Pharmacological Management of Common Soft Tissue Lesions of the Oral Cavity

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KEYWORDS

• Aphthous lesions • Oral herpes • Candidiasis • Ulcerative diseases • Pemphigus • Pemphigoid

KEY POINTS

- The diagnosis of soft tissue lesions in the oral cavity requires a thorough clinical evaluation; therefore, avoiding confusion between similar appearing lesions.
- Topical medications have been proven to be the most effective management of certain oral mucosal lesions.
- When managing candidiasis it is important to address any underlying factor when possible.
- Patients with ulcerative diseases may have superimposed candidiasis altering the clinical appearance of a lesion.
- The overall objective of steroidal therapy is to decrease the number, size, and discomfort of lesions.

Lesions of the oral cavity can arise from many different etiologies, inflammatory, infection, traumatic, immunologic, or neoplastic. Obtaining a detailed patient history and physical examination of the lesion may give us suspicion of associated conditions or diseases; whether or not there is a triggering factor; new or recurrent lesion; pain or painless, length of time the lesion has been present; and rate of growth of the lesion over time. Neoplastic ulcerated lesions are notorious in the oral cavity for their ability to mimic benign ulcerative lesions, highlighting the essential nature of biopsy to establish a diagnosis in cases that are not clinically identifiable or do not respond as expected to treatment.[1] Additional physical evaluations, laboratory tests, or adjunctive tests may be required for final diagnosis. This article divulges a selection of the most common oral lesions providers are likely to encounter and the recommended pharmacologic management.

COMMON SOFT TISSUE ORAL LESIONS

Recurrent aphthous stomatitis

Aphthous lesions are one of the most common oral lesions, they can affect up to 25% of the general population. Three month recurrence rates are as high as 50% with a predilection for women. Although it is unclear what causes aphthous ulcers, factors such as trauma, nutritional deficiency, stress, tobacco, food hypersensitivity, hormonal changes, and drugs, can contribute to the disease.[2,3] These lesions can occur as a single, isolated event, or in groups of 2 or more that may reoccur at intervals.[4] In such cases, the condition is known as recurrent aphthous ulcers or recurrent aphthous stomatitis (RAS). The lesions emerge in 4 stages, in first stage or prodromal stage, the individual will experience tingling and burning in the normal-appearing site; during the second stage or preulcerative stage, red oval papules appear

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that intensifies; in the third stage or ulcerative stage, classic ulcer appear. The 4 stages are the healing stage, in which granulation tissue followed by epithelialization occurs.[5]

Minor aphthae is the most common form of RAS and approximately 85% of patients have lesions of this type.[6] Minor aphthae are superficial mucosal ulcers with variable shape and size typically 4 to 5 mm diameter but less than 1 cm. Minor aphthae involve the nonkeratinized movable oral mucosa of the oral cavity (the labial and buccal mucosa (**Fig. 1**), the floor of the mouth and the ventral, or lateral surface of the tongue).[3] (**Fig. 2**) They tend to heal within a period of 10 to 14 days, at this stage, granulation tissue followed by epithelial migration and epithelial migration incurs in healing without a scar.[5]

Major aphthae have identical developmental stages in their general appearance except that are larger (exceeding 10 mm), deeper (extending to submucosal layers and underlying muscle at times), and longer lasting (can last up to 6 weeks).[5]

Herpetiform ulcerations are characterized by multiple recurrent small size ulcers from 2 to 3 mm in diameter. Multiple lesions may coalesce to form large irregular ulcers that last for about 10 to 14 days. These herpetiform ulcers, unlike herpetic lesions, are not preceded by vesicles and do not contain virally infected cells. Herpetiform aphthae are more common in women and have a later age of onset than other clinical variants.[2]

Treatment

The treatment of aphthous ulcers is palliative, the goal being to reduce the duration, size, and recurrence of lesions. Most individuals can endure minor levels of discomfort and are preferable to risking therapy with agents that can have potential side effects.[5]

First-line treatment options comprise antiseptics, such as chlorhexidine, antiinflammatory drugs, and analgesics for as long as the lesions persist.[7] A mixture often called magic mouthwash, which often consisting of diphenhydramine hydrochloride, viscous lidocaine, Kaopectate, and corticosteroids[8] may be useful in controlling the number, frequency, and duration of lesions. The patient is instructed to use 1 tsp at a time and swish, hold the solution in his or her mouth as long as possible, and swallow, three times daily.[5]

Topical steroids can decrease the symptoms and improve healing time, but do not affect the recurrence rate. If multiple lesions are present, an aqueous solution is preferred. A dexamethasone rinse can be considered or in isolated lesions, a high potency topical steroid (kenalog, clobetasol, or fluocinonide) for no more than 2 weeks[9,10] (**Table 1**). A trial with the antibiotic minocycline, which has immunomodulatory effects suppressing neutrophils, T lymphocytes, and collagenase activity, can be used. A blind crossover study shows a significant reduction in duration and severity of pain compared with placebo.[11]

In severe cases, whereby these regimens fail and the number, size, and discomfort of the lesions increases, and lesions, an injectable or systemic steroid, such as prednisone, are recommended. It is started at 1 mg/kg/d as a single dose in patients with severe lesions and tapered after 1 to 2 weeks. The recommendation is to use less than 50 mg per day, preferably in the morning, for 5 days.[9,12]

When managing patients with RAS, a thorough medical history and further work-up should be

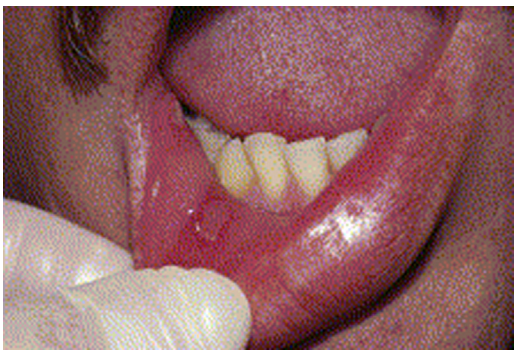

Fig. 1. Aphthous lesions in the mucosal surface of the lower lip. (*From* Saunders WB. Chapter 2: Ulcerative Conditions. In: Regezi JA, Sciubba JJ, Jordan RCK, eds. Oral Pathology. 6th ed. Elsevier; 2012: 22-78.)

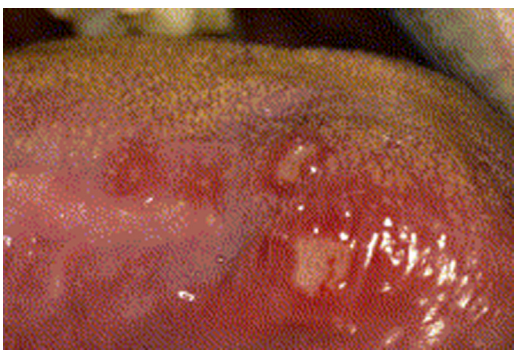

Fig. 2. Multiple aphthous ulcers in the lateral surface of tongue. (*From* Saunders WB. Chapter 2: Ulcerative Conditions. In: Regezi JA, Sciubba JJ, Jordan RCK, eds. Oral Pathology. 6th ed. Elsevier; 2012: 22-78.)

