

RECURRENT APHTHOUS STOMATITIS – AN OVERVIEW

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ABSTRACT

Recurrent aphthous ulcers are common painful mucosal conditions affecting the oral cavity. Despite their high prevalence and knowledge of many etiological factors, the exact mechanism of disease is still not fully understood. There are three different clinical forms of recurrent aphthous stomatitis and the therapy differs depending on it.

The aim of this article is to provide an overview of current knowledge about the possible causes and treatment of recurrent aphthous stomatitis. We discuss its pathogenesis which is currently the least explained in the literature. This review offers scientists and clinicians useful information about clinical presentation, diagnosis, predisposing aetiological factors and recent trends in the management of recurrent aphthous stomatitis.

Keywords: Recurrent aphthous stomatitis, oral ulcer, aphthae.



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INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most common disease of the oral mucosa characterized by recurrent episodes of solitary or multiple painful ulcers. The term "aphthae" was first used by Hippocrates to describe the pain that occurs due to ulcerations in the oral cavity (1). Ulcerations most often occur on the buccal and labial mucosa, as well as on the tongue, while the well-keratinized mucous membrane of the palate and gingiva is rarely affected (2). The aetiology of RAS has not been fully elucidated, but there are predisposing factors for the development of the disease such as local trauma, genetic factors, viral and bacterial infections, nutritional deficiencies, immune or endocrine system dysfunctions, oxidative stress, and systemic diseases. RAS affects up to 25% of adults and 40% of children (3,4).

RAS mostly affects non-keratinized oral mucosa, buccal, labial mucosa, and ventral surface of the tongue. There are three main forms of aphthous stomatitis depending on the size and duration of ulceration; minor (MiRAS), major (MaRAS) and herpetiformis (HeRAS) (Table 1). MiRAS is characterized by round or oval lesions whose bottom is covered with greyish-yellowish fibrin, up to 10 mm in size, edged by an erythematous halo (Figure 1A). They most often occur on the buccal mucosa, the mucous membrane of the lips, the floor of the oral cavity, and the lateral and ventral sides of the tongue. They heal in a period of 7-14 days without scar tissue (1). In contrast, MaRAS lesions exceed the size of 10 mm, and they are localized on the soft palate, lips, and pharynx (Figure 1B). The lesions persist for up to 6 weeks and have the possibility of healing with scarring (5). HeRAS have lesions that are irregular in shape and are more common in females, localized on the lips, tongue, gingiva, and on the floor of the oral cavity. The size of the ulceration does not exceed a diameter of 2-3 mm, but what separates them from the other two is that they occur in a group of several lesions at the same location. In most cases, the lesions heal within a period of 30 days without scar tissue (1). At the beginning of RAS, there is a prodromal phase characterised with burning sensations that last from 2 to 48 hours before an ulcer appears. Lesions are round, well-defined with an erythematous margin, and covered with fibrinous pseudomembrane at the centre. Histology is non-specific; lesion demonstrates inflammatory mononuclear cells, oedema of connective tissue, and lining of the margins with neutrophils. The surface layer consists of a fibrinous exudate infiltrated by polymorphonuclear leukocytes (6).

Since neither the aetiology nor the pathogenetic mechanisms of the RAS have been fully elucidated, RAS therapy is based on eliminating the symptoms of the disease.

EPIDEMIOLOGY

RAS is present in 20% of the total population, and this number depends on various factors, such as socioeconomic and ethnic characteristics (2). If it occurs in children, it is considered to have its peak between the ages of 10 and 19 (5,

6). Children whose both parents had RAS in some period of life have a 90% chance of getting RAS, while that percentage in children with negative family anamneses is 20% (7). MaRAS appears more frequently in younger patients, while HeRAS affects people in the third decade of life most commonly. Basically, the severity and the frequency of the episodes usually decrease by age, which can partially be attributed to the age-dependent lower function of the immune system, such as the phagocytic capacity and neutrophils' chemotactic (8). RAS is more frequent in females (57,3%), and occurs three times more often in Caucasians than in Afro-Americans (8, 9).

