



Acute oral ulcers

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Ulceration of the oral mucosa is a frequent occurrence producing painful “aphthae,” a term of ancient origin referring to ulceration of any mucosal surface. The oral mucous membranes are specialized frail membranes and are susceptible to erosion [1]. Full-thickness erosion of the epithelium into the lamina propria produces painful ulceration. Because oral ulcers are both common and painful, the clinician is often consulted for diagnosis and treatment. Etiologies range from minor irritation to malignancy and systemic disease. A practical approach to the diagnosis and management of oral ulcers allows the clinician appropriately to evaluate patients and institute therapy.

In general, oral ulcers are painful and may be single or multiple, symmetric or irregular in shape. They usually have a central friable yellow-white exudative base with a surrounding rim of bright erythema. Once an ulcer forms, it is subject to repeated irritation from saliva and microflora, and the acute inflammatory stage may be followed by a pattern of chronic inflammation. Although there are many diverse causes, oral ulcers frequently demonstrate similarity both clinically and histologically. An algorithmic approach based on duration, recurrent nature, morphology, location, and systemic symptoms is useful in evaluating etiology (Fig. 1).

Acute oral ulcers are of short-lived duration and 6 weeks is a reasonable point of differentiation between acute and chronic ulcers. The causes of chronic oral ulceration are multiple, ranging from malignancy to systemic disease and other chronic inflammatory or immunobullous disorders, such as pemphigus, paraneoplastic disease, mucous mem-

brane pemphigoid, and lichen planus. Discussion of chronic ulceration is beyond the scope of this article.

Acute oral ulceration refers to ulcerative episodes of less than 6-weeks’ duration, and for ease of classification these should be categorized based on the pattern of behavior. Oral ulcers may occur as a single episode or be recurrent in nature representing a different spectrum of mucous membrane disease. An understanding of these differing patterns of oral ulceration aids in work-up and diagnosis (see Fig. 1).

Recurrent oral ulceration

Trauma

Oral trauma is one of the most common causes of recurrent oral ulcers. This results from mechanical, chemical, or thermal irritation of the mucosa. These are generally acute short-lived events producing painful ulcers, which heal readily within a few weeks without scarring. The ulcers may be recurrent if the inciting stimulus is not removed. Dental appliances, dentures, and orthodontic hardware may be causative in recurrent oral ulceration (Fig. 2) [2]. Dentures can produce pressure ulcers, which are typically small, less than 1 cm in size occurring on the crest of the alveolar ridge [3,4]. Irritation from a sharp or broken tooth is usually readily identifiable. Patients may also inadvertently produce traumatic ulcers through biting of the oral mucosa either accidentally or through unconscious oral habit [5]. This usually occurs on the loose buccal mucosa, lower lip, or tongue. Habitual cheek biting produces erosion along the bite line, which corresponds to the closure of the upper and lower teeth. Lesions above or below the bite line are typically not caused by cheek biting.

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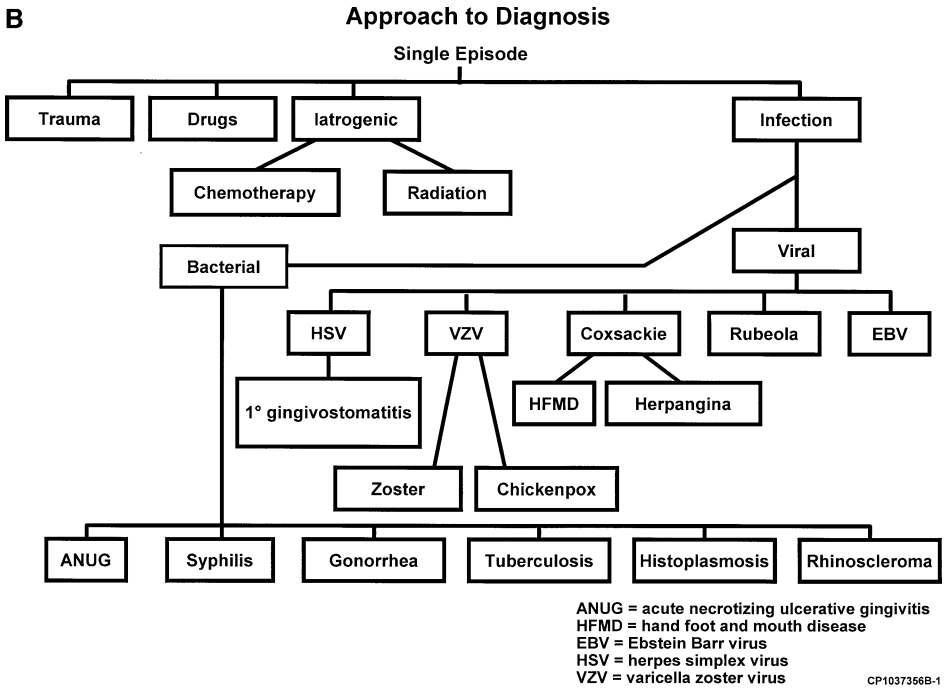
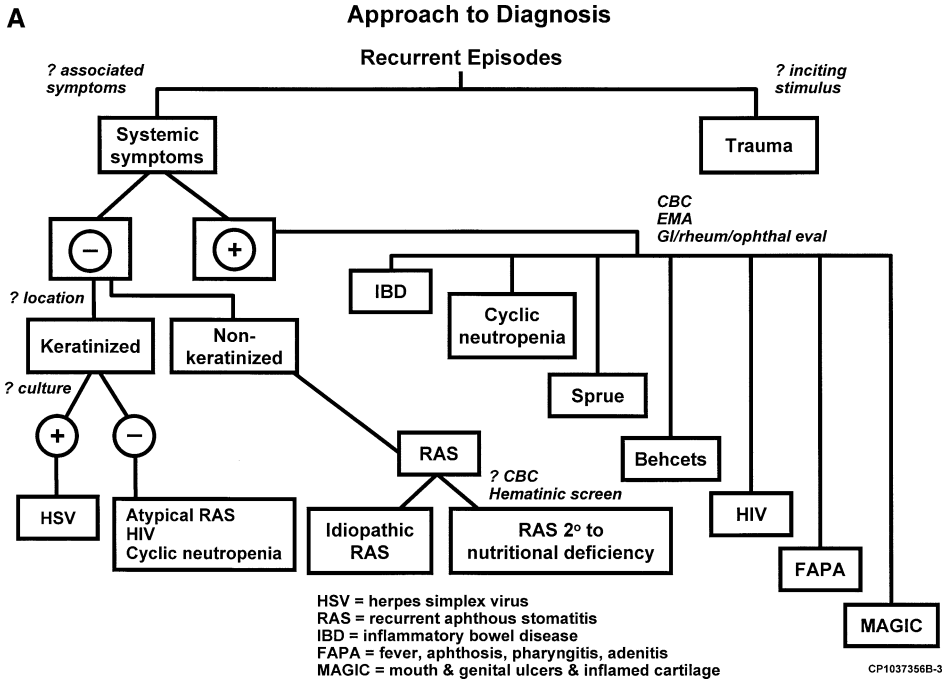


