ABSTRACT

Aphthous stomatitis is a painful and often recurrent inflammatory process of the oral mucosa that can appear secondary to various well-defined disease processes. Idiopathic recurrent aphthous stomatitis is referred to as recurrent aphthous stomatitis. The differential diagnosis for recurrent aphthous ulcerations is extensive and ranges from idiopathic benign causes to inherited fever syndromes, to connective tissue disease, or even inflammatory bowel diseases. A thorough history and review of systems can assist the clinician in determining whether it is related to a systemic inflammatory process or truly idiopathic. Management of aphthous stomatitis is challenging. For recurrent aphthous stomatitis or recalcitrant aphthous stomatitis from underlying disease, first-line treatment consists of topical medications with use of systemic medications as necessary. Herein, the authors discuss the differential diagnosis and treatment ladder of aphthous stomatitis as described in the literature.

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REVIEW

Recurrent Aphthous Stomatitis: A Review

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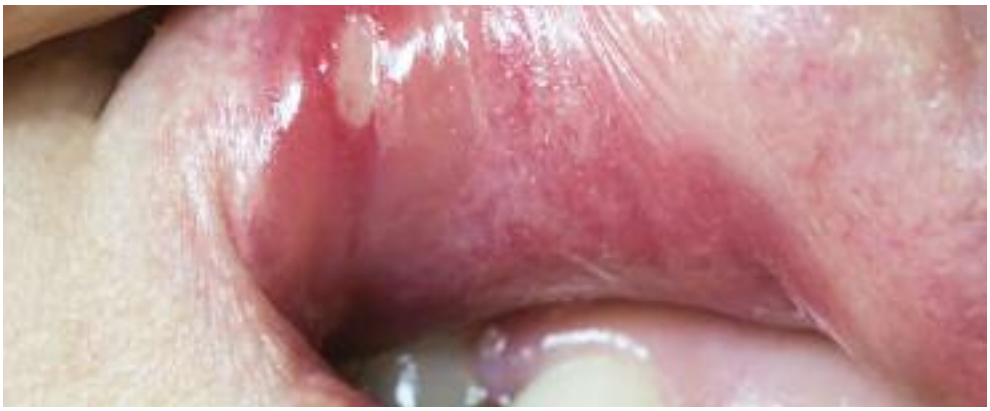

PAINFUL ORAL APHTHOUS ulcers, commonly referred to as aphthae, or canker sores, have been routinely appreciated by medical and dental professionals in otherwise healthy patients for thousands of years. They are the most common lesion of the oral mucosa in the general population.[1] The term aphthae is derived from the Greek word *aphthi*, which means "to set on fire" or "to inflame," and is thought to have been first used by the philosopher Hippocrates to describe the pain associated with a common disorder of the mouth during his time (likely, aphthous stomatitis).[2] Local trauma, genetic factors, nutritional deficiencies, viral and bacterial infections, and immune or endocrine disturbances have all been implicated as etiological factors of frequent oral ulcerations. In a subset of patients, no etiology can be identified and a diagnosis of exclusion must be made; such cases are referred to as recurrent aphthous stomatitis (RAS). Three forms of RAS exist: minor (>70% of cases), major (10%), and herpetiform (10%).[3] These subtypes differ in morphology, distribution, severity, and prognosis (Table 1). Despite their distinct characteristics, all forms of RAS have a significant impact on

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Table 1. Clinical features of minor, major, and herpetiform recurrent aphthous stomatitis (RAS)

	MINOR RAS	MAJOR RAS	HERPETIFORM RAS
Gender predilection	Equal	Equal	Female
Morphology	Round or oval lesions Gray-white pseudo-membranes Erythematous halo	Round or oval lesions Gray-white pseudo-membranes Erythematous halo	Small, deep ulcers that commonly converge Irregular contour
Distribution	Lips, cheeks, tongue, floor of mouth	Lips, soft palate, pharynx	Lips, cheeks, tongue, floor of mouth, gingiva
Number of ulcers	1–5	1–10	10–100
Size of ulcers	<10mm	>10mm	2–3mm
Prognosis	Lesions resolve in 4–14 days No scarring	Lesions persist >6 weeks High risk of scarring	Lesions resolve in <30 days Scarring uncommon

Adapted from Wallace A, Rogers HJ, Hughes SC, et al. Management of recurrent aphthous stomatitis in children. *Oral Medicine.* 2015;42(6):564–572.

quality of life and interfere with activities of daily living.