Table 1
Topical medications for the treatment of aphthous ulcers

Topical Medications for the Treatment of Aphthous Lesions	
Drugs	**Use**
Chlorhexidine 0.12%	5 mL swish and spit TID for 14 d
Dexamethasone 0.2%	5 mL swish and spit TID for 10 d
Kenalog 0.1%	Apply to affected areas TID for 10 d
Minocycline 0.5%	5 mL swish and spit QID for 10 d
Fluocinonide 0.05%	Apply ointment to affected areas TID for 10 d

conducted to rule out any systemic conditions associated with aphthous ulcers. Systemic conditions such as Behcet syndrome, hand-foot-and-mouth,[5] cyclic neutropenia, periodic fever with aphthae, pharyngitis and adenitis syndrome, Reiter syndrome, and Sweet syndrome, gluten-sensitive enteropathy, Crohn's disease, ulcerative colitis, and immune deficiencies, may all have oral manifestations; thus, need to be considered at the time of diagnosis.[12,13]

ORAL HERPES (HERPES SIMPLEX VIRUS)

Primary herpetic gingivostomatitis

Primary herpetic gingivostomatitis are caused by herpes simplex virus (HSV) and can be seen most commonly in children and young adults. Infection can be asymptomatic or can cause painful vesicular lesions on all mucosal surfaces and rupture and produce foul smell. Patients can become febrile and have significant malaise and tender cervical lymphadenopathy.[14] Lesions and acute illness can last from 5 to 10 days and resolve with scar formation. The clinical course is limited by the synthesis of viral-specific antibodies (IgM, days 3–5; IgG, days 5–21).[5] HSV gains access via direct or airborne water-droplet transmission. The lesions in mucosal membranes represent direct viral infection and the virus then ascends along the epineurium of the trigeminal nerve, establishing latency in the Gasserian ganglion, where it develops dormant existence within ganglion cell bodies (**Fig. 3**). It can become reactivated under various stimuli: stress, fever, ultraviolet light, trauma, or menstruation.[15]

Recurrent herpes infection

On reactivation of herpes lesions, the patient first experiences the prodromal symptoms of pain, itching, burning, or paresthesia.[16] Viral shedding occurs mostly during the time of active lesions and therefore, the time of greatest transmissibility. Recurrent secondary lesions may be more frequent and intense within the initial few years after primary infection and decrease in severity and increased intervals as time passes.[5]

Treatment

Herpes labialis is frequently occurring and self-limiting thus, many patients do not consult their general practitioners and use over-the-counter medication. Treatment with indifferent (zinc oxide and zinc sulfate), anesthetic, or antiviral cream has a small favorable effect on the duration of the symptoms, if applied promptly. A randomized controlled study with zinc oxide as a treatment showed that after 5 days, 50% of the patients in the treatment group were symptom-free compared with 35% in the placebo group.[17]

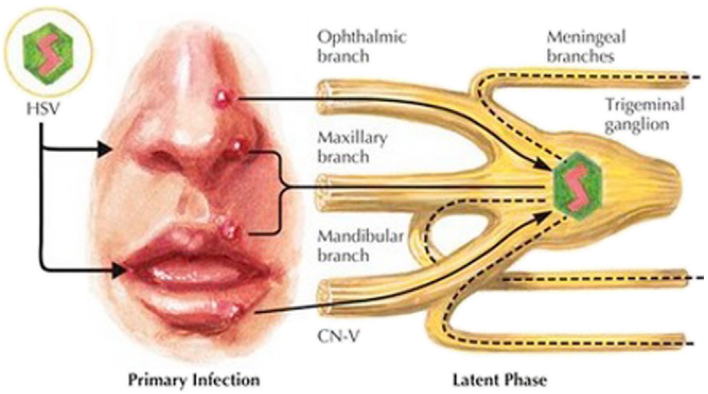

Fig. 3. Pathogenesis and clinical course of Herpes Simplex Virus. (*From* Traub M. Chapter 177: Herpes Simplex. In: Pizzorno JE, Murray MT, eds. Textbook of Natural Medicine. 5th ed. Churchill Livingstone/Elsevier; 2020: 1368–1371.e1.)

When using antiviral therapy, the aim is to block viral replication. Peak viral titers occur in the first 24 hours after lesion onset when most lesions reach the vesicular stage. Thus, for the treatment to be effective, it should be started at the first signs. Some topical agents include penciclovir 1% cream, acyclovir 5% cream, and docosanol cream. Penciclovir is inactive until it is phosphorylated within the virus, whereby it selectively inhibits herpes viral DNA synthesis and replication. Therefore, it has low toxicity and good selectivity.[18] Acyclovir 200 mg oral for 5 days can be started at first prodromal signs. Antivirals are used in primary and recurrent infections to decrease pain, viral shedding, and duration of symptoms. Prophylactic use of antivirals has proven useful in decreasing the frequency of recurrences, especially in immunocompromised patients and immunocompetent persons who experience frequent recurrences of oral or genital HSV infections[19] (Table 2).

For primary herpetic gingivostomatitis, the clinician might recommend only supportive care consisting of hydration, antipyretics, nutrition, and if secondary bacterial infections arise the use of antibiotics. However, severe cases may require systemic antiviral therapy.[5]

CANDIDIASIS

Oral candidiasis is caused by an overgrowth of the normally present organism *Candida albicans*. The infection is associated with alterations in the host's defense mechanisms. The incidence varies depending on age and certain predisposing factors. Some of the predisposing factors include impaired salivary gland function, drugs, dental prosthesis, high carbohydrate diet, and extremes of age, smoking, diabetes mellitus, Cushing's syndrome, malignancies, prolonged antibiotic use, and immunosuppressive conditions or agents

Table 2
Topical medications for the treatment of oral herpes lesions

Topical Medications for the Treatment of Oral Herpes	
Drugs	**Use**
Zinc Oxide 1% gel	Apply to affected area q 2 h for 5 d
Acyclovir 5% Ointment	Apply to affected area q 3–4 h for 4 d
Penciclovir 1%	Apply to affected area q 2 h for 4 d

Oral candidiasis can have multiple clinical presentations that vary greatly according to the predisposing factors.[20,21] Classifications of oral candidosis include Pseudomembranous form, hyperplastic form, and atrophic form. The symptoms of the acute form are rather mild and the patients may complain only of a slight tingling sensation or foul taste, whereas the severe chronic forms may involve the esophageal mucosa leading to dysphagia.[22,23]

Pseudomembranous candidiasis

Pseudomembranous candidiasis often referred to as *thrush*, can present as both acute and chronic forms. The affected mucosal surface becomes tender with red and white to whitish-yellow creamy plaques resembling milk curds or cottage cheese. These white plaques consist of cellular debris mixed with Candida organisms. The red areas correspond to the areas whereby organisms have invaded into the upper layers of the mucosa, resulting in parakeratinization, hyperemia, atrophy, and inflammation.[5] The white plaques or pseudomembrane characteristically can be easily removed, leaving behind an underlying erythematous and hemorrhagic area.[21] The oral surfaces frequently involved include labial and buccal mucosa, tongue, hard and soft palate, and oropharynx. The involvement of both oral and esophageal mucosa is prevalent in AIDS patients. Few lesions mimicking pseudomembranous, candidiasis could be white-coated tongue, thermal and chemical burns, lichenoid reactions, leukoplakia, secondary syphilis, and diphtheria.[24]

Atrophic (erythematous) candidiasis

Clinically, atrophic candidiasis manifests as a painful localized erythematous area. The chronic form usually involves the dorsum of the tongue, palate, and occasionally the buccal mucosa. Red lesions are seen on the dorsum of the tongue typically presenting as depapillated areas. Other forms of atrophic candidiasis includes *denture stomatitis*, *angular cheilitis,* and *median rhomboid glossitis* (Fig. 4).