Fig. 1. Algorithm to evaluate acute oral ulcers that (A) are recurrent in nature, and (B) occur as an isolated episode.

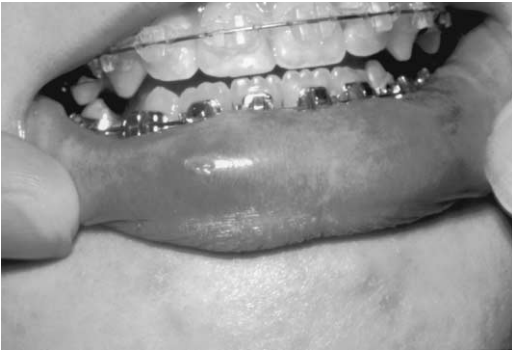


Fig. 2. Recurrent ulcer on the labial mucosa secondary to trauma from an adjacent dental appliance.

Chemical irritation also produces ulceration as the result of exposure to acidic or basic substances. Occasionally nonsteroidal anti-inflammatory drugs, such as aspirin, which patients may hold in their mouth to relieve toothache, produce local ulceration (Fig. 3). There are many other over-the-counter medications that similarly damage the mucosa with prolonged contact [4]. Factitial injuries can be seen in children or psychologically disturbed patients who repeatedly pick at the gingiva with fingernails or other objects.

Recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS), commonly known as *canker sores*, has been estimated to occur in as high as 20% of North American patients. RAS is reviewed elsewhere in this issue by Zunt. In most



Fig. 3. Mucosal ulceration related to use of aspirin to relieve toothache.

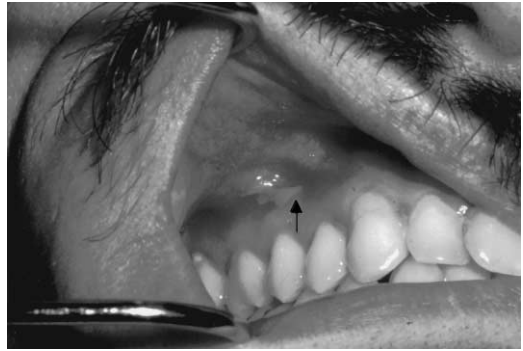


Fig. 4. Minor aphthous ulcer with a small superficial “kissing” ulcer tucked in the alveolar sulcus.

cases, recurrent aphthous ulcers are limited to the oral mucosa and tend to be multifactorial in etiology rather than attributable to a single factor. Trauma, smoking, stress, hormonal influences, genetics, food allergies, infections, and immunologic factors are all suggested causes [6–11].

Recurrent aphthous stomatitis can be classified in two systems based on morphology, or clinical presentation. Using the first classification, Cooke [12] delineated three categories of RAS based on morphology. Minor aphthous ulcers are the most common form accounting for about 80% of cases. Typically, these ulcers are superficial in nature, small in size, usually less than 1 cm in diameter, few in number, occurring singularly or in groups, and heal within about 7 to 10 days without scarring (Fig. 4). The second subtype, major aphthous ulcers, otherwise known as *peradenitis mucosa necrotica recurrens*, or Sutton's disease, occurs in about 10% of patients. These ulcers are larger in size, often over 1 cm in diameter, occurring either singly or as multiple lesions (Fig. 5). They are slower to heal and may



Fig. 5. Major aphthous ulcer. A large deep and painful ulcer involving an extensive area on the labial mucosa.

persist for several weeks, ultimately leaving a scar because of the extent of necrosis [13]. A third category, known as *herpetiform ulcers*, is a descriptor referring to the clustered morphology of lesions. It is unrelated to herpesvirus infection. Herpetiform ulcerations are large in number, ranging from 10 to 100 at a time and consist of multiple small lesions that ultimately coalesce becoming confluent into larger plaques. Because of the size and depth they may heal with scarring in 7 to 30 days (Fig. 6, Table 1).

Although lesions of RAS differ in size and extent, they are similar in appearance with yellow central slough and surrounding erythematous halo. There may be a premonitory stage lasting approximately 24 hours followed by 2 or 3 days of intense pain and then gradual lessening of the pain as healing begins [14].

The second useful classification of RAS is clinical, based on severity of affliction. Simple aphthosis represents the more usual scenario of episodic lesions that are few in number, healing within 1 to 2 weeks, and recurring infrequently. Conversely, complex aphthosis is a more severe phenomenon presenting as a clinical picture of severe, numerous, large, deep lesions, which are persistent, slow to resolve, and associated with marked pain or disability. New lesions may typically develop as older lesions resolve such that patients are frequently seldom disease-free. Occasionally, RAS may be part of a multisystem disease, such as Behçet's syndrome; fever, aphthosis, pharyngitis, and adenitis syndrome; or mouth and genital ulcers with inflamed cartilage syndrome [15]. Because the mouth is the origin of the gastrointestinal system, RAS is also seen with chronic inflammatory bowel disease including Crohn's disease, ulcerative colitis, or gluten-sensitive



Fig. 6. Herpetiform ulcers. A clustered group of aphthous ulcers on the mucosal lip, described morphologically as herpetiform in arrangement.

