tulsi), *Glycyrrhiza glabra* (yastimadhu), *Curcuma longa* (turmeric). These plants have antimicrobial, astringent, antiulcer and anti-inflammatory activity. HPMC was selected as polymer and plasticizer for the film formulation. The films were subjected to physicochemical examinations such as weight uniformity, folding endurance, surface pH disintegration time, % moisture absorption, % moisture loss, surface pH, swelling index etc. The obtained results for prepared herbal films disintegrate within 1 minute. These films are economic, convenient and do not show any side effect [56].

In 2016, Aslani developed an oral gel from *Punica granatum* (Pomegranate) flower extract for the treatment of recurrent aphthous stomatitis. Different formulations were prepared using different amounts of hydroxypropyl methylcellulose K4M, sodium carboxymethylcellulose (SCMC) and carbomer 934. After this, the condensed extract was uniformly dispersed in polyethylene glycol (PEG) 400 and added to gel bases. Form the results it was found that mucoadhesion of gel enhanced as the polymer amount in gel increases that lead to longer durability in mouth. Therefore, the formulation F4 having highest mucoadhesion and viscosity due to its higher polymer content which is able to remain for a longer period of time to release its active ingredient. Hence due to proper appearance, stability, uniformity, acceptable mucoadhesion and viscosity the F4 formulation was selected as best final formulation [57].

In 2016, Li W developed a film for the mouth ulcer treatment containing compound calculus bovis sativus (CBS) and ornidazole by employing three polymers (hydroxypropyl methyl cellulose, chitosan, poly(vinyl alcohol) (PVA)). The film was developed with the film-forming suspension, using casting-solvent evaporation technique. The prepared films were evaluated for drug content, swelling index, release behavior and mucoadhesive properties. The prepared films displayed desirable swelling properties and *in-vitro* drug release behaviors. It was concluded that prepared film was able to remarkably relieve the mucosal wounds in animals [58].

In 2015, Thorat developed thermoreversible mucoadhesive gel (TMG) containing curcumin for treatment of mouth ulcer. The formulations were developed by employing Xanthan gum and carbomers as bioadhesive material along with thermoreversible agent such as Pluronic F68 and Pluronic F127. The developed preparations were evaluated for pH, gel strength, spreadability, gelation temperature, *in-vitro* mucoadhesion and *in-vitro* drug release. From the results it was concluded that a sustain drug release pattern was obtained along with enhanced residence time as well as the contact area of curcumin at the site of ulcer thus making the curcumin thermoreversible gel a suitable candidate for the treatment of mouth ulcer [59].

In 2014, Ambikar developed a herbal oral dissolving film containing herbal plants extract and powders of *Ocimum tenuiflorum* (tulasi), *Azadiracta indica* (neem), *Syzygium aromaticum* (lavanga), *Boerhaavia diffusa* (punarnava), *Glycyrrhiza glabra* (yastimadhu), *Jasminum grandiflorum* (jasmine), (triphala) for treatment of mouth ulcer. These plants exhibit antiulcer, astringent, antimicrobial and anti-inflammatory activity. HPMC and ethyl cellulose were selected as polymer for film formation. The films were subjected to physicochemical examinations such as weight uniformity, folding endurance, surface pH disintegration time, % moisture absorption, % moisture loss, surface pH, swelling index etc [60].

In 2014, Bhutkar developed a mucoadhesive herbal buccal patch of Psidium Guava L. for the treatment of oral ulcers by employing HPMC K15 and Carbopol 940 as a rate controlling and mucoadhesive polymer. It was concluded that the patch containing polymer HPMC K15 and Carbopol 940 successfully delivered the herbal constituent quercetin isolated from *Psidium Guava L* [61].

In 2013, Alsadat developed a mucoadhesive paste of chlorhexidine and Betamethasone to study the effect on the process of oral ulcer recovery in rats. From the results obtained it was concluded that the best wound healing processes from clinical and histological aspects were achieved in the betamethasone (B) and betamethasone-chlorhexidine (BC) groups. Also, use of chlorhexidine alone had no significant effect on wound healing and other criteria; theefore, the authors concluded it is not effective, when it is used alone [62].