DIFFERENTIAL DIAGNOSIS OF ORAL ULCERATIONS

Before making a diagnosis of RAS, potentially overlooked causes for oral ulcers must be considered (Table 2). Several conditions can present with mucosal aphthous ulcers, necessitating a thorough workup to narrow the differential. Physical examination should be used to screen for trauma secondary to dental appliances, widespread vesiculobullous eruptions, and signs of hormone imbalance. The presence of a fever should prompt workup for infection, and if the fever is recurrent, fever syndromes (Table 2). Blood work should be used to rule out hematologic or nutritional deficiencies and antibodies related to autoimmunity. The differential diagnosis for oral ulcerations includes several entities, including recurrent aphthous stomatitis, drug-induced mucocutaneous syndromes, autoimmune disorders, hematologic disorders, nutritional deficiencies, fever syndromes, vesiculobullous diseases, and infection.[3] A diagnosis of RAS cannot be made unless other causes for aphthous stomatitis have been considered and dismissed.

Recurrent aphthous stomatitis. RAS, the most common ailment affecting the oral cavity, is characterized by recurrent disruption of the oral mucosa in the form of painful ulcers.[1] It is a diagnosis of exclusion, and other causes of ulcerative stomatitis should be explored before a diagnosis of RAS is made. RAS accounts for 25 percent of recurrent ulcers in adults and 40 percent in children.[4] The severity of the stomatitis is represented by one of three subtypes.

Minor RAS. Minor RAS is the most prevalent form and typically

Table 1. Differential diagnosis of acute and chronic aphthous ulcers[2,6,7,11–14,16,17,19,21,22,25]
Recurrent aphthous stomatitis (idiopathic)
Drug Induced Fixed Drug eruption, linear IgA bullous dermatosis, drug-induced bullous pemphigoid, drug-induced pemphigus Stevens-Johnson syndrome, toxic epidermal necrolysis
Autoimmune diseases Crohn's (orofacial granulomatosis), Behcet's, Celiac, systemic lupus erythematosus, Lichen planus Linear IgA bullous dermatosis, Wegener's granulomatosis
Trauma Dental appliances, necrotizing sialometaplasia
Hematologic Anemia, neutropenia, hypereosinophilic syndrome
Fever syndromes Cyclic neutropenia, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis), Sweet syndrome Familial Mediterranean fever, hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)
Vesiculobullous disorders Pemphigus vulgaris, linear IgA disease, erythema multiforme
Nutritional Deficiency iron, folate, zinc, B1, B2, B6, B12
Viral Coxsackie A, herpes simplex, herpes zoster, cytomegalovirus, Epstein-Barr, human immunodeficiency virus
Bacterial Tuberculosis, syphilis
Fungal Coccidioides immitis, Cryptococcus neoformans, Blastomyces dermatitidis
Inherited Epidermolysis bullosa, chronic granulomatous disease
Other MAGIC syndrome, hormonal disturbances, malignancy, smoking, hormonal (menstrual-associated)

occurs in patients who are 5 to 19 years old. Outbreaks are characterized by a few, superficial, round ulcerations that are <10mm and accompanied by a gray pseudomembrane and erythematous halo.[5] Minor aphthae are usually confined to the lips, tongue, and buccal mucosa.[4]

Major RAS. Major RAS has a wider distribution (commonly extending to the gingiva and pharyngeal mucosa), is larger in size, (>10mm), and has a longer duration of outbreak. Minor aphthae typically resolve within 14 days of presentation, whereas major aphthae may persist for over six weeks. Further, major aphthae pose a significant scarring risk as well.[5]

Herpetiform RAS. Herpetiform RAS presents with dozens of small, deep ulcers that often coalesce and therefore present as large ulcers with an irregular contour. Outbreaks are nonscarring and typically resolve within one month. Regardless of the subtype, RAS lesions can impair one's ability to effectively speak, swallow, and maintain dental hygiene.[5]