Table 1
Diagnosis of oral ulcers based on morphology

Morphology	Diagnosis
Discrete	Trauma
	Minor and major RAS
	Syphilis
Grouped	Viral
	Herpetiform RAS
	Recurrent intraoral HSV
	Zoster
Large	Major RAS
	EM
	Syphilis
Small	Minor RAS
	Cyclic neutropenia

Abbreviations: EM, erythema multiforme; HSV, herpes simplex virus; RAS, recurrent aphthous stomatitis.

enteropathy [16]. Hematinic deficiencies of iron, folate, and vitamin B₁₂ have also been linked to etiopathogenesis of aphthous stomatitis [17,18]. Although associated with these and other entities, such as menstrual irregularity or hematologic malignancy, only 40% of patients suffering from complex aphthosis have causes that remain idiopathic and are likely caused by multiple interrelated factors. It is postulated that cross-reaction occurs between the oral epithelium and microbial microorganisms, acting as

Table 2
Diagnosis of oral ulcers based on location

Location	Diagnosis
Interdental	ANUG
	AHGS
	Recurrent intraoral HSV
Masticatory mucosa (keratinized)	Cyclic neutropenia
	HSV
	Zoster
	Trauma
Nonattached mucosa	RAS
	Viral
	Syphilis
	Trauma
	EM
Posterior	Viral
	RAS
Diffuse	EM
	ANUG
	AHGS

Abbreviations: AHGS, acute herpes simplex virus gingivostomatitis; ANUG, acute necrotizing ulcerative gingivostomatitis; EM, erythema multiforme; HSV, herpes simplex virus; RAS, recurrent aphthous stomatitis.

an antigenic stimulus to humoral antibodies and cell-mediated immune responses. These act jointly or independently, producing ulceration of the mucosal surface [9,19,20].

Clinically, the major differential of RAS is the recurrent herpetic ulcer caused by herpes simplex virus (HSV) infection. These two common forms of acute recurrent ulceration can be distinguished primarily on the basis of location (Table 2). RAS ulcers occur on loosely attached, nonkeratinized mucosa. This includes the buccal mucosa, labial mucosa, floor of the mouth, and ventral surface of the tongue. This contrasts with herpetic ulcers, which affect keratinized mucosa [21,22]. Keratinized areas are intimately part of the masticatory process, including the hard palate, attached gingivae, and dorsal tongue, and are subject to routine oral trauma. In general, RAS is more common than recurrent intraoral HSV infection. Lesions of RAS do not have a vesicular phase and are usually larger than the individual ulcers of HSV infection (Table 3) [21].

Recurrent intraoral HSV stomatitis

Herpes simplex virus infection occurs uncommonly on intraoral locations. There are two distinct forms of herpetic infections that involve the oral cavity. Primary herpetic infection is known as *acute herpetic gingivostomatitis* and occurs following initial infection with the (HSV) virus. Patients usually have systemic manifestations accompanying infection, and are most often children because primary infection occurs typically before adulthood.

Recurrent HSV infection manifests as one of two entities. The most common form of recurrent infec-



Fig. 7. Recurrent intraoral herpes simplex virus infection with grouped, small punched-out ulcers on the keratinized surface of the hard palate and attached gingivae.

tion is herpes simplex labialis, otherwise known as *cold sores* or *fever blisters*. These typically occur on the cutaneous lip and vermillion and do not form within the spectrum of intraoral ulceration. A more unusual form of recurrent herpetic infection, however, is intraoral herpesvirus infection [22,23]. It is likely that many patients with intraoral HSV infection are asymptomatic and unaware of infection. When lesions are evident, however, the appearance of the HSV ulcer may be clinically indistinguishable from RAS on morphology alone. Intraoral HSV infection, like RAS, may be precipitated by minor trauma. The major distinguishing feature of HSV infection from RAS is site of involvement. HSV infection typically affects keratinized surfaces where mucosa is tightly adherent to underlying bone (Fig. 7) [9,20,22,23]. Conversely, RAS, as indicated, rarely develops on keratinized mucosa and is usually on the loose mucosal surfaces. The difference in location of recurrent HSV versus RAS is well recognized as being the key clinical feature allowing diagnosis (see Table 2) [22,23]. It has also been suggested that the pain of herpes infection is usually mild in severity, contrasting with RAS, which is frequently intensely painful. Intraoral HSV lesions are often grouped (see Table 3).

Confirmation of HSV infection can usually be achieved by cytology or viral cultures, which are both reliable diagnostic methods [24,25]. Exfoliative cytology (Tzanck smear) obtained from an ulcer base may demonstrate typical features of intracellular viral infection with a ground-glass appearance to the nuclear chromatin and multinucleated giant cells. The Tzanck smear is probably the best way to obtain rapid results at low cost. Culture is traditionally the gold standard. When performing a culture, the ulcer base should be swabbed vigorously because HSV is an

Table 3

Discriminating features of RAS versus recurrent intraoral HSV infection

	RAS	HSV
Location	Loosely attached, nonkeratinized mucosa, including lateral and ventral tongue	Keratinized mucosa adherent to underlying bone and dorsal tongue (masticatory mucosa)
Frequency	Common	Uncommon
Pain	Intensely painful	Mild
Morphology	Variable	Usually grouped
Size	Typically larger than HSV	Usually small, discrete
Vesicular phase	None	Initially

Abbreviations: HSV, herpes simplex virus; RAS, recurrent aphthous stomatitis.

intracellular infection, and adequate cell sampling is required. More recently, however, DNA amplification techniques, such as polymerase chain reaction, are available in some institutions, which are able to demonstrate minute levels of DNA in infected tissue. This is more rapid and sensitive than viral culture [26–28]. Should culture or cytology fail to demonstrate HSV infection, a biopsy may be helpful in confirming diagnosis. This is particularly useful in the immunocompromised patient where ulcers may be atypical. In the immunocompromised patient, intraoral HSV infection can occur on any location, making differentiation from RAS almost impossible. This is not the case, however, in immunocompetent patients.