## Conclusion

Aphthous stomatitis is the most common inflammatory ulcerative condition of the oral mucosa, it occur as painful ulcers and recur from time to time. The etiopathogenesis of this disease is unclear. Much research has been done to find treatments to reduce pain related to, duration of and frequency of ulcer outbreaks. There are several treatment options, both local and systemic, that could be helpful for management of aphthae in the primary care setting. 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. Treatment strategies must be directed toward providing symptomatic relief by reducing pain, increasing the duration of ulcer-free periods, and accelerating ulcer healing. Future research should focus on identifying RAS etiology, developing standardized diagnostic criteria for RAS, and improving the design and reporting of clinical trials.

## Acknowledgements

The authors are grateful to Central Library Department of I.K. Gujral Punjab Technical University, Jalandhar and Rayat Bahra Institute of Pharmacy, Hoshiarpur, Punjab for the providing us the literature search facilities for accomplishing this review work.

## Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this review article.

## References

1. Preeti L, Magesh K, Rajkumar K, Karthik R (2011) Recurrent aphthous stomatitis. J Oral Maxillofac Pathol 15: 252-256.
2. Pongissawaranun W, Laohapand PP (1991) Epidemologic study on recurrent aphthous stomatitis in a thai dental patient population. Community Dent Oral Epidemiol 19: 52-53.