Drug-induced mucocutaneous syndromes and their idiopathic counterparts. There is strong evidence to suggest that several mucocutaneous eruptions occur as a result of pharmacological treatment. These mucocutaneous eruptions vary in severity (the spectrum can range from benign to life-threatening) and have been associated with several classes of medications including antibiotics, chemotherapy drugs, antiepileptics, diuretics, anti-inflammatories, and antiretrovirals. While the following entities vary histologically, a tissue diagnosis is often not necessary in reaching a diagnosis of a new or recurrent aphthous ulceration. The patient's age and a thorough history including any recent hospitalizations and any over-the-counter or prescription drugs in relation to onset of symptoms is valuable in evaluating the possibility of a drug-induced mucocutaneous syndrome. In addition to fixed drug eruptions, several dermatitides, such as linear immunoglobulin A (IgA) bullous dermatosis, cicatricial pemphigoid, pemphigus vulgaris, or their drug-induced counterparts can present as aphthous stomatitis. The clinical presentation and characteristic histopathological findings associated with each eruption are crucial to achieving a diagnosis.

Fixed drug eruptions (FDE) typically appear within one to two weeks of a first exposure of a drug, and within 1 to 2 days of repeat exposure. Cutaneous manifestations include one or a few sharply demarcated, round, edematous plaques. Within the lesion, there may be a central area of duskiness, ulceration, or epidermal detachment. The distribution of these lesions favors the lips, face, hands, feet and genitalia. When localized to oral mucosa, FDE can manifest as ulcerative aphthous stomatitis.[6] Classically, sulfonamides are the most frequent drug associated with FDE, with nonsteroidal anti-inflammatories (NSAIDs), barbiturates, tetracyclines, and carbamazepine also being commonly implicated.[7,8] More specifically to oral ulcerations, bisphosphonates, chemotherapy drugs (i.e., methotrexate), vasodilators (nicorandil), and propylthiouracil have all been implicated as precipitants of recurrent ulcerative stomatitis. Naproxen and cotrimoxazole were found to be the main inducers of drug-related oral lesions located on the dorsum of the tongue or on the hard palate.[6] When fixed drug eruption is suspected, it is generally acceptable to discontinue all drugs that are not acutely essential to the patient's wellbeing. Administering topical corticosteroids and antihistamines, in addition to discontinuing all possible drug culprits, is reasonable management of a suspected fixed drug eruption.

Linear IgA bullous dermatosis (LABD) manifests with tense vesicles and bullae that appear anywhere from 1 to 15 days after a medication has begun. It is caused by IgA autoantibodies produced against several different antigens in the basement membrane zone.[9] The gold standard for establishing a diagnosis of LABD is direct immunofluorescence (DIF). In DIF, there are linear deposits of IgA along the basement membrane at the dermal-epidermal junction (DEJ). There may also rarely be coexistence of IgG, IgM, and C3.[9] The drug most commonly implicated is vancomycin, followed by penicillins and cephalosporins, captopril, NSAIDs, phenytoin, rifampin sulfonamides, amiodarone, furosemide, lithium, and granulocyte colony-stimulating factor (G-CSF). Resolution typically occurs within four weeks of drug discontinuation, though dapsone or sulfapyridine are effective treatments for accelerated resolution.[9]

Cicatricial pemphigoid, also known as mucous membrane pemphigoid, is an autoimmune blistering disease that affects the basement membrane zones of the conjunctiva, oral cavity, nasopharynx, larynx, esophagus, genitourinary tract, and anus. Oral disease manifests as vesicles, erosions, desquamative gingivitis, and in certain cases, scarring. Diagnosis is achieved via a combination of clinical findings and direct immunofluorescence studies of perilesional mucosa demonstrating deposition of IgG, C3, and occasionally IgA along the basement membrane zone. Treatment depends upon affected sites and extent of disease; severe cases are usually initially treated with systemic corticosteroids followed by a steroid-sparing regimen.[10]

Drug-induced pemphigus accounts for 10 percent of total cases of pemphigus in developed countries. There is significant evidence to suggest that a humoral immune response against desmosomes is triggered by a sulfhydryl, or thiol group, found on specific drugs. The thiol groups are thought to interact with proteins that induce antigenicity of desmogleins, which leads to antibody production. Penicillamine and captopril are most commonly implicated, with penicillin, ACE-inhibitors, gold sodium thiomalate and pyritinol also being common culprits. In contrast to classic pemphigus vulgaris, direct immunofluorescence of perilesional skin is not always positive in drug-induced pemphigus. Drug-induced pemphigus often resolves after the drug is discontinued.[11]