Cyclic neutropenia

Cyclic neutropenia is a rare cause of recurrent oral ulceration. Again, the lesions clinically resemble either recurrent intraoral HSV infection or RAS; however, differentiation is usually made on the basis of other features (see Fig. 1B). Patients usually present in childhood with recurrent ulceration in a very cyclic fashion, recurring with predictable periodicity. The rhythmicity is constant for each patient [29]. In addition, patients are systemically unwell at the time of oral ulceration, with accompanying fever, malaise, lymphadenopathy, and other constitutional symptoms. Cyclic neutropenia is thought to be the result of an arrest in the maturation of polymorphonuclear leukocyte, precipitating an eruption of oral ulcers at a predictable time. The diagnosis can be confirmed by the demonstration of neutropenia (may be less than $500/\text{mm}^3$) on a full blood count during

episodes of ulceration, and the association with other recurrent infections. Cyclic neutropenia is a rare disorder, and although it should be borne in mind when considering the differential of oral ulcers, it is not common in day-to-day practice.

Systemic disease

Ulcerations of the oral mucosa may be part of a multisystem disease where involvement of the oral mucosa is a manifestation of more widespread mucosal involvement. About 15% of patients with complex aphthosis have a systemic disorder, such as Behçet's syndrome, inflammatory bowel disease, gluten-sensitive enteropathy, or rarely Wegener's granulomatosis (Fig. 8) [15,19,30–35]. In this case, the oral ulcers are mucocutaneous markers of systemic disease [9,35]. The patient may give a history of ulceration affecting other mucosal sites or symptoms of gastrointestinal involvement, providing clues to diagnosis. Serologic screening including antinuclear antibody tests (ANA), endomysial and tissue transglutaminase antibody tests, and a multisystem evaluation, is important in patients with systemic symptoms.

The HIV infection is another multisystem disorder, which can have oral ulceration as part of its protean manifestations. Patients with HIV infection may have very large, painful, or unusual oral ulcerations, which are refractory to standard therapy. Recurrent episodes of oral ulceration may be more severe and more prolonged than in immunocompromised patients, and diagnosis of HIV should be borne in mind when evaluating patients with an atypical presentation or unusually severe symptomatology.

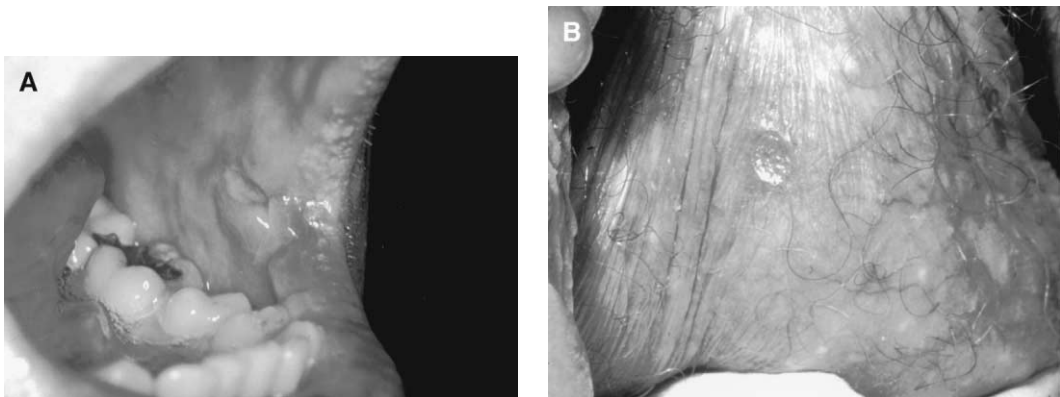


Fig. 8. Large aphthous ulceration of both oral and genital regions in a patient with Behçet's syndrome. (A) Buccal mucosa. (B) Scrotum.

Nutritional deficiencies

Nutritional deficiencies have been implicated as a cause of oral ulceration, and as many as 15% to 25% of patients with complex aphthosis may have an associated hematinic deficiency (see Fig. 1) [9,17,18]. These include iron deficiency anemia, folate, zinc, or vitamin B₁₂ deficiency. These dietary deficiencies easily can be screened on basic laboratory testing and if present are easily correctable.

Isolated oral ulceration

There are multiple causes of an isolated episode of oral ulceration. Such episodes may not necessarily come to the attention of the clinician because they are short-lived, and many patients are cognizant of the cause of their oral discomfort, and do not seek medical consultation. It is, however, useful to have a working approach to the evaluation of an acute isolated episode of oral ulceration (see Fig. 1B).

Trauma

Traumatic ulcers may be inflicted by the patient, or iatrogenically during dental procedures. Thermal burns may be sustained during ingestion of hot retentive foods (such as cheese), which may adhere to the mucosal surface, particularly the palate. This is known as the “pepperoni pizza burn.”

An ill-fitting denture, broken tooth, or dental appliance is more likely to cause recurrent or persistent oral ulceration, but dental procedures can result in inadvertent trauma. This may be the result of lip biting following an anesthetic procedure, or be directly caused by dental instrumentation or manipulation within the oral cavity. The patient usually identifies this with ease.

Other factitial causes of ulceration include traumatic injuries frequently seen in children with ulceration sustained during a fall with a popsicle stick, pencils, or other sharp or pointed object.