Denture stomatitis, commonly known as "chronic atrophic candidiasis" is a chronic inflammation of mucosa that involves the denture area. Here the high-frequency, low-intensity trauma of the denture compressing the palatal mucosa alters the barrier mechanism allowing for the overgrowth of *candida* organisms.[5,25]

Angular cheilitis, also known as perleche, presents as erythematous or ulcerated fissures affecting the commissures of the lip unilaterally or bilaterally. This form is commonly associated

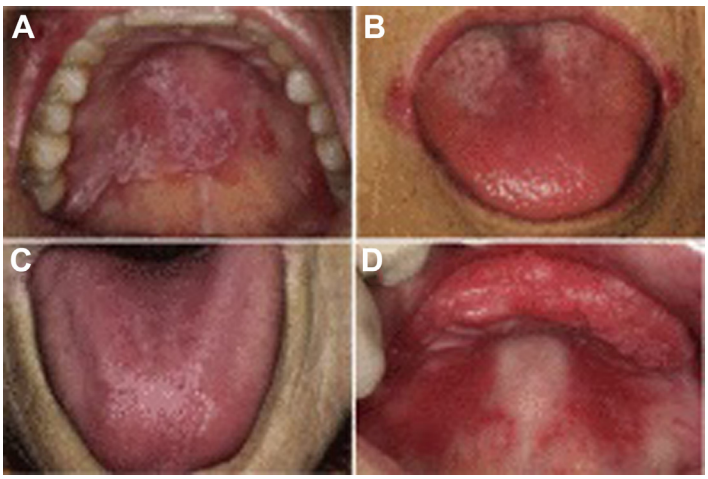

Fig. 4. Variations in clinical manifestation of oral candidiasis. (*A*). Thrush (pseudomembranous candidiasis). (*B*). Chronic erythematous candidiasis and angular cheilitis. (*C*). Chronic atrophic candidiasis. (*D*). *Candida*-associated denture stomatitis. (*From* Hu L, He C, Zhao C, Chen X, Hua H, Yan Z. Characterization of oral candidiasis and the Candida species profile in patients with oral mucosal diseases. Microb Pathog. 2019 Sep;134:103575.)

with patients with chronic lip-licking habit or loss of the occlusal vertical dimension. The constant moisture and cracking at the commissure and predispose the tissue to Candida proliferation and invasion.[5]

Median rhomboid glossitis appears as a well-demarcated, symmetric, depapillated area arising anterior to the circumvallate papillae typically located around the midline of the dorsum of the tongue. Although most cases are asymptomatic, some patients may report persistent pain, irritation, or pruritus. The lesion is believed to be a localized chronic infection by *C. albicans*. It is commonly seen in tobacco smokers and inhalation-steroid users.[26]

Hyperplastic candidiasis

Hyperplastic candidiasis also referred to as "candidal leukoplakia", mainly presented in chronic form. Clinically, it will present as a well-demarcated, raised lesion that may vary from small translucent whitish areas to large opaque plaques less likely to be scraped off. Unlike the pseudomembranous type, the hyperplastic type seems to have a positive association with immunosuppression, malnutrition, smoking, and in addition, may present with varying degrees of dysplasia.[27] The whitish lesion surface may often present localized erythematous areas.[28]

Treatment

Diagnosis of oral candidosis includes the physical examination of clinical signs and symptoms, presence of the candida organisms on the direct examination of a smear from the lesion or biopsy examination showing hyphae in the epithelium, positive culture, and serologic test. The concern of non–candida albican candida species is a concern in certain mucosal lesions, oral cancer, and elderly hospitalized patients, this is due to NCAC species to be naturally resistant to some of the common antifungal drugs.[29]

When managing all forms of candidiasis, it is important to address any underlying factor when possible. Specific therapy for mild oral disease remains the standard nystatin oral suspension, 100,000 U/mL to be taken 5 mL (1 teaspoon) at a time as an oral swish and spit or swish and swallow 4 times daily. For chronic, candidiasis limited to the oral cavity and upper digestive tract, nystatin as noted above combined with clotrimazole troches, 10 mg five times daily, or the vaginal suppositories used as an oral troche three times daily, is very effective. In addition, the oral solution of itraconazole 10 mg/mL as 10-mL swish and swallow twice daily, is also effective, as is the oral solution of posaconazole 20 mg/mL as 5-mL swish and swallow twice daily (**Table 3**). Regular dental evaluation is recommended as the clotrimazole troches contain sugars that may stimulate active caries, especially in xerostomic patients. Patients with dentures can also benefit from sprinkling nystatin powder into their dentures twice a day, and those with angular cheilitis may also want to apply nystatin cream to the skin 4 times a day.[5]

For patients with refractory candidiasis, mucocutaneous candidiasis, women with concurrent candida vaginitis, or patients in whom compliance is a problem, a systemic antifungal therapy with ketoconazole or fluconazole 200 mg first day, followed by 100 mg daily for 2 weeks is recommended.[30,31]

Table 3
Topical medications for the treatment of oral candidiasis

Drugs	Use
Nystatin Suspension 100,000 IU/mL	5 mL swish and spit for 14 d
Clotrimazole Troche 10 mg	Dissolve in 10 mL and swish and swallow BID for 14 d
Nystatin-Triamcinolone Acetonide 15g	Apply to corners of mouth after meals and at bedtime for 14 d

AUTOIMMUNE VESICULOBULLOUS AND ULCERATIVE DISEASES

Lichen planus (LP), the spectrum of pemphigus, pemphigoid, and lupus erythematosus are a gamut of autoimmune vesiculobullous and ulcerative diseases which are responsible for an onslaught of oral soft tissue lesions which affect the entire mucosa. It would behoove all practitioners to be well versed in recognizing and treating these lesions as they can prove to be difficult to differentiate. For that reason, it is imperative that the provider biopsy lesions when an autoimmune process is suspected. When selecting a site for biopsy, the target site should be a clinically involved area with an intact surface and some adjacent normal-appearing tissue.[5]

Lichen planus

LP is a mucocutaneous disease that manifests as a result of a delayed T cell-mediated hypersensitivity whereby the basal layer of skin and/or mucosa is attacked.[5] This disease corporealizes as one of the 3 clinical forms which have a global prevalence of ~0.1–2.2% and tend to present in patients older than 40 with a predilection for women.[32,33] All forms have a predilection for the buccal mucosa, tongue, and buccal surface of the attached gingiva. In order of advancing severity and symptomatology, LP has a reticular, plaque, and erosive form.

The reticular form (**Fig. 5**) is most notably characterized by the pathognomonic Wickham's striae which are lacy, white, interlacing lines found mostly on the characteristic sites of the posterior bilateral buccal mucosa, attached gingiva, and tongue.[34] The aforementioned striae are usually asymptomatic; they wax and wane over a period of weeks to months while assuming a limited rather than disseminated territory of oral mucosa.[5]

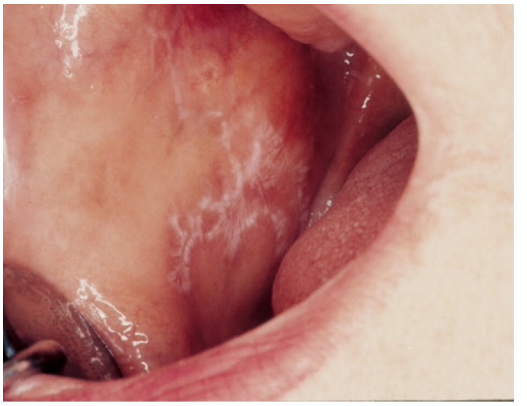

Fig. 5. Classical clinical presentation of reticular oral lichen planus in a 42-year-old asymptomatic woman. The lesions occurred bilaterally on the buccal mucosa. The disease was discovered during a routine dental examination, and the disease duration was estimated to be about 1 year. (*From* Chainani-Wu N, Silverman S Jr, Lozada-Nur F, Mayer P, Watson JJ. Oral lichen planus: patient profile, disease progression and treatment responses. J Am Dent Assoc. 2001 Jul;132(7):901-9.)