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening (25% and 35% mortality rate, respectively) mucocutaneous eruptions that occur as a result of separation of the skin at the dermal-epidermal junction. As SJS and TEN represent a single disease spectrum and differ only in extent of body surface area involvement, they are often triggered by the same medications.[12] Antibiotics, followed by NSAIDs and anticonvulsants, are the most common precipitants of the SJS/TEN spectrum. Trimethoprim-sulfamethoxazole, phenytoin, nevirapine, phenobarbital, and lamotrigine are specific drugs commonly implicated. Within one to three weeks of initiating the offending drug, patients may develop systemic symptoms, such as malaise, fever, headache, and cough, followed by a macular rash. Lesions appear as coalescing tender, erythematous or dusky macules with a positive Nikolsky sign. There is almost always involvement of the oral, ocular, or genital mucosa. When SJS or TEN is suspected, the patient must be admitted to an intensive care unit for aggressive treatment to avoid fluid loss and infection.[13]

Malabsorption disorders and their associated hematologic deficiencies. Recurring oral ulcers often occur as a manifestation of a malfunctioning gastrointestinal tract. Inflammatory bowel disease, celiac disease, and other malabsorption syndromes are commonly associated.

Oral lesions are found in up to 20 percent of patients with Crohn's disease, and while these lesions can vary in gross morphology, their histology reveals granulomas in 90 percent of cases.[14] Oral aphthae associated with Crohn's disease typically occur as linear erosions along the mandibular and maxillary sulci. Pyostomatitis vegetans (the oral equivalent of pyoderma gangrenosum, seen in ulcerative colitis and Crohn's disease) is a separate entity distinguishable on biopsy, but is also in the differential of painful oral lesions in a patient suffering from Crohn's disease. Histopathology of an oral ulcer of Crohn's disease displays the classic granulomatous inflammation, whereas pyostomatitis vegetans displays acanthosis with neutrophils.[15]

In a large Canadian study of patients with biopsy-proven celiac disease, 16 percent of children (<16 years of age) and 26 percent of adults admitted to having recurrent aphthous ulcers.[16] The pathogenesis of aphthous ulcers in celiac disease is unclear, though it may be related to low serum iron, folic acid, and B12 levels secondary to malabsorption in these patients.[16] It should be acknowledged that oral lesions associated with celiac disease may precede gastrointestinal symptoms by several years, so screening for tissue transglutaminase and endomysial antibodies should be performed even in the absence of gastrointestinal lesions.

A number of hematologic deficiencies have been found to be more common in patients with recurrent aphthous ulcers than in the general population. A recent study found that deficiencies of vitamin B12, folate, and iron, occurring alone or together, have been associated

with aphthous stomatitis in patients of all ages. The study found that the overall frequency of hematologic deficiencies was 56.2 percent in 32 adult patients with recurrent aphthosis versus seven percent of controls living in the same geographical area.[2] Anemia, possibly caused by these deficiencies, was found in 34.4 percent of patients with recurrent aphthosis versus 6.9 percent of controls. A complete blood count can be diagnostic of these deficiencies and the aphthous stomatitis has been found to dramatically respond to supplementation in these patients.[2] The possibility of vitamin C deficiency should also be explored, as one study found that daily administration of 2000mg/m^2 ascorbate resulted in a 50-percent reduction in oral ulcer outbreaks and a decline of pain levels in patients with minor recurrent aphthous stomatitis.[5]

Behcet's disease. Behcet's disease, a vasculitis with a complex etiology, is associated with significant oral and genital ulcerations. In 80 percent of cases, mucosal aphthosis is the presenting sign. Ocular involvement in the form of anterior or posterior uveitis, skin lesions such as erythema nodosum, and less commonly, central nervous system deficits may be observed. Vascular lesions in small and large vessels often occur and can manifest as coronary arteritis, arterial or venous thrombosis. A positive pathergy test can be useful, but is not necessary in establishing a diagnosis of Behcet's disease.[17] Patients may present with mucosal aphthosis and hemoptysis as their only complaints. There is no pathognomonic finding in Behcet's disease; rather, diagnosis is made based on a scoring system (recurrent ocular involvement, recurrent oral aphthosis, and recurrent genital aphthosis are each two points, and skin lesions, CNS involvement, and vascular lesions are each 1 point) in which >4 points indicates Behcet's disease.[17] Histopathology is nonspecific, demonstrating a leukocytoclastic vasculitis. Treatment of mucocutaneous disease is not curative and consists primarily of topical and intralesional steroids, anti-inflammatories, and immunosuppressant drugs in severe cases.