Drugs

Drug-induced oral ulceration is rare but should be borne in mind when evaluating oral ulcers. Most often, a drug etiology is considered in the evaluation of a chronic oral ulcer, but all chronic ulcers start out as acute, and a detailed drug history is important when evaluating recent-onset oral ulceration without other apparent cause. Drugs that have been impli-

Box 1. List of drugs implicated in producing oral ulceration

Antithyroid drugs
 Nicorandil [59]
 Hydroxyurea [39]
 Alendronate [38]
 Calcium channel blockers [37]
 Captopril
 Nonsteroidal anti-inflammatory drugs
 Piroxicam, indomethacin, ibuprofen
 Cytotoxic drugs
 Methotrexate, doxorubicin

cated in the development of oral ulceration are listed in Box 1 [36].

The drugs most commonly associated with oral ulceration are the antineoplastic chemotherapeutic agents and the nonsteroidal anti-inflammatory drugs. As new drugs are developed, however, the list of medications that have the potential to create untoward reactions, such as oral ulceration, continues to expand [37–39]. Drug-induced ulceration may occur on the basis of either immunologic or nonimmunologic mechanisms. In the immunologic mechanism, the drug or a component triggers an immune response producing a reaction directed at the epithelial surface. Humoral immunity is predominantly involved in this type of reaction. The likelihood of such reaction depends on the innate immunogenicity of the drug, the frequency, the route of administration, and the inborn reactivity of the patient’s immune system. With cell-mediated immunity, T cells may be simulated by antigen-presenting cells, resulting in the release of cytokines and other immune inflammatory mediators. This brings about a local cytotoxic effect with ulceration.

In a nonimmunologic reaction, a drug directly stimulates monocytes or lymphocytes to release cytotoxic chemical mediators. No immune response is involved in this situation, and these reactions are not antibody dependent.

Drug-induced ulcers are often large, isolated, and are often formed along the lateral borders of the tongue. They may have a white halo and be extremely persistent, progressing to chronic ulcers, which persist for months or years [37]. Diagnosis is based on an appropriate drug history and the response to withdrawal of potential drug culprits.

Stevens-Johnson syndrome (erythema multiforme major) represents the severe end of the spectrum of drug-induced ulceration and can be seen with numer-

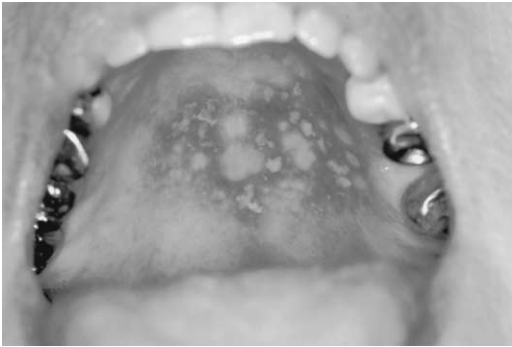


Fig. 9. Erythema multiforme with a large area of erosion and sloughing on the hard palate.

ous medications, although the sulfonamides are most frequently implicated (Fig. 9). Erythema multiforme has also been attributed to infective etiologies, most commonly HSV infection (see Fig. 9) [40].

Iatrogenic

Chemotherapy

Intensive anticancer therapy affects not only malignant cells but is also toxic to normal tissues. This can result in disruption of the mucosal barrier of the mouth, allowing subsequent infection by both acquired and endogenous organisms, which become pathogenic, perpetuating the mucositis and ulceration. Controlling infectious components by antiseptic mouthwashes until the mucosal barrier is allowed to regenerate can reduce the morbidity of chemotherapy-induced mucositis and ulceration. Mucosal protectants may also reduce the mucositis.

Radiation injury

Management of head and neck cancers with external beam radiation typically produces mucosal ulceration, with desquamation 2 to 3 weeks after the introduction of therapy. The severity of ulceration depends on the extent of treatment and on the pre-existing condition of the oral mucosa. Typically, radiation mucositis resolves between 2 weeks and 2 months following the termination of treatment [4]. Radiation is not usually associated with increased outbreaks of recurrent HSV, but is associated with bacterial colonization by both fungi and gram-negative infections [41,42]. Patients wearing dentures or other dental appliances are particularly at risk for ulceration following radiotherapy, and may warrant a dental consult before initiation of therapy. Treatment should be aimed at reducing pain and inflammation, and managing the secondary colonization.

Bacterial infection

Several bacteria can be responsible for producing ulceration of the oral mucosa.

Acute necrotizing ulcerative gingivitis

(“trench mouth”)

Acute necrotizing ulcerative gingivitis is an ulcerative disease of the gingiva typically of sudden onset. It is a destructive periodontal infection that primarily affects the gingiva, although other areas may be involved (see Table 2). It is encountered in susceptible individuals, who are usually either malnourished or immunocompromised. In developed countries it is more typical in young adults with risk factors, such as fatigue, smoking, and poor oral hygiene [4,43]. In less developed countries it occurs in malnourished children. The disease is associated with lymphadenopathy; fever and malaise may or may not be present. The gingiva are bright red and hemorrhagic, and painful (Fig. 10).

Ulcerations first appear on the interdental papillae (the triangular tissue between adjacent teeth) and are not vesicular. The ulcers extend along the margin of the gingivae, ultimately being covered by a necrotic gray-white pseudomembrane. Invasive and anaerobic bacteria are causative, but impaired host resistance is usually a factor because the bacteria are opportunistic endogenous organisms [43]. It is not communicable. Treatment is aimed at local debridement, irrigation, and appropriate antibiotic therapy.

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum*. All three stages of syphilis may be associated with mucosal ulceration. In primary syphilis, the



Fig. 10. Acute necrotizing ulcerative gingivostomatitis. Boggy erythematous and inflamed gingiva affecting in particular the interdental papillae.

lesions are known as *chancres* and occur at the site of penetration of the organism into the mucosa. This is a painless, indurated ulcer with a raised border, which may last several weeks. The lesions are not exudative and ultimately heal without scarring.