The plaque form is characterized by a slightly elevated, homogenous hyperkeratotic white patch with irregular borders that closely resemble leukoplakia. These patches are usually asymptomatic and present on the characteristic sites (bilateral buccal mucosa, attached gingiva, tongue). Rarely, this form may be associated with some discomfort. Given the striking resemblance to leukoplakia, the biopsy of this form is required to differentiate from premalignant or malignant mucosal changes. Differential diagnosis includes nonspecific benign hyperkeratosis, a spectrum of epithelial dysplasias, verrucous hyperplasia, verrucous carcinoma, invasive squamous cell carcinoma, or hypertrophic candidiasis.[5,35]

Erosive lichen planus (ELP) is the most severe in symptomatology and presentation. It is characterized by intense pain and erythematous mucosal inflammation. When involving the buccal mucosa or tongue, lesions present as fibrinous based ulcers in an atrophic erythematous background with occasional white, hyperkeratotic foci and borders of fine, white radiating striae. If involving the attached gingiva, presentation is often a boggy, red, and friable tissue that bleeds easily (**Fig. 6**). This reaction pattern is known as desquamative gingivitis.[34] If the erosive component is severe, the basal layer is compromised by the immune cells resulting in vesicle formation with a positive Nikolsky sign. This is a particularly rare presentation known as bullous LP.[5,34] These lesions must undergo biopsy. Differential diagnosis includes

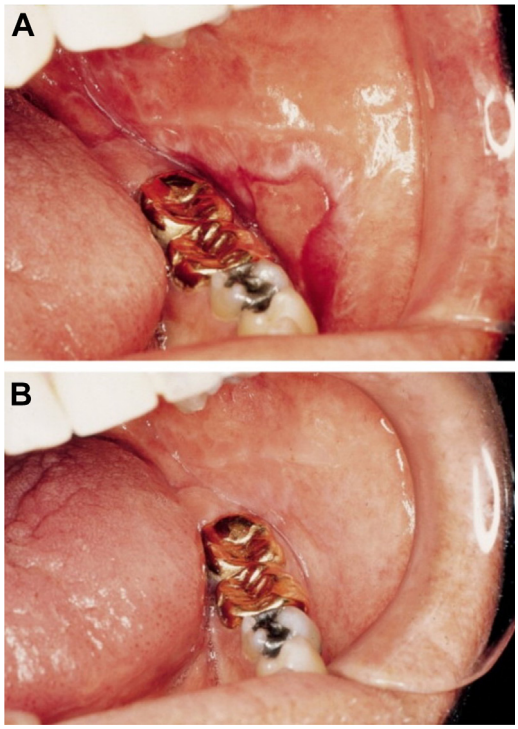

Fig. 6. (*A*) Painful, erosive oral lichen planus, or OLP, of the left buccal mucosa in an otherwise healthy 60-year-old man. He had no other complaints or findings, and the results of a recent physical examination were within normal limits. The gold crowns were placed after the OLP appeared, because the dentist thought that the lesion might have been due to some old molar amalgam restorations, although this was unlikely. (*B*). Daily doses of prednisone (60 mg) for 1 week led to complete remission. After 1 month, the disease recurred, but was controlled indefinitely with topical corticosteroid treatment. (*From* Chainani-Wu N, Silverman S Jr, Lozada-Nur F, Mayer P, Watson JJ. Oral lichen planus: patient profile, disease progression and treatment responses. J Am Dent Assoc. 2001 Jul;132(7):901-9.)

lupus erythematosus, chronic ulcerative stomatitis, dysplasia, squamous cell carcinoma, and pemphigoid. ELP may progress to squamous cell carcinoma in approximately 2% to 3% of cases as a function of disease duration (15 years or more).[5,34]

Treatment

Treatment for the reticular and plaque forms is reassurance and follow-up.[5,34] In some cases, patients may have superimposed candidiasis and complain of a burning sensation in the mouth. These instances necessitate treatment with antifungal therapy such as miconazole gel or chlorhexidine mouthwash rinses.[34,36] Some authors have suggested topical retinoids (isotretinoin 0.1%) and other vitamin A analogs (etretinate, 0.05% tretinoin, retinoic acid in orabase 0.05%, tazarotene 0.1%); however, almost all reticular LP is asymptomatic and nonprogressive; additionally, almost all striae return if the drug is discontinued. Common side effects of topical retinoids include transient burning sensation and taste abnormalities. Typically, improvement in lesion presentation is noticeable after 3 weeks.[37] Dapsone has also been effective for mild cases of LP involving skin. If used, the patient's serum should be tested for the presence of glucose-6-phosphate dehydrogenase because dapsone may precipitate a G6PD-deficiency hemolytic episode. Dapsone can be given in a dose of 50 mg per day and may be continued for several weeks.[5]

Milder forms of erosive LP can be treated with topical corticosteroids, usually 0.05% clobetasol propionate gel, 0.1%–0.05% betamethasone valerate gel, 0.05% clobetasol ointment or cream, 0.1% triamcinolone acetonide ointment in orabase or lozenge, or 0.05% fluocinonide gel (Lidex gel) 4 times daily.[38] Fluocinonide gel may be combined with antifungal agent griseofulvin 250 mg twice daily. Efficacy of the agent is related to the side effect of promoting epithelial differentiation and maturity. Topical 0.1% tacrolimus cream (Protopic) also may be used.

Resistant or extensive lesions may be treated 2 to 4 times weekly with intralesional subcutaneous injections of 0.2–0.4 mL of a 10 mg/mL solution of triamcinolone acetonide by means of a 1.0 mL 23 or 25 gauge tuberculin syringe.[39]

Most severe erosive LP are resistant to topical and intralesional approaches and require systemic corticosteroids, prednisone is typically the drug of choice given as recommended by Regimen I or II or less commonly IIIA or IIIB (**Tables 4–7**).[5] Oral griseofulvin, topical 0.05% fluocinonide, or 0.1% protopic can be added to either regimen to reduce the prednisone requirements or help maintain a remission. In refractory cases, systemic tacrolimus or rituximab can be effective.[5]

It is imperative to educate patients on the side effects of prolonged corticosteroid use (sodium and water retention, hypertension, hypernatremia/hypokalemia, hyperglycemia, infections including iatrogenic candidiasis, mood changes, increased risk for peptic ulcer disease, muscle wasting/fat deposit, delayed wound healing, osteoporosis, cataracts, and increased risk for cancer). Complete treatment at low doses of prednisone (5–10 mg every other day) may be extended for up to 3 years.[5] A milder, residual clinical disease usually persists. Consequently, a drug-free total

Table 4
Systemic corticosteroid regimen I for autoimmune vesiculobullous and ulcerative diseases

Systemic Corticosteroid Regimen I	Rationale
Prednisone 100–120 mg qd (1.5 mg/kg/d) x 2 wk	Objective: Gain rapid suppression with an initial high loading dose
A tapering schedule reduces prednisone by 20 mg per day each week over several weeks until a dose of 20 mg/d is reached. This dose is continued for 1 month followed by 10 mg per day for 3 mo.	Objective: taper off dose rapidly enough to avoid serious side effects of high dose prednisone
Dose reduced to 10 mg every other day for 3 mo followed by 5 mg every other day for 6 mo	Tapered dose extended in length to avoid exacerbation at the time of dose reduction or after drug discontinuation
After 6 mo, a 5 mg dose of prednisone every other day, the drug may be discontinued a high possibility of an extended remission in a drug-free state.	Designed to permit the hypophyseal-adrenal cortical axis to regain its function