3. Shashy RG, Ridley MB (2000) Aphthous Ulcers: A difficult clinical entity. Amer J Otolaryngol 21: 389-393.
4. Wadhawan R, Sharma S, Solanki G, Vaishnav R (2014) Alternative medicine for aphthous stomatitis: A Review. Int J Adv Case Rep 1: 5-10.
5. Munoz-Corcuera M, Esparza-Gomez G, Gonzalez-Moles MA, Bascones-Martinez A (2009) Oral ulcers: clinical aspects. A tool for dermatologists, Part I, Acute ulcers. Clin Exp Dermatol 34: 289-294.
6. Tarakji B, Gazal G, Al-Maweri SA, Azzeghaiby SN, Alaizari N (2015) Guideline for the diagnosis and treatment of recurrent aphthous stomatitis for dental practitioners. J Int Oral Health 7: 74-78.
7. Swain N, Pathak J, Poonja LS, Penkar Y (2012) Etiological factors of recurrent aphthous stomatitis: A common perplexity. J Contemp Dent 2: 96-100.
8. Slebioda Z, Szponar E, Kowalska A (2014) Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: Literature review. Arch Immunol Ther Exp 62: 205-215.
9. Scully C, Porter S (2008) Oral mucosal disease: Recurrent aphthous stomatitis. Br J Oral Maxillofac Surg 46: 198-206.
10. Jurge S, Kuffer R, Scully C, Porter SR (2006) Recurrent aphthous stomatitis. Oral Dis 12: 1-21.
11. Ship JA, Chavez EM, Doerr PA, Henson BS, Sarmadi M (2001) Recurrent aphthous stomatitis. Quintessence Int 31: 95-112.
12. Edgar NR, Saleh D, Miller RA (2017) Recurrent Aphthous Stomatitis: A Review. J Clin Aesth Dermatol 10: 26-36.
13. Akintoye SO, Greenberg MS (2005) Recurrent aphthous stomatitis. Dent Clin North Amer 49: 31-47.
14. Shastri A, Srivastava R (2015) Etiopathogenesis, Diagnosis and Recent Treatment Modalities for Recurrent Aphthous Stomatitis: A Review. Int J Contemp Med Res 2: 1-5.
15. Scully C, Nur FL (2003) Diagnosis and management of recurrent Aphthous stomatitis. The J Amer Dent Assoc 134: 200-207.
16. Swain N, Pathak J, Poonja LS, Penkar Y (2012) Etiological Factors of Recurrent Aphthous Stomatitis: A Common Perplexity. J Contemp Dent 2: 96-100.
17. Arun Kumar M, Ananthakrishnan V, Goturu J (2014) Etiology and pathophysiology of recurrent aphthous stomatitis: A review. Int J Cur Res Rev 6: 16-22.
18. Ship JA, Arbor A, Mich (1996) Recurrent aphthous stomatitis: An update. Oral Surg Oral Med Oral Patho 81: 141-147.
19. Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, et al. (2004) Recurrent aphthous ulcers today: a review of the growing knowledge. Int J Oral Maxillofac Surg 33: 221-234.
20. Rhee SH, Kim YB, Lee ES (2005) Comparison of Behcet's disease and recurrent aphthous ulcer according to characteristics of gastrointestinal symptoms. J Korean Med Sci 20: 971-976.
21. Aydemir S, Tekin NS, Aktunç E, Numanoglu G, Ustundag Y (2004) Celiac disease in patients having recurrent aphthous Stomatitis. Turk J Gastroenterol 15: 192-195.
22. Rogers RS (1997) Recurrent aphthous stomatitis: Clinical characteristics and associated systemic disorders. Seminars in Cutaneous Medicine and Surgery 16: 278-283.
23. Vivek V, Bindu JN (2011) Recurrent aphthous stomatitis: Current concepts in diagnosis and management. J Ind Acad Oral Med Radiol 23: 232-236.
24. Guallar IB, Soriano YJ, Lozano AC (2014) Treatment of recurrent aphthous stomatitis. A literature review. J Clin Exp Dent 6: 168-174.
25. Pramod GV (2013) Management strategies for recurrent oral aphthous ulcers. e-J Dent 3: 352-360.
26. Eisenberg E (2003) Diagnosis and treatment of recurrent aphthous stomatitis. Oral Maxillofacial Surg Clin N Am 15: 111-122.
27. Casiglia JM (2002) Recurrent aphthous stomatitis: Etiology, diagnosis, and treatment. Gen Dent 50: 157-166.
28. Al-Namah ZM, Carson R, Thanoon IA (2009) Dexamucobase: A novel treatment for oral aphthous ulceration. Quintessence Int 40: 399-404.
29. Meng W, Dong Y, Liu J, Wang Z, Zhong X, et al. (2009) A clinical evaluation of amlexanox oral adhesive pellicles in the treatment of recurrent aphthous stomatitis and comparison with amlexanox oral tablets: A randomized, placebo controlled, blinded, multicenter clinical trial. Trials 10: 30.
30. Aljbab AA, Almuhaiza M, Patil SR, Alanezi K (2015) Management of recurrent aphthous ulcers: An Update. Int J Dent Oral Health 2: 1-4
31. Piccione N (1979) Use of chlorhexidine in the therapy of some stomatological diseases. Minerva Stomatol 28: 209-214.
32. Graykowski EA, Kingman A (1978) Double-blind trial of tetracycline in recurrent aphthous ulceration. J Oral Pathol 7: 376-382.
33. Pimlott SJ, Walker DM (1983) A controlled clinical trial of the efficacy of topically applied fluocinonide in the treatment of recurrent aphthous ulceration. Br Dent J 154: 174-177.
34. Altenburg A, Zouboulis CC (2008) Current concepts in the treatment of recurrent aphthous stomatitis. Skin Therapy Lett 13: 1-10.
35. Khandwala A, Van Inwegen RG, Alfano MC (1997) 5% Amlexanox oral paste, a new treatement for recurrent minor apthous stomatitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 83: 222-230.
36. Ricer RE (1989) Sucralfate vs. placebo for the treatment of aphthous ulcers: a double-blinded prospective clinical trial. Fam Pract Res J 9: 33-41.
37. Qnane PA, Graham GG, Ziegler JB (1998) Pharmacology of Benzydamine. Inflammopharmacology 6: 95-107.
38. Nolan A, Baillie C, Badminton J, Rudralingham M, Seymour RA (2006) The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration. J Oral Pathol Med 35: 461-465.
39. Scheinfeld N, Rosenberg JD, Weinberg JM (2004) Levamisole in dermatology: a review. Am J Clin Dermatol 5: 97-104.
40. Genvo MF, Faure M, Thivolet J (1984) Treatment of aphthosis with thalidomide and with colchicine. Dermatologica 168: 182-188.
41. Pizarro A, Navarro A, Fonseca E, Vidaurrazaga C, Herranz P (1995) Treatment of recurrent aphthous stomatitis with pentoxifylline. Br J Dermatol 133: 659-660.
42. Puri N, Gill JK, Kaur H, Kaur N, Kaur J (2015) Recurrent aphthous stomatitis: Therapeutic management from topicals to systemics. J Adv Med Dent Sc Res 3: 165-170.
43. Bor NM, Karabiyikoglu A, Karabiyikoglu T (1990) Treatment of recurrent aphthous stomatitis with systemic zinc sulphate. J Islam Acad Sci 3: 343-347.
44. Cui RZ, Bruce AJ, Rogers RS (2016) Recurrent aphthous stomatitis. Clin Dermatol 34: 475 481.
45. Sarmadi M, Ship JA (2004) Refractory major aphthous stomatitis managed with systemic immunosuppressants: A case report. Quintessence Int 35: 39-48.
46. Kudur MH, Hulmani M (2013) Rebamipide: A novel agent in the treatment of recurrent aphthous ulcer and Behcet's Syndrome. Indian J Dermatol 58: 352-354.
47. Nanke Y, Kamatani N, Okamoto T, Ogiuchi H, Kotake S (2008) Irsogladine is effective for recurrent oral ulcers in patients with Behçet's disease : an open-label, single-centre study. Drugs R D 9: 455-459.
48. Vujevich J, Zirwas M (2005) Treatment of severe, recalcitrant, major aphthous stomatitis with adalimumab. Cutis 76: 129-132.
49. Pedersen A (1992) Acyclovir in the prevention of severe aphthous ulcers. Arch Dermatol 128: 119-120.
50. Femiano F, Buonaiuto C, Gombos F, Lanza A, Cirillo N (2010) Pilot study on recurrent aphthous stomatitis (RAS): a randomized placebo-controlled trial for the comparative therapeutic effects of systemic prednisone and systemic montelukast in subjects unresponsive to topical therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 109: 402-407.
51. Robinson ND (2003) Recalcitrant, recurrent aphthous stomatitis treated with etanercept. Arch Dermatol 139: 1259-1262.