In secondary syphilis, the oral lesions are diverse, including a nonspecific pharyngitis, glistening plaques, and oral ulcers (Fig. 11) [44]. The most characteristic oral manifestation is the mucous patch (Fig. 12). This is a shallow, irregular ulceration covered by a gray-white necrotic membrane, with surrounding erythema. Lesions are occasionally painful. Snail-track ulcers result when multiple mucous patches become confluent.

Lesions of tertiary syphilis manifest as locally destructive granulomas (gummas), or as glossitis with mucosal atrophy; the latter tending to malignant transformation (Fig. 13). Oral lesions of syphilis are uncommonly encountered, but with the increasing incidence of HIV infection, it is important to consider lues in the evaluation of unusual oral lesions.

Gonorrhea

Gonorrhea is caused by the gram-negative bacteria *Neisseria gonorrhoea*, and is transmitted sexually. The oral mucosa can be involved through orogenital contact. Although oral gonorrhea is rare, patients can present with multiple ulcers and a fiery red appearance to the mucosa with scattered white pseudomembranes [1]. Patients with this infection may be asymptomatic, or present with severe oral symptoms and complaints of a sore throat. Lymphadenopathy may be associated. The lesions of oral gonorrhea, however, are not specific and may mimic a wide variety of other diseases including HSV, erythema multiforme, and the immunobullous diseases.

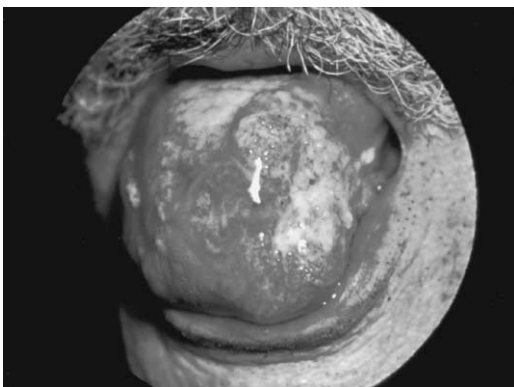


Fig. 11. Extensive luteic leukoplakia in a patient with secondary syphilis.

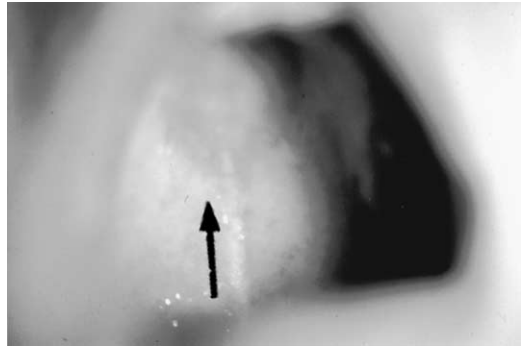


Fig. 12. The mucous patch of secondary syphilis. An ill-defined slightly eroded erythematous plaque on the posterior pharynx.

Rhinoscleroma

Rhinoscleroma is a rare disease caused by *Klebsiella rhinoscleromatis*. Infection produces proliferative granulomas within the oral mucosa, which may, on occasion, ulcerate.

Tuberculosis

Mycobacterium tuberculosis present in sputum can invade the oral mucosa producing nonhealing indurated ulcers. These ulcers are typically chronic in nature. A granulomatous inflammation is produced with associated caseous necrosis. These lesions are not distinctive, and diagnosis requires tissue culture.

Histoplasmosis

In patients with disseminated histoplasmosis, oral ulcers may occur [1]. There are usually multiple areas of involvement, affecting the larynx, posterior tongue, palate, and buccal mucosa with associated



Fig. 13. The rubbery, well-demarcated gumma of tertiary syphilis seen on the lateral and dorsal tongue.



Fig. 14. Histoplasmosis infection of the tongue with diffuse involvement.

pain, weight loss, and hoarseness (Fig. 14). Biopsy and culture confirm the diagnosis.

Viral infection

There are several viral families capable of both direct infection of the oral mucosa and the production of characteristic enanthems. These can produce acute ulceration (see Fig. 1B). Viral infections of the oral



Fig. 15. Acute herpes simplex virus gingivostomatitis in a young adult, presenting with systemic symptoms and extensive areas of ulceration and sloughing affecting the labial mucosa and gingivae of the lower alveolar ridge.

mucosa are reviewed by Hairston, Bruce, and Rogers in this issue.

Herpes simplex virus

Primary HSV infection refers to initial infection of the oral mucosa with the herpes virus. This is known as *primary (acute) herpetic gingivostomatitis*. Primary infection, unlike recurrent HSV, affects both the keratinized and nonkeratinized mucosal surfaces (Fig. 15). Acute herpetic gingivostomatitis infection typically occurs in childhood. It is currently thought that most primary HSV infections in children and young adults are asymptomatic or subclinical. Active disease produces widespread areas of vesiculation, which rapidly ulcerate. Pharyngitis, fever, and lymphadenopathy accompany infection (Fig. 16). Lesions can affect the lip, the labial commissures, or even the face and the intraoral mucosa. Infection usually resolves within 7 to 10 days in immunocompetent patients.

Zoster

Varicella zoster virus (VZV) may affect the oral mucosa with two distinct entities. The first is caused by primary VZV infection (chicken pox). In this setting, shallow, vesicular ulcers occur on the oral mucosa in association with cutaneous vesicles (Fig. 17). The infection is usually seen in childhood and early adolescence, although it is becoming rare in this age group since the introduction of the varicella zoster vaccine.



Fig. 16. Acute herpes simplex virus gingivostomatitis producing ulceration of the posterior pharynx and soft palate. The posterior pharyngitis form of primary herpes simplex virus infection is seen more typically in young adults, rather than children.