PREDISPOSING AETIOLOGICAL FACTORS

The exact cause of RAS is still unknown, but many factors, such as local, systemic, nutritional, microbiological, genetic, and immune, have been linked to the development of this disease. Also, the use of certain medications have a big impact on the frequency of RAS (3,10,11). The factors that may contribute to the development of RAS are presented in the Figure 2 and Table 2.

Local factors

Local trauma which leads to oedema and cell infiltration of the oral mucosa is the most common local factors for the development of RAS (12). It can be a consequence of a sharp tooth, tooth brush injury, local anaesthetic injections or dental treatments (13). Similarly, psychological stress as one of the emphasized causative factors RAS may indirectly induce trauma to oral soft tissues by parafunctional habits such as cheek or lip biting. A recent investigation showed a lack of direct correlation between the severity of RAS and levels of stress, suggesting that stress may act as a triggering factor rather than an aetiological factor in susceptible RAS patients (14).

In addition to the above, the pH values of saliva affecting the level of salivary cortisol, was associated with the development of RAS (15). Vanada *et al.* (16) showed higher levels of salivary cortisol in RAS patients, while Rezaei *et al.* (17) found lower salivary cortisol levels in active lesions and the healing phase compared to healthy patients.

Several studies have examined the effect of cigarette smoking on the incidence of RAS and revealed a negative correlation between the above parameters (18). Possible explanations include increased mucosal keratinization after prolonged exposure to nicotine which could reduce the possibility of RAS (19). Also, the increased keratin layer serves as a protective and mechanical barrier against trauma and microbes (20-22). Nicotine is deemed to be the protective factor as it reduces the production of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α , and also has the ability to stimulate the production of adrenal steroids by its action on the hypothalamic adrenal axis (23). De Souza *et al.* (24) also confirmed the protective effect of cigarette smoking on RAS. The study on the effect of nicotine on aphthous ulcers in non-smoking patients demonstrated its plausible therapeutic



effect, as the ulcers healed and no new ulcers appeared during therapy with nicotine (25).

Microbiological factors

The various viruses and bacteria have been linked the pathogenesis of RAS. Several opposing results have been reported in various published studies.

Many authors believe that the Herpes simplex virus (HSV) plays an important role in RAS development. It was shown that patients with antibodies to HSV type I have a significantly higher incidence of RAS compared to patients with no antibodies to HSV type I (26). However, some studies showed that HSV does not affect the development of RAS. These conclusions follow the results of serum interferon levels which were not increased in patients with RAS (27), as well as the absence of HSV antigens in the lesions after biopsy (28, 29). Additionally, PCR analysis has shown that some other viruses such as Cytomegalovirus, Varicella Zoster virus and, Epstein-Barr virus do not participate in the pathogenesis of RAS (30, 31). Therefore, it is important to recognize and differentiate the RAS from other oral diseases of viral aetiology in order for the therapy to be adequate and effective. Recent research has shown a significant association between COVID-19 and RAS, where the prevalence of RAS in patients with COVID-19 is higher than in the control group, indicating the role of COVID in the etiopathogenesis of RAS. However, additional studies are needed to elucidate the mechanism of their association (32).

Infection with *Helicobacter pylori* (*H. pylori*), a gram-negative, S-shaped bacterium is responsible for the development of ulcers on the stomach and duodenum, which raises a question whether it affects the development of ulcers or RAS in the oral cavity. Some investigations showed that there is no correlation between this bacteria and RAS, as this it has been identified in both patients with healthy mucosa and with RAS (33). In fact, the incidence of anti - *H. pylori* seropositivity was not shown significantly higher in patients with RAS (30.6%) compared with patients with other oral ulcerative lesions (33.0%) and healthy patients (24%) (34). As well, some research investigated *H. Pylori* DNA from oral ulcers showing its presence in only 2% (35). However, some findings indicated that there might be an association between *H. Pylori* and RAS. The authors used a commercially available rapid urease test (RUT) kit to determine the presence of *H. Pylori* in subgingival and supragingival plaque, where RUT results were positive in 89,5% of RAS patients (36). Interestingly, in patients with RAS after eradication of *H. pylori*, there is a significant reduction in the number of aphthae which can be explained as a product of increased levels of vitamin B12 (37). However, other studies shown contrary results where patients positive on *H. Pylori* had a lower RAS prevalence than *H. Pylori* negative patients (38).