52. De Abreu MA, Hirata CH, Pimentel DR, Weckx LL (2009) Treatment of recurrent aphthous stomatitis with clofazimine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 108: 714-721.

53. Zhou Y, Chen Q, Meng W, Jiang L, Wang Z et al. (2010) Evaluation of penicillin G potassium troches in the treatment of minor recurrent aphthous ulceration in a chinese cohort: a randomized, double-blinded, placebo and no-treatment-controlled, multicenter clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 109: 561-566.

54. Zhang C, Liu Y, Li W, Gao P, Xiang D et al. (2018) Mucoadhesive buccal film containing ornidazole and dexamethasone for oral ulcers: in vitro and in vivo studies. Pharm Dev Technol 25: 1-9.

55. Heng-Zhong X, Jing L, Xiao-xiu F (2017) Pharmacological evaluation of oral fast disintegrating films containing local anaesthetic agent Lignocaine. Biomed Res 28: 1135-1141.

56. Joshi P, Waghamare N, Karande M (2017) Herbal oral disintegrating film. Sci J 1: 1-4.

57. Aslani A, Zolfaghari B, Davoodvandi F (2016) Design, formulation and evaluation of an oral gel from Punica Granatum Flower extract for the treatment of recurrent aphthous stomatitis. Adv Pharm Bull 63: 391-398.

58. Li W, He WX, Gao P, Zhang C, Cai H et al. (2016) Preparation in vitro and in vivo evaluations of compound calculus bovis sativus and ornidazole film. Biol Pharm Bull 39: 1588-1595.

59. Thorat S, Sarvagod AM, Kulkarni SV, Hosmani AH (2015) Treatment of mouth ulcer by curcumin loaded thermoreversible mucoadhesive gel: A technical note. Int J Pharm Pharm Sci 7: 399-402.

60. Ambikar RB, Phadtare GA, Powar PV, Sharma PH (2014) Formulation and evaluation of the herbal oral dissolving film for treatment of recurrent aphthous stomatitis. Int J Phytother Res 4: 11-18.

61. Bhutkar KG (2014) Formulation and evaluation of mucoadhesive herbal buccal patch of psidium Guava L. J Cur Pharm Res 5: 1372-1377.

62. Alsadat Hashemipour M, Borna R, Gandjaliphan Nassab A (2013) Effects of Mucoadhessive Paste of Chlorhexidine and Betamethasone on Oral Ulcer Recovery Process in Rats. Wounds 25: 104-112.