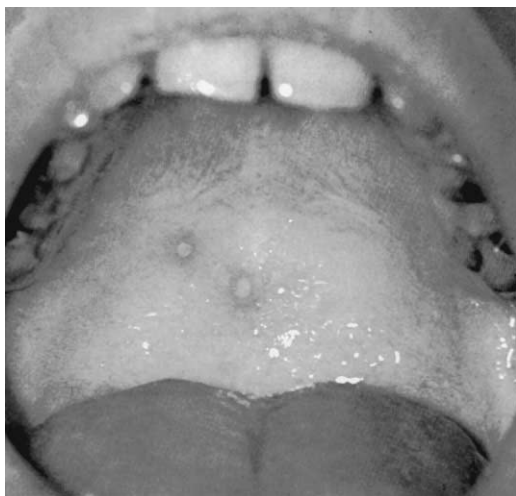


Fig. 17. Papulovesicles occurring intraorally in a patient with chicken pox and simultaneous cutaneous lesions.

The course is usually uncomplicated in normal children, and the oral lesions resolve rapidly. Confirmatory testing is seldom necessary because the clinical features are characteristic [45]. Reactivation of VZV in adulthood (following childhood infection) produces lesions characteristically known as *zoster* (shingles). VZV remains dormant within neural tissue, and reactivation produces a cutaneous eruption in a dermatomal distribution, corresponding to the affected nerve root [46–48]. VZV involving branches of the trigeminal nerve may produce oral ulcers. These lesions are highly characteristic, because they are unilateral with preceding pain and dysesthesia. Oral vesicles rapidly erode into ulcers, which may involve the palate, buccal mucosa, tongue, or pharynx (Fig. 18). Therapy for



Fig. 18. Shingles. Unilateral clustered vesicles on the upper mucosal lip, associated with facial pain in a patient with recurrent zoster. Distribution follows the mandibular division of the trigeminal nerve.

Table 4
Available therapies for managing oral ulcers

Preventative	Stop smoking
	Adjust diet
	Reduce oral trauma
	Correct nutritional deficiencies
Supportive	Correct poor oral hygiene and dental caries
	Fluids
	Antipyretics Acetaminophen
	Analgesics Acetaminophen Narcotics if needed
Topical therapies	Maintenance of oral hygiene
	Hydrogen peroxide 1% as a mouthwash
	Topical analgesics
	2% viscous lidocaine directly to lesions
	2.5 mL lidocaine diluted in 10 mL of water as gargle
	Benzocaine preparations (Anbesol, Orajel Mouth-Aid)
	Diphenhydramine elixir 12.5 mL/5 mL as a mouthwash (Benadryl)
	Coating agents
	Antacids (Maalox, Milk of Magnesia, Kaopectate)
	Dental pastes: Orabase, Zilactin (applied with a cotton swab)
	Antiseptics
	Chlorhexidine (with severe infection [eg, ANUG])
Cetylpyridium chloride solution (Cepacol)	
Tetracycline oral suspension concentration swished 1–2 min qid, then expectorated	
Anti-inflammatories	
Amlexanox (Aphthasol)	
Systemic	Antiviral
Acyclovir, Famciclovir, Valacyclovir	
Antibacterial	
Penicillin (syphilis, ANUG)	
Tetracycline	
Metronidazole (ANUG)	
Antineutrophilic	
Colchicine (RAS)	
Dapsone (RAS)	
Immunosuppressive	
Azathioprine	
Cyclosporin	
Thalidomide	
Miscellaneous	
Pentoxifylline	

Abbreviations: ANUG, acute necrotizing ulcerative gingivostomatitis; RAS, recurrent aphthous stomatitis.

varicella zoster consists of supportive measures, and the use of antiviral drugs as dictated by the patient's immune status (Table 4).

Coxsackie virus

The Coxsackie virus produces an entity known as *hand-foot-and-mouth disease*, which accurately describes the cardinal clinical features. Hand-foot-and-mouth disease typically occurs in epidemics in young children [5,49]. There is a mild prodromal illness with a slight fever and flu-like symptoms. There is accompanied lymphadenopathy with the development of skin and oral lesions. The lesions develop as vesicles on a red base that may ulcerate. Lesions are seen not only on the oral mucosa of the soft palate, but also on the hands and feet as the name implies. Oral lesions may occur throughout the mouth but especially on the palate, tongue, and buccal mucosa.

Herpangina is also caused by Coxsackie virus infection, but lesions are usually limited to the soft palate and are not found on other cutaneous surfaces. Children are typically affected, with epidemics occurring in the summer and fall [50]. Systemic symptoms are mild, and lesions are localized to the mouth where vesicles are seen on the pharynx and posterior region of the mouth. Oral pain may be secondary to the pharyngitis associated with the disease. The disease runs a benign course, is self-limiting, and treatment is supportive. Specific viral cultures or evaluation are not necessary.

Rubeola

Infection with this virus produces measles. The primary oral feature is the Koplik's spot, which presents as a small erythematous macule on the buccal mucosa. It may have a white necrotic center. The lesions usually appear 1 to 2 days before systemic symptoms begin, and the oral lesions resolve rapidly. They are followed by the typical cutaneous exemplum of measles beginning on the head, neck, and progressing caudally.

Epstein-Barr virus

Infection with Epstein-Barr virus is often subclinical but can produce a glandular fever syndrome, which may be associated with oral ulcers on the posterior oropharynx. Infectious mononucleosis typically has associated features of profound fatigue, lymphadenopathy, and disturbance of liver function. Oral lesions are usually trivial. Diagnosis is usually made on the basis of a positive Monospot Test, which demonstrates the pathognomonic heterophile antibody.

Cytomegalovirus infection may have a similar clinical presentation to Epstein-Barr virus infection. Although usually an asymptomatic disease, it may, on occasion, produce oral lesions.

Approach to diagnosis

Accurate diagnosis of the cause of oral ulceration depends on an understanding and knowledge of the various patterns of oral ulcers as reviewed. There are several important features to be determined on history. These include differentiating acute from chronic oral ulcers based on the time frame and length of affliction. If an ulcer is acute in presentation, the clinician needs to determine whether this is an isolated episode or recurrent phenomenon. Determination of this allows differentiation into two differing subsets of etiology (see Fig. 1).