Oral streptococci are often associated with the pathogenesis of RAS, especially *S. Sanguis* which was long thought to be the first bacterium isolated from a RAS lesion. However,

later it was determined that it was actually a strain of *S. Mitis*, a bacterium that is an integral part of dental plaque in patients with Behcet's disease (39). These bacteria are directly involved in the pathogenesis of RAS or indirectly as an antigenic stimulus, which in turn challenge antibody production that cross-react with the oral mucosa (40).

Systemic diseases

The most common disease associated with RAS is Behcet's disease. It is characterized by changes in the oral and genital mucosa, and lesions in the eyes (41). Behcet's disease occurs as a consequence of vasculitis of small and medium blood vessels and inflammation of the epithelium. It affects adults more often, but it can also occur in children (42). Various tests were performed to better distinguish RAS from Behcet's disease. Based on the antibody titer test on *Saccharomyces cerevisiae*, research shown a significantly higher antibody titer in patients with Behcet's disease compared to RAS and healthy patients (43, 44). In addition to this test, the human leukocyte antigen (HLA) showed a significant difference in the frequency of individual HLA antigens in RAS patients and patients with Behcet's disease. However, the difference between these two disorders is still not fully elucidated (45).

Autoimmune sensitivity to gluten i.e., celiac disease was also stated as a predisposing factor for RAS. However, given that oral ulcers in patients with celiac disease do not have all the characteristics of RAS, and that the incidence of aphthae in these patients varies widely (from 3% - 60%), the correlation between RAS and celiac disease could not be concluded (46, 47).

Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, have important extra-intestinal manifestations, especially in the oral cavity. It was estimated that in about 10% of patients with Crohn's disease, oral ulceration precedes intestinal symptoms, while some authors state that these lesions are a consequence of inflammation of the small salivary glands (48). Studies showed that aphthous ulcers in patients with Crohn's disease and healthy patients did not differ visually in the morphological study. However, a group with Crohn's disease had granulomatous inflammation of the oral mucosa with a high infiltration of macrophages, and T lymphocytes, while healthy patients have had fibrinous inflammation (49). Oro-facial granulomatosis, presented in the form of recurrent aphthous stomatitis, may precede Crohn's disease by several years, and could be the only indicator of the existence of the intestinal disease (50).

HIV - positive patients represent a population in which the occurrence of RAS is more frequent and the clinical picture is more severe. Lesions in these patients last longer, they are more painful and harder to heal (51). In some instances, oral ulcers can be the first sign of the HIV infection, so clinicians must be very careful during each intraoral examination. Interestingly, the lesions that occur in HIV patients have the characteristics of large aphthae, i.e., aphthae major, and most



commonly occur when the CD4⁺ lymphocyte count is below 100 cells/mm³ (52). HIV patients with non-healing ulcers require biopsies to exclude the possibility of deep fungal or viral infections and neoplasms. The major form of ulcer can be progressive and destructive and in an advanced case, it can lead to dysphagia and secondary malnutrition (53). Shu *et al.* (54) suggested that CD4⁺ cell count can be used as an indicator for the existence of the oral disease and the need for therapy in HIV patients. They examined the most common types of oral lesions and showed that a higher incidence of oral ulcers with lower CD4⁺ count indicates the importance of CD4⁺ cell count in identifying disease progression (54).

Allergic factors

Allergies have always been considered a possible cause of RAS as well as hypersensitivity to certain foods, such as almonds, chocolate, coffee, tomatoes, strawberries, or wheat flour which contains gluten (55). It was shown that 30% of subjects who consumed food that did not lead to the release of histamine, experienced regression of RAS. However, the diet did not completely eliminate the oral lesions. Based on these findings, the study concluded that food hypersensitivity played a minor role in the development of RAS (56).

Sodium lauryl sulfate-containing toothpaste was reported in many investigations as a possible cause of RAS. It is believed that, due to its denaturing effect, it degrades the mucin layer in the oral cavity leaving the epithelial layer exposed and thus more susceptible to ulceration (2, 57, 58). However, the widespread use of Sodium lauryl sulfate-containing dentifrice suggests that this may not truly predispose to RAS (13).