Periodic fever syndromes and other autoinflammatory diseases. Mucosal aphthosis is often a feature of a systemic syndrome that includes recurrent fever with no known source of infection; such syndromes are referred to as autoinflammatory diseases. PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome, cyclic neutropenia, and hyperimmunoglobulin D are some autoinflammatory diseases to consider in the differential of recurrent aphthous stomatitis when unremitting or cyclical fevers are also present.

PFAPA syndrome, also known as Marshall syndrome, is a hereditary autoinflammatory disease characterized by three- to six-day episodes of fevers every four to eight weeks.[18] Episodes of fever are accompanied by aphthous stomatitis, cervical adenitis, pharyngitis, abdominal pain, and joint pain.[19] PFAPA is the most common fever syndrome in children, yet the exact genetic marker responsible has not been determined. Patients are completely asymptomatic between episodes and attacks typically respond rapidly to a single dose of corticosteroids. Although corticosteroids decrease severity of attacks, they do not prevent future attacks. In some cases, the administration of steroids actually increased the frequency of attacks. It has been suggested that levels of interleukin 1 (IL-1), specifically IL-1β, are elevated in PFAPA, and treatment with a recombinant IL-1 receptor antagonist has yielded promising patient responses. Colchicine administration, by decreasing neutrophil migration and adhesion, has also shown promise in decreasing the number of PFAPA attacks, although additional studies with more subjects are needed. In certain refractory cases, adenotonsillectomy is a possible solution.[18]

When recurrent aphthous ulcers occur with a periodicity of approximately every three weeks, the dermatologist should be alerted to the possibility of cyclic neutropenia.[20] Cyclic neutropenia is inherited in an autosomal dominant pattern, so there is usually a family history present and episodes of neutropenia are present at or soon after birth. Mutations in the ELANE gene, which codes for neutrophil elastase, are responsible for causing cyclic neutropenia.[20] Episodes occur every 21 days and last between three to five days. Patients present with painful oral and colonic ulcers, pharyngitis, recurrent fever, and abdominal pain. Dermatologists and dentists alike

should be alerted to the possibility of cyclic neutropenia in a pediatric patient that presents with recurrent oral ulcers or periodontitis.[21]

Hyperimmunoglobulin D syndrome (HIDS) is an autosomal recessive disorder that presents during the first year of life with febrile episodes lasting four to seven days, palpable lymphadenopathy, splenomegaly, and mucocutaneous lesions. Aphthous ulcers occur in large numbers in 49 percent of cases of HIDS, with such prominence that cases have been misdiagnosed as Behcet's disease before reaching a diagnosis of HIDS.[22,23]

Infection. While difficult to implicate due to normal colonization of the oral mucosa, several bacteria, viruses, and fungi have been thought to play a role in either precipitating or perpetuating recurrent aphthous stomatitis.

Helicobacter pylori (*H. pylori*) is a gram-negative bacteria best known for colonizing the gastric mucosa and playing a large role in the formation of peptic ulcer disease. The role of *H. pylori* in RAS, however, is more controversial. It was once considered to be a precipitant of RAS when *H. pylori* bacteria was isolated from active ulcers and eradication of infection led to resolution of oral ulcers. More recent literature suggests that *H. pylori* is more likely a passenger infection and not an actual trigger of RAS.[24] There is little evidence to suggest that there is a bacterial trigger of RAS, although the large bacterial load in normal oral flora may impair or delay healing of active ulcers.

In the pediatric population, oral enanthems are common in association with systemic viral infection. Herpangina and hand-foot-and-mouth disease both present with oral vesicles and are caused by strains of non-polio enteroviruses including echovirus and coxsackievirus. Herpangina usually manifests as several small vesicles on the anterior faucial pillars, tonsils, soft palate, or uvula. The vesicles of hand-foot-and-mouth disease affect the buccal mucosa, tongue, soft palate, and gingiva. Lesions on the hands and feet are red papules that evolve into vesicles surrounded by a red halo. Both viral syndromes are associated with malaise, fever, and upper respiratory tract disease managed only by supportive care.[25,26]

In both pediatric and adult populations, herpetiform RAS is commonly misdiagnosed as herpetic gingivostomatitis, so it is reasonable to perform a Tzanck smear, viral culture, or viral polymerase chain reaction (PCR), or skin biopsy of the lesions to rule out herpes simplex infection. The presence of malaise, fever, headache, anorexia, and irritability may suggest a clinical diagnosis of herpetic gingivostomatitis, as there are typically no prodromal symptoms associated with herpetiform RAS.