Data from Marx RE, Stern D. Oral and Maxillofacial Pathology: A Rationale for Diagnosis and Treatment. 2nd ed. Quintessence Publishing. 2012; 200.

remission is less common than a maintenance-control remission. Often, the disease can be suppressed with prednisone to a point at which topical fluocinonide and/or griseofulvin can maintain remission without continued prednisone or with only a low, every other day prednisone schedule. Any ELP that does not respond to therapy, especially prednisone, should be viewed with suspicion for malignant transformation to squamous cell carcinoma.[5]

Pemphigus vulgaris

Pemphigus vulgaris is a potentially fatal painful autoimmune mucocutaneous disease that

Table 5
Systemic corticosteroid regimen II for autoimmune vesiculobullous and ulcerative diseases

Systemic Corticosteroid Regimen II	Rationale
Prednisone 100–120 mg qd (1.5 mg/kg/d) x 2 wk, drug then abruptly discontinued	Objective: Gain rapid suppression with initial dose and discontinue before side effects or significant adrenal suppression develop Advantage: approach is effective and straightforward Disadvantage: exacerbations are more frequent, disease process is less controlled

Data from Marx RE, Stern D. Oral and Maxillofacial Pathology: A Rationale for Diagnosis and Treatment. 2nd ed. Quintessence Publishing. 2012; 200.

Table 6
Systemic corticosteroid regimen IIIA for autoimmune vesiculobullous and ulcerative diseases

Systemic Corticosteroid Regimen IIIA	Rationale
Prednisone 100–120 mg qd (1.5 mg/kg/d) × 2 wk	Objective: Gain rapid suppression with an initial high loading dose
A tapering schedule reduces prednisone by 20 mg per day each week over several weeks until a prednisone level is reached without exacerbating the disease. T	Many individuals remain on 20 mg/d or higher doses due to disease exacerbation with lower doses Appropriate for cases of disease intensity and organ involvement that lower doses of prednisone cannot control

Data from Marx RE, Stern D. Oral and Maxillofacial Pathology: A Rationale for Diagnosis and Treatment. 2nd ed. Quintessence Publishing. 2012; 200.

Table 7
Systemic corticosteroid regimen IIIB for autoimmune vesiculobullous and ulcerative diseases

Systemic Corticosteroid Regimen IIIB	Rationale
Prednisone 100–120 mg qd (1.5 mg/kg/d) × 2 wk	Objective: Gain rapid suppression with initial high loading dose
A tapering schedule reduces prednisone by 20 mg per day each week over several weeks until a prednisone level is reached at which the disease is exacerbated. This and slightly higher prednisone levels may still be associated with disease activity ergo other immunoregulatory drugs (cyclophosphamide, azathioprine, methotrexate, mycophenolate, rituximab, infliximab) are added	Objective: Attack disease with double or triple drug therapy in order to reduce drug dosage and side effects. Reserved for refractory cases and persons in whom corticosteroid complications pose a greater risk (diabetics, history of tuberculosis, peptic ulcer disease, cataracts, osteoporosis).
Dose reduced to 10 mg every other day for 3 mo followed by 5 mg every other day for 6 mo	Tapered dose extended in length to avoid exacerbation at the time of dose reduction or after drug discontinuation
After 6 mo, a 5 mg dose of prednisone every other day, the drug may be discontinued a high possibility of an extended remission in a drug-free state.	Designed to permit the hypophyseal–adrenal cortical axis to regain its function

Data from Marx RE, Stern D. Oral and Maxillofacial Pathology: A Rationale for Diagnosis and Treatment. 2nd ed. Quintessence Publishing. 2012; 200.

manifests as a result of a B-cell mediated process whereby autoantibodies develop against the epidermal cell surface glycoproteins desmoglein 1 and 3 or against desmoglein 3 only. Desmogleins are components of desmosomes, the structures which bond squamous epithelial cells together.[5,34] The consequence is a cascade of events that results in the destructive fixation of complement followed by a bout of inflammation which causes a suprabasilar split and intraepithelial blisters (**Fig. 7**). Ultimately, individual squamous cells lose their desmosomal attachment and become rounded polygonal acantholytic cells known as *Tzanck* cells.[5,34]

The clinical ramification of this process is the formation of a fragile vesicle that is superficial in nature and thus rapidly ruptures (**Fig. 8**). Exposed is a basal layer that is in close proximity to free nerve endings whereby fixation of complement initiates inflammation and pain. Oral lesions form on all mucosal surfaces and may exhibit a Nikolsky sign. Individuals may present with irritability due to pain, fever from secondary infection, dehydration, and cervical lymphadenitis from secondary

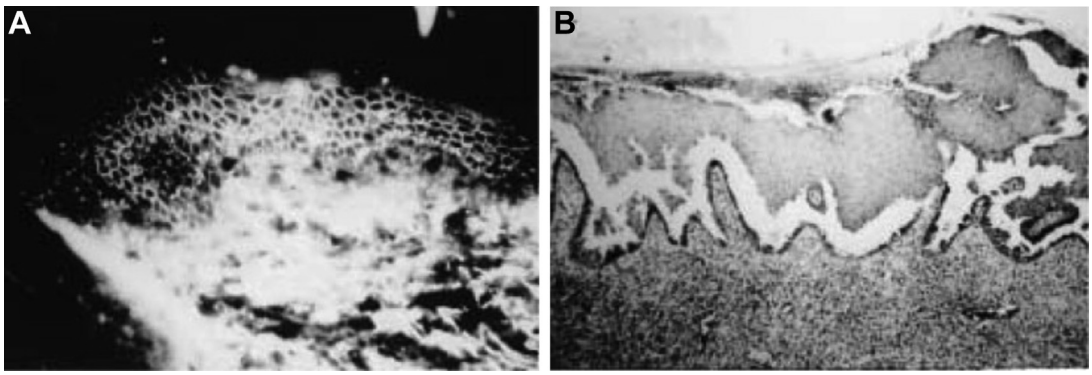

Fig. 7. (*A*). Direct immunofluorescent staining (immunoglobulin G) revealing pemphigus vulgaris antigen distribution in the oral epithelium. Note the "spider-web" distribution of reaction product in the spaces between squamous epithelial cells (obtained from perilesional biopsy specimen containing intact epithelium). (*B*). Hematoxylin-and-eosin–stained section revealing acantholysis, mononuclear infiltrate, and suprabasilar separation. (*From* Sirois D, Leigh JE, Sollecito TP. Oral pemphigus vulgaris preceding cutaneous lesions: recognition and diagnosis. J Am Dent Assoc. 2000 Aug;131(8):1156-60.)