Immunological factors

There are numerous studies on the association between the immune response and the development of RAS. The development of RAS is thought to be based on the T lymphocytes' cytotoxicity to the oral epithelium, a defect in a subpopulation of lymphocytes or as a result of autoimmunisation to oral epithelium (59, 60, 61). It was found that in the development of RAS, the immune responses become disrupted in response to a trigger factor that is yet to be determined. This disruption involves both innate and adaptive mechanisms which manifests as an increased number of NK cells and B lymphocytes, reactivation of neutrophils, disrupted CD4/CD8 ratio, and increased number of CD25⁺ cells in peripheral blood. Based on the cytokine profile in RAS patients it is believed that Th1 type immune response plays a crucial role in RAS development (61). Many studies showed elevated levels of proinflammatory cytokines such as IL-2, interferon (INF)- γ , and TNF- α in RAS lesions or elevated serum IgA levels, as well as the decrease in the levels of anti-inflammatory cytokines, TNF- β and IL-10 (2, 62, 63). That imbalance, between pro-and anti-inflammatory cytokines, could lead to the development of RAS and auto immunization in predisposed persons. Th1 type immune response was also observed in other autoimmune-mediated conditions like Chron's disease, celiac disease and others (61). When RAS

was compared with autoimmune-mediated vesiculobullous diseases, like Pemphigus Vulgaris or Pemphigoid, using immunofluorescent methods, previous study found deposits of immune complexes in the oral mucosa of patients with these diseases, which were not presented in patients with RAS. This could be an important differentiating marker between RAS and autoimmune-mediated diseases. Some physiologic states like pregnancy or drug therapy with tetracycline for example, are inhibitors of Th1 immune response and may affect the course of RAS (64).

According to the literature, TNF- α as a proinflammatory cytokine, plays important role in the pathogenesis of RAS by stimulating the expression of major histocompatibility (MHC) class I which could contribute to targeting local mucosal tissue for attack by cytotoxic T cells. In fact, previous research showed increased levels of MHC antigen expression in the ulcerative stages of the RAS, while in the period of healing, the MHC antigen expression was undetected (65). Natah *et al.* (66) compared the number of cells containing TNF- α in oral aphthous ulcers and mechanically injured ulcers. They observed aphthous cells containing TNF- α more frequently which indicate the role of this cytokine in the activation of the lymphocytes during the development of RAS (67).

Nutritional factors

It is believed that folate, zinc, iron, and vitamins like B1, B2, B6, and B12 are associated with the pathogenesis of RAS (68, 69, 70, 71). Bao *et al.* (71) investigated serum vitamin B12, ferritin, and folate levels in patients with RAS and healthy controls. They found high deficiency of serum B12 levels in the RAS group, while the serum ferritin and folate levels in RAS patients and control group showed no difference. They also found many differences in hematinic deficiencies across genders and age groups which should be examined furtherly (71). A deficiency of calcium and vitamin C has also been related to RAS, which could be associated with the deficiency of vitamin B1, supporting the thought of combined nutritional deficiency in RAS patients (72). Zinc deficiency was also shown as a predisposing factor for RAS as a study on RAS patients receiving replacement therapy achieved therapeutic success (73). There is evidence to suggest that decreased levels of vitamin D in serum also might be a risk factor for RAS (74). However, this statement was contradictory to others (75). Daily administration of vitamin C was found to significantly reduce oral ulcer outbreaks and pain in patients with RAS, but more studies are needed to explore the potential association between vitamin C and RAS development (76). Some of these nutritional deficiencies may develop secondary as a result of other diseases such as malabsorption syndrome or gluten sensitivity with or without association to enteropathy (6).

Other factors

All previous factors can disturb the oxidant/antioxidant balance of an individual and trigger the formation of free radicals. An increase in the concentrations of these free radicals



can cause cellular damage suppressing the activity of the immune system. Their damaging effects on cells may be achieved through the peroxidation of protein, lipid, or DNA (77). Ziaudeen *et al.* (78) showed that the mean value of salivary superoxide dismutase and malondialdehyde were increased, while the activity of uric acid and glutathione peroxidase were decreased in patients with RAS compared to the control group. Also, Li *et al.* (79) showed higher serum levels of malondialdehyde in RAS patients, while serum levels of vitamin E were decreased. The studies also investigated the serum's total oxidant status, total antioxidant status, oxidative stress index, prolidase, and paraoxonase levels, showing that the total oxidant status and oxidative stress index were higher in RAS patients (80). These results indicate that oxidative stress plays a significant role in the pathogenesis of RAS.