Environmental factors. For several years, sodium laurel sulfate (SLS), a synthetic detergent used in dentrificies, cosmetics, and personal care products was believed to be a precipitant of RAS outbreaks. It was postulated that SLS denatured the oral mucin layer, thereby exposing the underlying epithelium.[27] A more recent randomized controlled clinical trial compared the frequency of RAS outbreaks in affected versus control patients using formulations with varying amounts of SLS. It was concluded in this trial that SLS-free products positively affected the ulcer healing process but did not reduce the number of aphthae or number of episodes in subjects.[28]

A recent study explored the relationship between psychological stress, RAS, and oral lichen planus. It was concluded that there is a high correlation between levels of anxiety, depression, and psychological stress with symptoms of both RAS and oral lichen planus.[29] A separate smartphone survey performed in 2014 found that RAS was not associated with overall depression severity as measured by features such as sadness, insomnia, impaired concentration, self-blame, thoughts of death, or anhedonia. In this study, RAS was, however, associated with increased sleep, decreased appetite, low energy, and feeling sluggish.[30]

Interestingly, several studies have reported a protective effect of smoking on aphthous stomatitis.[31,32] A recent cross-sectional survey acknowledged a protective effect of nicotine on RAS in a dose-dependent fashion. It was concluded that smoking is only protective with high enough levels of consumption to result in very high nicotine concentrations that form a protective layer of keratin over the oral mucosa. No correlation between duration of smoking and severity of RAS lesions was found. Of note, there was also no change in already existing ulcers with smoking.[32]

PATHOGENESIS OF RECURRENT APHTHOUS STOMATITIS

Several theories describing the

etiopathogenesis of RAS have been described in the literature. The pathogenesis of RAS is multifaceted with significant physiological interplay between the immune system, genetics, and environmental factors. Similar to other chronic inflammatory conditions, deoxyribonucleic acid (DNA) damage secondary to oxidative stress is thought to play a large role in recurrent ulcerations. In a recent case-control study, total oxidative status (TOS), total antioxidant status (TAS), and the TOS:TAS ratio (oxidative stress index, OSI) were used as parameters to assess oxidative damage in RAS patients against unaffected controls. The results strongly suggested that RAS patients have a systemic imbalance in the oxidant-to-antioxidant ratio favoring oxidative damage.[33] The cause for this imbalance is likely multifactorial.

Evidence also suggests an immunological basis for the chronic inflammation in RAS patients. It is currently thought that an unknown antigen stimulates keratinocytes, resulting in cytokine secretion and leukocyte chemotaxis. TNF-α has been found to be significantly increased in the saliva of RAS patients. A recent study explored the significance of single nucleotide polymorphisms (SNP) in the genes for proinflammatory cytokines IL-1 and IL-6 in RAS.[34] The average frequency of IL-6 C-174C haplotype, which is associated with an increase in IL-6 secretion, was detected in higher amounts in affected patients than in controls.[34] This suggests a genetic component to the immunopathogenesis of RAS. Further implicating a genetic component, there is evidence in the literature that RAS may be associated with a specific HLA haplotype. HLA haplotype A*038B*07DRB1*13 is the most commonly associated with minor, major, and herpetiform RAS.[35]

MANAGEMENT OF RAS

Management of RAS can be very challenging, especially in patients with severe disease. When oral aphthosis is secondary to an underlying disease, it is advisable to treat the primary disease to hopefully improve the oral aphthae. In the case of RAS, and even some cases of secondary oral aphthosis, the following treatment ladder may be utilized.

Topical therapies. Currently, the management of RAS is aimed at supportive care. No pharmacological treatment has been curative, although several modalities have been effective in decreasing pain and erythema and increasing the rate of reepithelialization associated with healing lesions. It is advisable to approach management in a stepwise fashion, establish appropriate expectations for the patient, and investigate possible underlying causes (Table 2). It is reasonable to begin treatment with topical medication and advance to systemic medication and laser as necessary with a goal of decreasing recurrence rate and severity of the outbreaks.