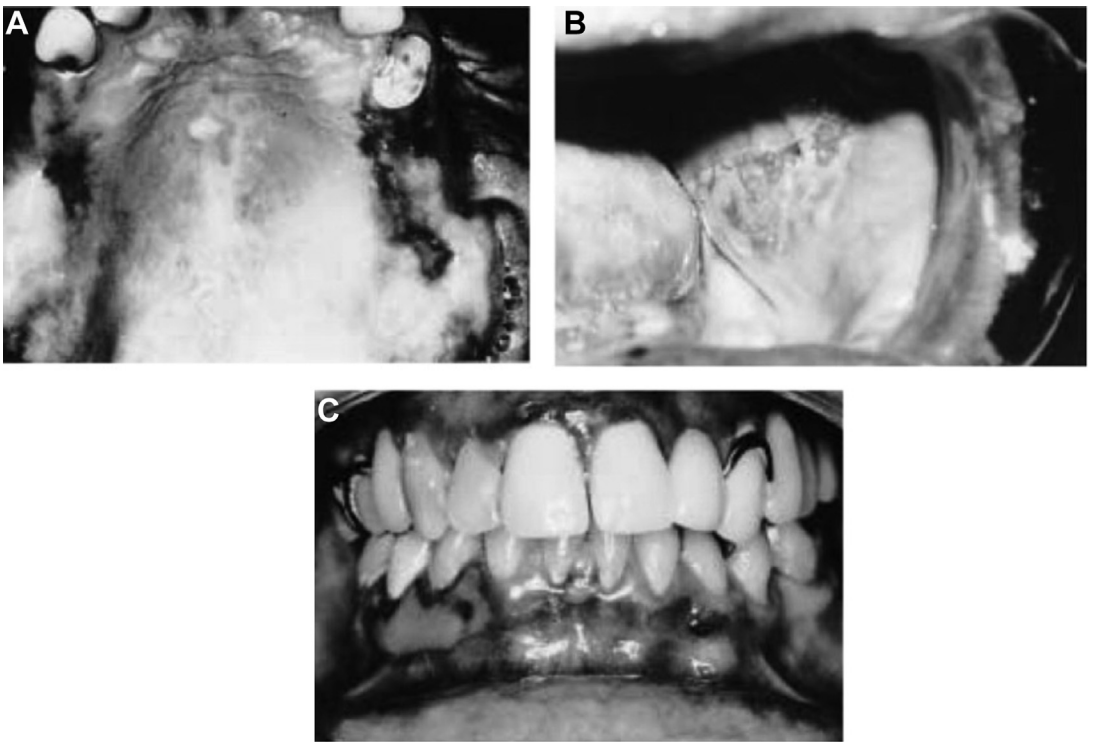

Fig. 8. A. variety of clinical presentations of oral pemphigus vulgaris, which generally appears in the form of shallow, irregular nonspecific ulcers. (*A*). The palate. (*B*). The buccal mucosa. (*C*). The gingivae. (*From* Sirois D, Leigh JE, Sollecito TP. Oral pemphigus vulgaris preceding cutaneous lesions: recognition and diagnosis. J Am Dent Assoc. 2000 Aug;131(8):1156-60.)

infections of numerous oral ulcers. This primarily affects individuals in their fourth to sixth decade, blacks, south Asian, and those of Ashkenazic Jewish descent. The estimated incidence is 1 to 5 cases per million people diagnosed each year. These lesions have the notoriety of "first to show, last to go" as the oral lesions are the first sign of the disease and are the most difficult to treat.[5,34]

Skin lesions are more likely to show vesicles or even bullae due to increased thickness of skin epithelium and keratin layer as compared with mucosa. The lesion will frequently form on otherwise normal-appearing skin which subsequently becomes inflamed and then ruptures leaving a denuded surface. Ocular involvement is rare and is manifested as bilateral conjunctivitis without any incidence of scarring and symblepharon formation (**Fig. 9**).[5,34]

Treatment

As mentioned previously, individuals will often present with dehydration secondary to poor oral intake and frequently with a secondary infection. Therefore, appropriate initial management includes starting hydration with intravenous fluids, beginning antibiotic therapy, and pain control measures. Lesions should be biopsied in the interim and direct immunofluorescent studies will demonstrate intercellular deposition of IgG.[40] Pemphigus is a systemic disease, therefore, this disease responds well to systemic corticosteroids. Initiation of corticosteroid therapy should not preclude a definitive biopsy. If the first biopsy

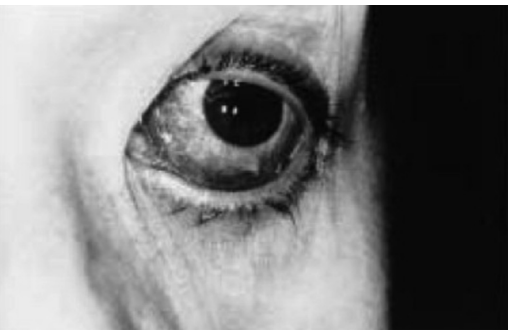

Fig. 9. Corneal erosion due to pemphigus vulgaris. (*From* Sirois D, Leigh JE, Sollecito TP. Oral pemphigus vulgaris preceding cutaneous lesions: recognition and diagnosis. J Am Dent Assoc. 2000 Aug;131(8):1156-60.)

specimen is nondiagnostic, a second biopsy would have an altered tissue response which will obscure diagnosis and complicate treatment.[5,34]

The accepted treatment is with high doses of systemic steroids (prednisone 1–2 mg/kg/d). Once the disease is under control, prednisone can be reduced to the lowest possible maintenance levels.[40] About a small percentage of cases respond incompletely to and require the addition of rituximab 375 mg/m^2 of the body surface, cyclophosphamide 50–100 mg po twice daily or azathioprine 50 to 100 mg twice daily to reduce corticosteroid doses and mortality from the side effects of systemic corticosteroids. If refractory, methotrexate 25 mg per week may be substituted for azathioprine or rituximab. Plasmapheresis may also be used as an adjunctive method to reduce corticosteroid dosage. Isolated oral lesions may be treated with injectable corticosteroids.[5,34]

If untreated, pemphigus vulgaris is fatal in 2 to 5 years. Treatment of cutaneous pemphigus results in a residual 10% to 15% mortality rate at 15 years because of complications from long-term prednisone therapy and other immunosuppressive drugs. The most common cause of death is *Staphylococcus aureus* septicemia which is often difficult to detect because of immunosuppression caused by concomitant corticosteroid therapy.[5,34]

Paraneoplastic pemphigus

Paraneoplastic pemphigus is a severe variant of pemphigus vulgaris that represents a heralding sign of an undiscovered or uncontrolled malignancy. The most frequent culprits are Hodgkin's lymphoma, non–Hodgkin's lymphoma, chronic lymphocytic leukemia, and thymoma.[5,34,40] One may expect to see the rapid onset of numerous painful lesions on oral mucosa, skin, conjunctiva, and progressive pulmonary involvement in up to 40% of patients. Lesions may resemble a lichenoid drug reaction, erythema multiforme, LP, or pemphigus clinically and histologically. Unfortunately, despite steroid and/or immunosuppressive therapy, the disease course is rapidly progressive over weeks to months and is often fatal. The oral lesions most commonly manifest as large erosive lesions covering the lips, tongue, and soft palate.[5,34,40] To date there are no definitive diagnostic criteria, but the most accepted conditions include painful, progressive stomatitis with preferential involvement of the tongue, identification of circulating antibodies to envoplakin or periplakin and the presence of a neoplasm.[5] The gold standard for diagnosis is immunoprecipitation.

Treatment

A combination of prednisone and immunosuppressive drug therapy may be used to help control the severity of the skin lesions, but the oral, conjunctival, and pulmonary diseases are frequently resistant to treatment.