According to previous study, there is a suggestion that the pathogenesis of RAS could be drug related. Hasan *et al.* (81) revealed a possible relationship between aphthous-like ulcers and intake of non-steroidal anti-inflammatory drugs.

TREATMENT

Treatment of RAS differs depending on the symptoms, frequency, size, and a number of ulcers. However, it can be specific in patients with severe primary disease. Sometimes it is enough to treat primary disease, leading to improvement of oral ulcers (27). Atraumatic oral hygiene should be recommended for all patients and all dental procedures should be non-tissue-damaging.

Chlorhexidine-digluconate 0.2% (CHX) is most commonly used in local therapy of small lesions reducing the duration of ulcers and increasing the number of ulcer-free days (82). However, it is being less recommended recently due to its side effects such as tooth and tongue staining. Previous studies compared the effects of chlorhexidine and many other agents to find the most effective therapy for RAS (83, 84). Halboub *et al.* (83) examined the effects of N-acetyl cysteine (NAC), 200 mg distilled in water and 0.12% chlorhexidine digluconate mouthwashes for 30 sec. They measured pain reduction and average healing time and showed that NAC reduced pain more than CHX on the second and fourth day, with no differences in ulcer size between groups. Ozler *et al.* (84) compared the effects of CHX with sucralfate suspension. The mean value of pain scores was higher in the CHX group. However, the mean healing time of ulcers was shorter in the CHX group.

Antibiotic mouthwash containing tetracycline reduces the size and duration of ulcers because of its ability to block the activity of collagenase, but its association with oral candidiasis and allergic reactions have limited the use of these rinses (85).

In patients with more frequent or more severe disease, use of a topical glucocorticoid is frequently indicated. It decreases the size and healing time of ulcers, especially in the

early stage of lesions' development. Administration of dexamethasone ointment three times a day after meals has been shown to reduce pain and healing time, but has also been related to side effects such as the development of oral pseudomembranous candidiasis (86). Yang *et al.* (87) compared the effects of dexamethasone topical ointment and 0.2% hyaluronic acid gel. Both treatments showed a reduction in pain and ulcer size between day 1 and day 7. Also, both treatments were well tolerated and showed no side effects (87). In patients with major lesions, topical steroids showed to be less effective, for which intralesional injections are recommended for these lesions. Also, topical cauterisation with silver nitrate pencil (1-2%) in one dose, is recommended for pain reduction lasting one day (88).

Laser therapy is rising in popularity in general dentistry because of its therapeutic effects, such as analgesia, wound healing, and anti-inflammation. It is believed that laser therapy acts through different mechanisms such as effects on lymphocyte metabolism, modulation of histamine, prostaglandin, IL, INF, and TNF (89). Prasad *et al.* (90) showed that CO₂ lasers can induce pain relief after a few seconds of exposure. These lasers appear to stimulate quick healing to oral ulcers when compared to the placebo. Neodymium-doped yttrium aluminium garnet lasers have also been used in the treatment of RAS. A major disadvantage of these lasers is the long irradiation time (2-3 min) that can be dangerous to the health of the patient and the doctor (91).

Some clinical controlled trials showed the efficacy and safety of topical treatment of RAS with natural herbal medicines like Berberine plant or ginger extract. Studies reported a statistically significant reduction of the ulcer size in the group receiving herbal medicine therapy compared with the control (92, 93).

For a relatively small group of patients, who experience frequent episodes of multiple minor RAS or patients with major RAS, systemic therapy should be considered. On the other hand, this therapy raises the risks for the patients due to the potential side effects. Systemic corticosteroids such as prednisone may be used in therapy for patients with severe episodes of major RAS (94). Femiano *et al.* (95) showed that 25 mg of prednisone daily for 15 days brings rapid healing and reduces the frequency of ulcers. However, prednisone is shown to cause depression, hyperglycaemia, and hypothalamic-pituitary-adrenal axis suppression, thus its use should be limited (67).