Several topical medications with distinct mechanisms are effective in managing RAS lesions. Topical treatment is aimed at prevention of superinfection, protection of existing ulcers, analgesia, decreasing inflammation, and treating active ulcers. It is reasonable to administer chlorhexidine 0.2% rinse to all patients presenting with RAS to decrease the likelihood of superinfection with gram-positive and gram-negative bacteria and fungi.[3] Additionally, *in vitro*, chlorhexidine has been shown to have activity against enveloped viruses (herpes simplex virus [HSV], cytomegalovirus [CMV], influenza, and respiratory syncytial virus [RSV]). Chlorhexidine is also effective in eliminating and preventing the formation of biofilms that are commonly found in dental plaque.[24]

Topical antibiotics in the form of doxycycline or minocycline mouthwash are also effective, likely secondary to inhibition of metalloproteinases. Protective coating of existing ulcers can be achieved with bioadhesive pastes formulated with benzocaine 20% for pain relief. Lidocaine 5% ointment and lidocaine 10% spray is also effective for temporary analgesia. The anti-inflammatory properties of diclofenac 3% with hyaluronic acid 2.5% have also been effective. Amlexanox 5% ointment, which has been discontinued in the United States, has been reported to decrease healing time of aphthous ulcers secondary to its anti-inflammatory and immunomodulating properties. Topical corticosteroids (betamethasone mouthwash, fluticasone propionate spray, triamcinolone in an oral preparation) are commonly successful in the treatment of active ulcers and can be administered with antifungals to reduce risk of oral candidiasis for

long term use.[3]

Systemic therapies. When a patient reports little to no improvement in frequency or severity of outbreaks with topical therapy alone, there are a number of oral options that can be pursued (Figure 1). Several systemic medications have been reported as effective for treating RAS in the literature. There is evidence to suggest that oral antimicrobials, such as penicillin G (50mg QIDx 4 days), decrease ulcer size and pain. Clofazimine, an antimicrobial, in combination with rifampin and dapsone, has been shown to prevent the formation of new lesions. Zinc at 50mg/day has also produced beneficial effects on wound reepitheliazation and healing.[3] Pentoxifylline has shown promising results in reducing severity of outbreaks, but has little effect in preventing new outbreaks and has numerous GI side effects.[3] Low-dose oral tetracyclines may also be helpful due to their anti-inflammatory properties. Oral prednisone (initial dose of 25mg/day with taper) is the first-line systemic therapy and is typically reserved for the acute treatment of severe RAS outbreaks. Systemic corticosteroids are not without side effects and are relatively or absolutely contraindicated in certain patients; for these cases, leukotriene-receptor antagonists are a safer alternative. Montelukast 10mg daily was found to be equally effective in pain reduction and accelerating healing of lesions when compared to oral systemic corticosteroids. When disease is not adequately controlled with oral corticosteroids, immunomodulators have shown promise in reducing severity of outbreak and preventing further outbreaks. Steroid-sparing agents, such as colchicine at starting at 0.5mg/day and gradually increasing to 1.5mg/day or dapsone 25mg/day and gradually increasing to 100mg/day may also be effective. Thalidomide at a dose of 50 to 100mg/day is considered the most effective immunomodulator for RAS, but is obviously limited by its side-effect profile.[3]

Additionally, a recent study explored the effects of daily ascorbic acid 2000mg/m^2/day for managing minor RAS. A 50-percent reduction in oral ulcer outbreaks and a significant reduction in pain level was noted in these patients. There is strong evidence to suggest that ascorbate decreases neutrophil-mediated inflammation via modulation of reactive oxygen species (ROS).[5] Ascorbic acid as an adjunctive therapy to topicals should be considered as well because of its relatively benign side-effect profile.

Light therapy. Low-level laser therapy at a wavelength of 658nm may also be beneficial in RAS patients as an adjunctive. It was shown to be equal or even superior to pharmacological treatment in managing pain and inflammation and increasing reepitheliazation of aphthous ulcers.[37]

CONCLUSION

Oral aphthosis has numerous potential causes with an extensive differential of possible underlying diseases. Medical and dental professionals should pursue further workup for ulcers if they are recurrent and impose a significant impediment to the patient's activities of daily living. Oftentimes, no distinct underlying disorder will be found and a diagnosis of minor, major, or herpetiform RAS will be made based on the history, presentation, and morphology of lesions. Although several topical and systemic medications are useful in controlling the symptoms of RAS, it remains an incurable ailment that interferes with the lives of otherwise healthy individuals. There are many treatment options for clinicians to consider. A treatment ladder ranging from topical medications to systemic medications may aid clinicians in determining which treatment is right for their patient.