Pemphigoid group

This is a group of B-cell-mediated autoimmune diseases that characteristically form vesicles and bullae in the skin and mucous membranes. There are classically 2 subtypes of the pemphigoid group: bullous (cutaneous) pemphigoid and mucous membrane (cicatricial) pemphigoid. In cases of overlapping clinical presentations, patients may present with skin, oral mucosa, ocular mucosa, and other mucous membrane involvement.[5] Direct immunofluorescence will show a homogenous band of IgG in the basement membrane zone as well as C3.[5] With the advent of specific direct immunofluorescent markers, it has been made clear that the presentation of cutaneous and mucous membrane pemphigoid is due to autoantibodies to at least 3 different molecules in the lamina lucida region of the basement membrane and on the hemidesmosomes of epithelial basal cells.[5,40]

Bullous pemphigoid (BP) is the most commonly occurring in the pemphigoid group, it usually presents in the 6th decade and greater with an equal affliction for both sexes.[40] BP usually emerges on the skin (scalp, axilla, arms, legs, groin) with the oral mucous membranes involved ~30% of the time. When compared with pemphigus vulgaris, the oral lesions of BP are smaller, less extensive, less painful, and form more slowly. Desquamative gingivitis has been reported to be the most common and often the only oral presentation of BP.[40] BP occurs as a result of the production of autoantibodies (IgG) against 2 proteins (BPAG1 and BPAG2) in the basal cell-basement membrane zone junction and the basement membrane proper. When the IgG type autoantibodies attack the BPAG1 and BPAG2, the antibody–antigen complex fix complement and initiate a series of steps which lead to the degradation of the basement membrane at the lamina lucida level. This generates pain by the formation of bradykinin, kallikrein, and substance P.[5] As a result, the separation occurs within the basement membrane zone and the skin lesions formed are characteristically large bullae (3–15 cm in diameter) which are tense, erythematous, pruritic, and painful. The disease process usually waxes and wanes with periods of remission over a period of 2 to 3 years with

the disease usually subsiding into remission or mild symptomatology after 5 to 6 years.

Mucous membrane (cicatricial) pemphigoid is chronic and typically has a predilection for the oral and ocular mucosa with the skin involved ~ 20% of the time and with lesser severity.[5] This disease is often seen in individuals in their fifth decade and occurs twice as frequently in women. The lesions initially blister, ulcerate, and then form scars due to the deeper subepithelial location.[40] The oral mucosa and ocular conjunctiva are most commonly affected in order of decreasing frequency. Oral lesions are most commonly a bright red desquamative gingivitis (**Fig. 10**).[40] When the conjunctiva is involved, if not treated, there is a high incidence of the development of scarring and adhesions between the bulbar and palpebral conjunctiva known as symblepharon. This may progress to corneal damage and blindness in 15% of the affected population.[40] Laryngeal involvement may result in pain, hoarseness, difficulty breathing; esophageal involvement may cause dysphagia which may lead to debilitation and death in severe cases.[40]

Treatment

The treatment of choice for mild or localized oral lesions is a high potency topical corticosteroids or intralesional corticosteroids such as 0.05% clobetasol in orabase, 0.1% triamcinolone acetonide, 0.05% fluocinonide, or betamethasone applied 3 to 4 times daily for 9 to 24 weeks[40,41] If there is no response to topical therapy alone or if the patient cannot tolerate corticosteroids, a regimen of tetracycline, or erythromycin 500 mg twice daily alone or combined with nicotinamide 500 mg twice

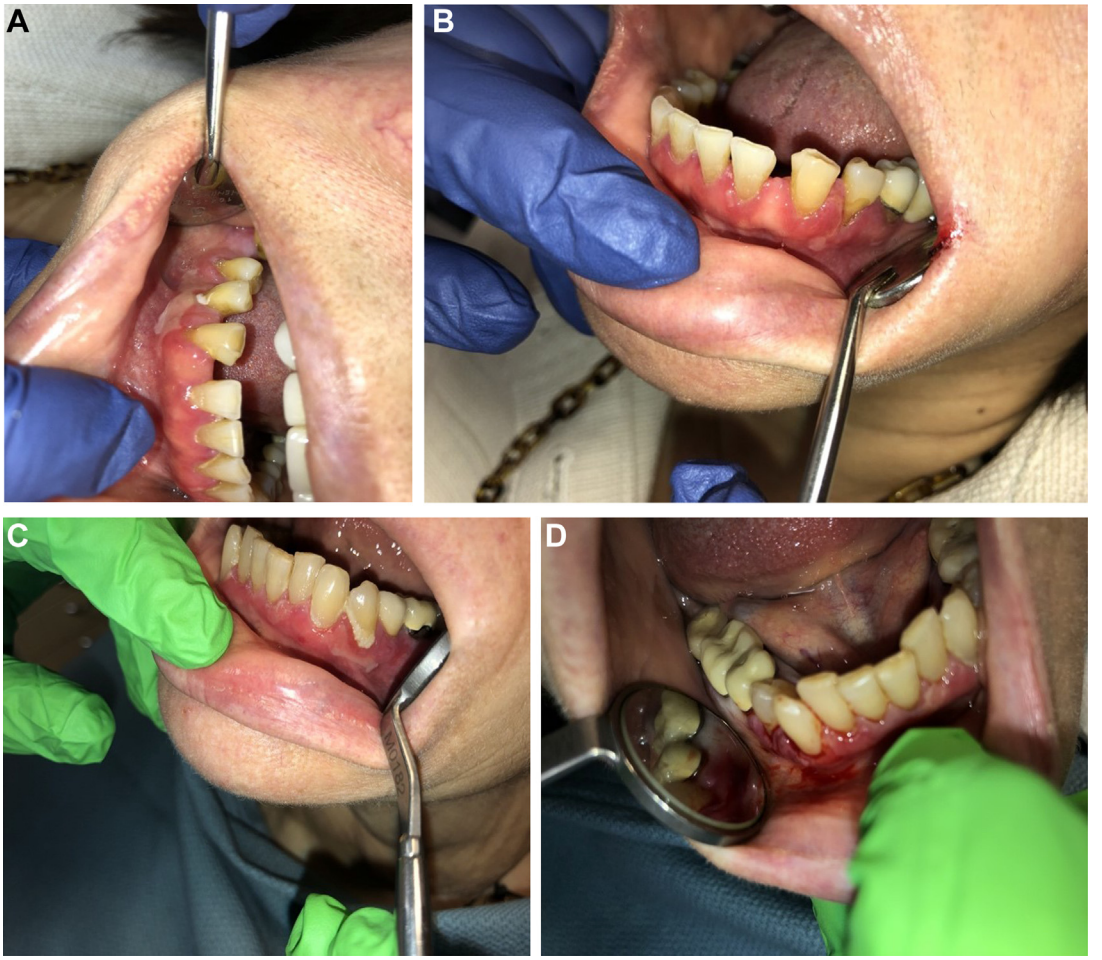

Fig. 10. Female patient diagnosed with mucus membrane pemphigoid manifested as desquamative gingivitis and buccal mucosal ulcerations. (*A*) Grey ulcerative lesion with erythematous borders on the buccal attached gingiva. (*B-D*) Generalized tender, erythematous, sloughed buccal attached gingiva representing desquamative gingivitis. (*Courtesy of* Scott M Peters, New York, NY.)