In order to avoid the serious side effects of systemic corticosteroids, other drugs have been studied previously. It was reported that pentoxifylline (PTX), colchicine, dapsone, and thalidomide could have potential effectiveness in reducing the formation of new RAS lesions (96). PTX, which is related to caffeine, was shown to decrease the inflammation by its effect on the function of white blood cells and their cytokines. Several studies reported successful use of PTX in the treatment of RAS, in dose 400mg three times a day. Patients treated with PTX have had smaller ulcers and significant pain



reduction without any side effects reported (97). Colchicine has been used to treat gouty arthritis for decades. It has anti-inflammatory activity and inhibits the cell-mediated immune response. Control trials in the use of this drug in therapy of RAS have not been done up to date, although Altenburg *et al.* (98) showed that 0,6-1,12 mg/day reduced the number and duration of aphthous lesions. Its use, however, remains limited due to side effects such as hepatotoxicity and adverse drug interactions (99). When the disease control cannot be obtained, immunomodulators are often indicated for the reduction of the severity of lesions' outbreaks. The most effective immunomodulator for RAS was shown to be Thalidomide at a dose of 50 to 100mg/day, but its use is also limited due to side-effects (100). Dapsone and zinc sulfate were both found to be effective in the control of RAS. Dapsone in a dose of 100 mg/day reduced the number, duration, and frequency of the ulcers (101), however, a faster and more sustained action with the reduction in size and number of lesions was observed with the use of zinc sulfate in a dose of 150 mg/day for 12 weeks with no side effects (102).

Ozone therapy as a powerful oxidant with strong antimicrobial activity, analgesic effects, and a possibility to stimulate blood circulation and immune response, has gained a lot of attention in medicine and dentistry (103). The authors tested the effects of ozone therapy in RAS patients by applying a 2350 ppm of ozone gas on ulcer lesions for 15 days through special disposable silicone cups which ensured the safety of the machine for human use. Their results showed that the application of ozone therapy on RAS lesions leads to a reduction of pain, ulcer size, and duration of disease without differences between age and gender (104). Ozone therapy was also shown to reduce the inflammation and oedema, and lead to the disappearance of necrobiotic processes, epithelialization of ulcers, decrease in number of inflammatory cells, change in the cellular ratio, and to the restoration of the cellular layers of the epithelium. The observed changes in oral tissues indicate the efficacy of ozone therapy in the treatment of RAS (105). However, if inhaled in high doses, ozone can induce allergy and asthma because of its irritant effect to the respiratory system (103).

Summary of all mentioned therapeutic modalities are presented in Table 3.

Table 1. Different types of Recurrent Aphthous Stomatitis and their main clinical features

Clinical Feature	Type of RAS		
	Minor	Major	Herpetiform
Number of Ulcers	1-5	1-10	10-100
Size (mm)	<10	>10	1-2 (coalescing)
Duration	7-14 days	4-6 weeks	3-4 weeks
Site	Non-keratinized mucosa	Keratinized and non-keratinized mucosa	Non-keratinized mucosa
Healing	Without scar	With scar	Without scar

Table 2. Predisposing aetiological factors

Local factors	Local trauma, psychological stress, parafunctional habits, level of salivary cortisol, smoking
Microbiological factors	Herpes simplex, Cytomegalovirus, Varicella Zoster, Epstein-Barr, Covid-19, Helicobacter Pylori, S.Sanguis, S.Mitis
Systemic disease	Behcet's disease, Celiac disease, Chron's disease, HIV positive patients
Allergic factors	Hypersensitivity to almonds, chocolate, coffee, tomatoes, strawberries, gluten, sodium lauryl sulfate
Immunological factors	Disruption of innate and adaptive mechanisms manifested as an increased number of NK cells and B lymphocytes, reactivation of neutrophils, disrupted CD4/CD8 ratio, and increased number of CD25 ⁺ cells in peripheral blood
Nutritional factors	Folate, zinc, iron, vitamin B1, B6 and B12 deficiencies
Other factors	Oxidative stress, anti-inflammatory drugs



Table 3. Local and systemic treatment options for Recurrent Aphthous Stomatitis and their therapeutic effects