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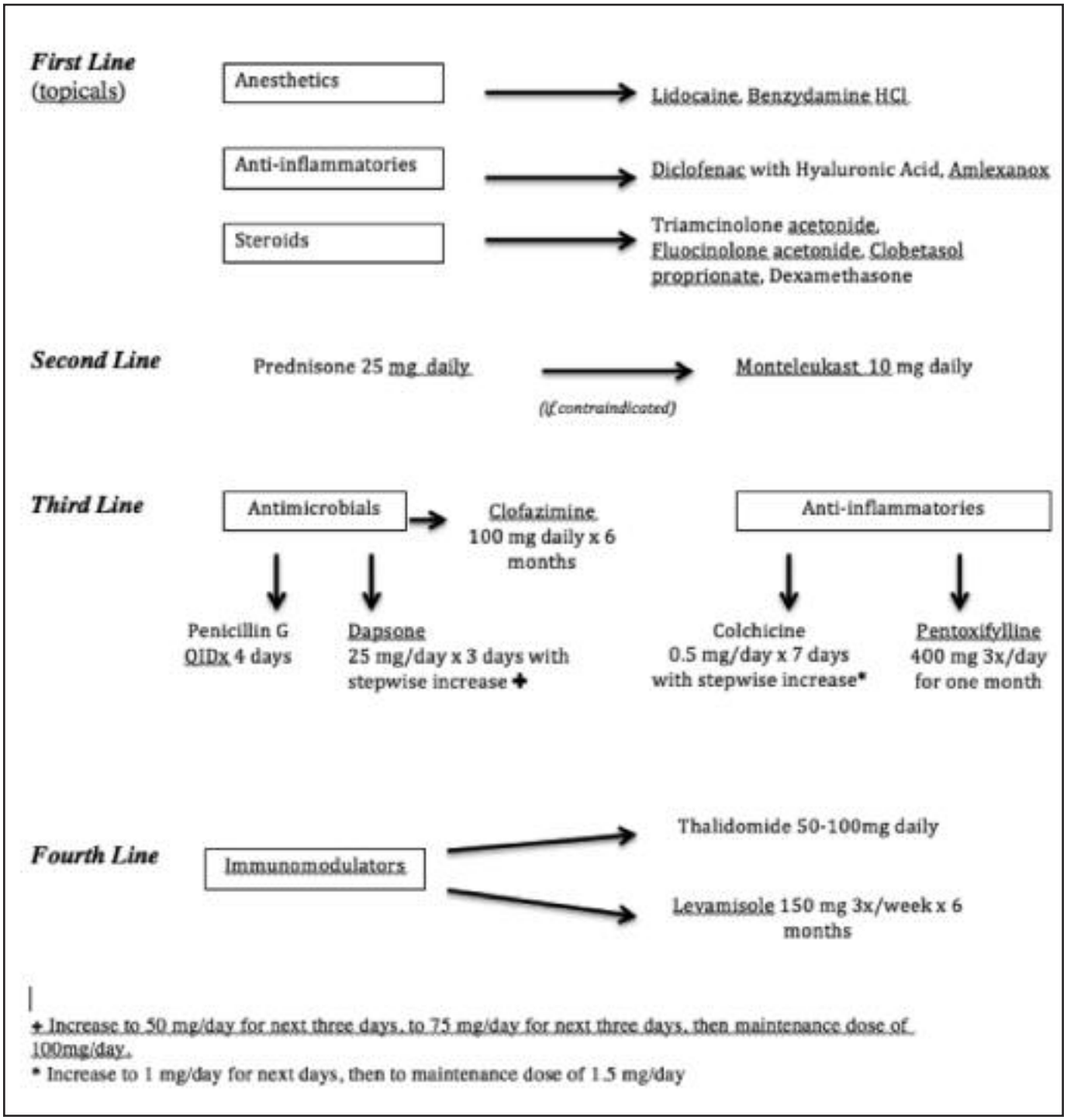

Figure 1. Suggested treatment ladder for recurrent aphthous stomatitis

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