Table 8
Alternative drugs to corticosteroid therapy for treating immune-based diseases

Drug	Mechanism of Action	Dose
Cyclophosphamide (Cytoxan, Bristol-Myers Squibb)	Biotransformed principally in the liver to active alkylating metabolites by a mixed-function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.	IV: 40–50 mg/kg given in divided doses over 2–5 d (when used alone in a patient without hematologic deficiency); or 10–15 mg/kg every 7–10 d or 3–5 mg/kg twice weekly Oral: 1–5 mg/kg/d
Tacrolimus	Inhibits T-lymphocyte activation, although the exact mechanism of action is not known.	0.1 mg/kg per day for 1 mo, then reevaluate
Methotrexate	Inhibits dihydrofolic acid reductase, interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate.	Immune-based disorders: Starting dose of 10 mg/m2 once weekly, followed by 7.5–10 mg weekly; doses may be adjusted by no more than 30 mg/wk to achieve optimal clinical response
Etanercept (Enbrel, Amgen)	Binds specifically to tumor necrosis factor (TNF), a naturally occurring cytokine involved in normal inflammatory and immune responses, and blocks its interaction with cell surface TNF receptors.	50 mg given as one subcutaneous injection using a single-use, prefilled syringe or autoinjector; may also be given as two 25-mg injections
Rituximab (Rituxan, Genentech)	Binds specifically to the antigen CD20. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis in vitro. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.	First infusion: 50 mg/h, but may be increased by 50 mg/h every 30 min (max 400 mg/h) if no toxicity Subsequent infusions: 100 mg/h, but may be increased by 100 mg/h every 30 min (max 400 mg/h) if no toxicity

(*continued on next page*)

Table 8
(*continued*)

Drug	Mechanism of Action	Dose
Azathioprine (Imuran, Azasan)	Inhibits purine synthesis which results in decreased production of DNA and RNA for the synthesis of white blood cells, thus causing immunosuppression	Oral: 1–2 mg/kg/d
Mycophenolate Mofetil	Exhibits a cytostatic effect on B and T lymphocytes by means of inhibiting inosine monophosphate dehydrogenase which in turn inhibits de novo guanosine nucleotide synthesis, a pathway needed by B and T lymphocytes for proliferation.	Oral: 750 mg - 1 g twice daily

Data from Marx RE, Stern D. Oral and Maxillofacial Pathology: A Rationale for Diagnosis and Treatment. 2nd ed. Quintessence Publishing. 2012; 200.

daily may slowly and gradually decrease the disease activity. In severe cases, systemic corticosteroids (prednisone 1–2 mg/kg/d) alone or combined with adjuvant immunosuppressive agents such as azathioprine, cyclophosphamide or mycophenolate may be beneficial (Table 8).[5,40,42] Treatment often reduces symptoms, alleviates large bullae formation induces, and/or hastens remission.[5]

Lupus erythematosus

Lupus erythematosus is an immunologically mediated condition with 3 clinical forms: systemic, chronic cutaneous, and subacute cutaneous. Systemic lupus erythematosus (SLE) is a multisystem disease whereby there is a combination of increased activity in B lymphocytes and abnormal function of T lymphocytes which in conjunction result in a variety of cutaneous and oral presentations. Chronic cutaneous lupus erythematosus (CCLE) is a different but related process that primarily affects the skin and oral mucosa, those afflicted face a good prognosis. Subacute cutaneous lupus erythematosus (SCLE) has clinical features which are intermediate between that of SLE and CCLE.[34]

SLE affects women ~8 to 10 times more frequently than men and is often diagnosed in the third decade of life. SLE initially is nonspecific with patients presenting with constitutional symptoms of fever, weight loss, malaise, fatigue, and arthritis with periods of remission or disease inactivity. 40% to 50% of affected patients have a characteristic butterfly patterned rash over the malar area and nose with sparing of the nasolabial folds. Renal and cardiac involvement is a common complication. Oral lesions develop in 5%–40% and tend to affect the palate, buccal mucosa, and gingiva. Lesions may have a lichenoid, nonspecific, or granulomatous appearance in addition to varying degrees of ulceration, pain, erythema, and hyperkeratosis.[34]

Individuals with CCLE are usually spared from systemic signs or symptoms with a disease course limited to lesions appearing on skin or mucosa. Skin lesions are termed discoid lupus erythematosus (DLE)—this describes the scaly, erythematous patches usually distributed on sun-exposed skin with a concentration in the head and neck area. DLE lesions are often exacerbated by sun exposure. Lesions are notorious for healing in one area spontaneously and then appearing in another. The healing process results in cutaneous atrophy and hypo- or hyperpigmentation and scarring. Oral manifestations of CCLE seem clinically identical to that of ELP (painful, ulcerated or atrophic erythematous central zone surrounded by fine, white radiating striae) (Fig. 11). However, unlike ELP, CCLE oral lesions seldom occur in the absence of skin lesions.[34]

The disease course of SCLE is characterized by prominent, photosensitive skin lesions which do not show the induration and scarring that is seen with CCLE. The systemic manifestations are usually limited to arthritis or musculoskeletal abnormalities. SCLE is typically triggered by one of a variety of medications.[34]

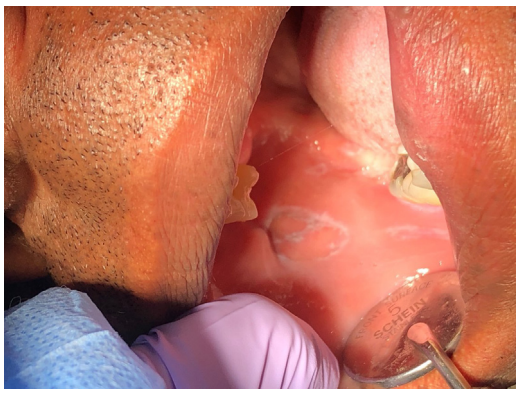

Fig. 11. CCLE oral lesion on the buccal mucosa. (*Courtesy of* Scott M Peters, New York, NY.)

Treatment

Patients should be counseled to avoid sunlight as this may precipitate and exacerbate disease activity. A mild disease course can be effectively managed with a combination of nonsteroidal anti-inflammatory drugs (NSAIDs) and antimalarial drugs such as hydroxychloroquine. More severe episodes, including those with oral presentations, are effectively managed with systemic steroids. Topical steroids appropriately manage CCLE lesions. Potent topical steroids such as clobetasol propionate gel 0.05%, betamethasone dipropionate 0.05%, or fluticasone propionate spray 50 mg aqueous solution are usually required. The treatment may begin with applications 2 to 3 times a day followed by a tapering during the next 6 to 9 weeks. Lesions resistant to topical steroids may be managed with systemic antimalarial drugs or low-dose thalidomide.[34] The overall objective is to use a minimum of steroids to obtain relief.

From this article, one can appreciate that soft tissue lesions commonly seen in the oral cavity tend to overlap in their onset, presentation, and location making it difficult to appreciate whether the etiology is inflammatory, immunologic, traumatic, infectious, or neoplastic. This may be overwhelming to the practitioner with an untrained eye who is not typically exposed to such diseases. Furthermore, as one can imagine, the patient who suffers from such lesions requires not only reassurance, but also appropriate management as these lesions may be detrimental physically and emotionally. As such, this article serves as an important resource for the medical and dental professional to understand these lesions, their management, and the necessity of obtaining a thorough history and physical to guide making a correct diagnosis. Many of these soft tissue lesions can be managed effectively with similar pharmacotherapy regimens; however, many drugs have serious side effects ergo it is imperative that if not pathognomonic, lesions are biopsied to confirm a suspected diagnosis before instituting the suggested treatment. Furthermore, if managed inappropriately, some lesions may progress in a manner that may worsen morbidity or/and mortality.

CLINICS CARE POINTS

- Always obtain a detailed medical history, allergies, drug reactions or other medications contraindications before starting the treatment.
- Monitor and document therapeutic treatment doses, progress, and adjust pharmacologic treatment if necessary.
- In the management of viral or immune-related diseases, set proper expectations before commencing any pharmacologic treatment.
- Close follow-up and biopsy should be considered in nonresolving suspicious mucosal lesions.

DISCLOSURE

The authors have nothing to disclose.

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