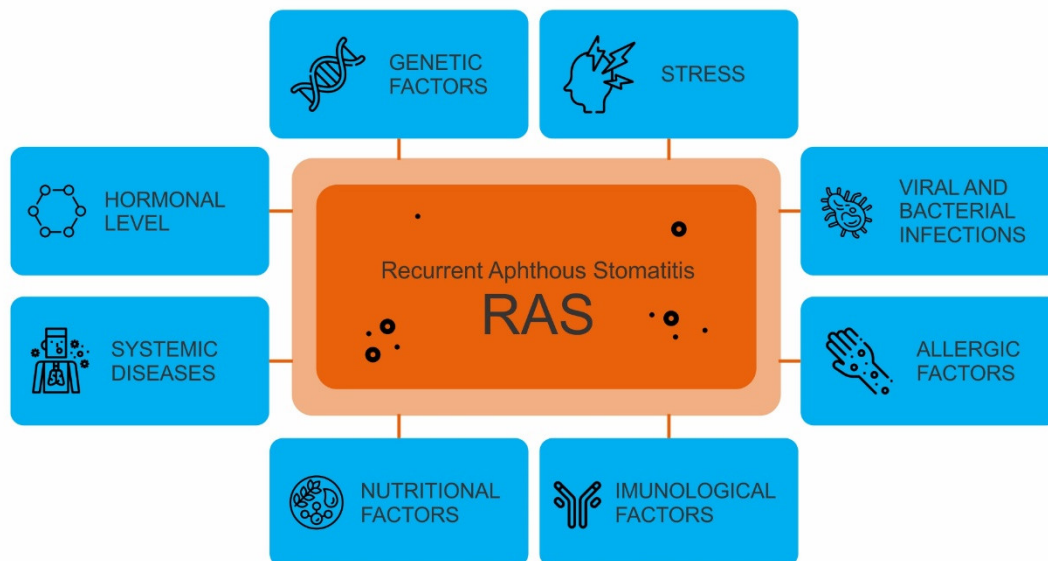
Local		Systemic	
Chlorhexidine-digluconate	Reduces the duration of ulcers and increases the number of ulcer-free days; it is less recommended recently due to side-effects (e.g. teeth staining)	Corticosteroids	They might be used in patients with severe episodes of major RAS
Antibiotic mouthwashes	The use is limited because of their association with oral candidiasis and allergic reactions	Pentoxifylline	Decreases the inflammation by effecting the function of white blood cells; shows significant pain reduction without any side effects
Topical glucocorticoid	Decreases the size and shortens the healing time of ulcer, especially in the early stages of development	Colchicine	It has anti-inflammatory activity and inhibits the cell-mediated immune response. Hepatotoxicity and adverse drug interactions have limited its use
Silver-nitrate	It is recommended for pain reduction lasting one day	Dapsone	Reduces the number, duration and frequency of the ulcers
Laser therapy	It can induce pain relief after a few seconds of exposure	Thalidomide	It is the most effective immunomodulator for RAS but its use is limited due to side-effects
Herbal medicine	Significant reduction of the ulcer size in patients receiving herbal medicine therapy is reported	Ozone therapy	It is a powerful oxidant with strong antimicrobial activity, analgesic effects and a possibility to stimulate blood circulation and immune response. It reduces the inflammation and oedema and leads to epithelization of ulcers

Figure 1. Clinical presentation of aphthae minor (A) and aphthae major (B)





Figure 2. Predisposing aetiological factors of RAS



CONCLUSION

Despite its frequency, the etiopathogenesis of this disease is still fairly unknown. Better understanding of the immune responses and predisposing factors could help in the prevention of the development of RAS especially in immunocompromised patients who develop RAS with more severe clinical picture. Still, most patients develop a mild form of the disease, simple aphthosis, with a few episodes per year and spontaneous remission. Fortunately, even patients that develop a severe disease, mostly need only symptomatic therapy.

Elimination of the predisposing factors is the most important in the treatment of RAS. Treatment strategies are also aimed to decrease the pain and the size of the ulcer, promote healing and decrease the frequency of recurrence. A definitive treatment protocol still remains unclear and needs further examination.

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