The presence of systemic features must be sought on direct inquiry. These include constitutional symptoms, such as fever, malaise, and weight loss; symptoms of gastrointestinal disturbance; genital or ocular involvement; or other features suggestive of systemic disease. A dietary history must be obtained and a detailed review of other medical illnesses and a thorough drug history. Patients who have symptoms suggestive of bowel involvement require further evaluation. In the absence of associated systemic features, further evaluation of patients with oral ulcers includes a full blood count and differential, screen for hematinic deficiencies, routine serum chemistry, thyroid screen, and an endomysial antibody (Box 2). The need for further investigation

Box 2. Evaluation of oral ulcers

Complete blood count and differential
 Hematinic screen (serum iron, ferritin, zinc, folate, B₁₂)
 Liver function, routine chemistry
 Sedimentation rate
 Serum endomysial antibodies for gluten-sensitive enteropathy
 Cytology (Tzanck smear)
 Culture (bacteria, viral, fungal); swab and tissue if indicated
 Biopsy: hematoxylin and eosin (direct and indirect immunofluorescence if indicated)
 Gastrointestinal evaluation if relevant

including culture, biopsy, or serologic studies is dictated by clinical impression.

Management

Management of oral ulcers often requires a comprehensive approach sometimes involving more than one subspecialty (see Table 4).

Management of underlying disease

Correction of causative factors needs to be addressed. Discontinuation of suspected medications may be necessary, and removal of potential irritant stimuli is indicated. The patient may need to be referred to dentistry to remove or repair ill-fitting dental appliances, correct rough-edged teeth, or attend to periodontal hygiene. If oral ulceration is part of a general multiorgan illness, this may need to be brought under control with immunosuppressive or other appropriate therapy. Primary nutritional deficiencies, or those secondary to inflammatory bowel disease, must be corrected (see Table 4).

Supportive measures

Irrespective of the cause of oral ulceration, attention must be given to immaculate oral hygiene. Patients should regularly cleanse their teeth using a soft-bristled toothbrush, fluoride toothpaste, and dental floss as necessary. Periodontal disease needs to be addressed. A dilute antiseptic or alkaline mouthwash is a useful adjuvant. Patients may need to adjust their diet, following a soft, bland diet eliminating sharp-edged, hard, acidic, or irritating foods, such as popcorn, chips, pretzels, and other salty foods. A gluten-free diet is indicated in patients with RAS secondary to celiac disease.

Symptomatic management is often adequate for many types of acute oral ulcers, particularly if short-lived. Topical anesthesia may be necessary to provide pain relief and allow patients to eat. This can be achieved by applying viscous lidocaine to the ulcer base with a cotton-tipped applicator. Alternatively, patients may gargle with viscous lidocaine (Xylocaine) diluted in water, swishing in the mouth for 2 to 3 minutes (half a teaspoon of Xylocaine to two teaspoons of water). Several other over-the-counter products are available to provide relief for oral ulcerations [51]. These include emollient dental pastes, such as Orabase. Cytoprotective or coating agents, such as Sucralfate (Carafate), or aluminum-magnesium antacids (Maalox) can be used as a gargle.

Maalox may be combined with a topical anesthetic, such as diphenhydramine (Benadryl), which provides additional relief (see Table 4).

Specific therapy

Corticosteroids

Corticosteroids are frequently used to shorten the duration and pain of an individual ulcer [52]. It must be remembered, however, that topical or systemic corticosteroids are contraindicated if the ulcer is caused by an infective etiology, either bacterial or viral (HSV). When appropriate, 0.1% triamcinolone acetonide (Kenalog) in an emollient dental paste, such as Orabase, can be used, applying to the mucosa several times a day. This may be sufficient for many patients. Other authors have suggested that a corticosteroid solution, such as a 0.1% solution of mometasone furoate, is a practical strategy for management of oral ulcers (three drops applied to the ulcer, massaged in with the tongue and expectorated) [53]. Other more potent topical corticosteroids, such as fluocinonide gel (Lidex) or clobetasol ointment (Temovate), are also effective. The preference of a gel versus an ointment or cream depends on physician preference and patient desire, but in general the authors favor the use of topical gels, which adhere reasonable well to the oral mucosa.

Numerous mouthwashes are available for symptomatic relief of ulcers. Most of these contain an antibacterial agent, which may have an anti-inflammatory and an analgesic property. Mouth rinses containing Triclosan (a lipid-soluble antimicrobial agent) have been shown to reduce the incidence of recurrent aphthous ulcers [54]. There are a variety of “magic mouthwashes” particular to various institutions, which usually contain a combination of tetracycline oral suspension and mycostatin, together with an anesthetic, such as diphenhydramine, and sometimes an additional corticosteroid component.

Anti-infective

In addition to control of oral microflora, systemic therapy with oral or occasionally intravenous antiviral or antibacterial antibiotic is sometimes necessary. Systemic acyclovir may be indicated for treatment of oral herpesvirus infection, particularly in severe disease or in immunocompromised individuals. Newer antiviral agents, such as famciclovir and valacyclovir, have more elegant and convenient dosing schedules, and are increasingly used in management of oral herpesvirus infections. Prophylactic antiviral therapy is helpful in managing recurrent episodes of intraoral HSV infection.

Systemic antibiotic treatment is generally necessary to control oral ulcers resulting from bacterial infections, particularly with severe gingival disease as seen in acute necrotizing ulcerative gingivitis. Specific infective diseases, such as syphilis, gonorrhea, and so forth, naturally require appropriately directed antibiotics.

Other agents

Additional or other therapeutics targeted to manage oral ulcers depend on the etiology. In the case of RAS, a number of regimens have been found to be effective including the use of colchicine, dapsone, pentoxifylline, and even transdermal nicotine patches [55–58]. Ulcers related to systemic disease usually require immunosuppressive therapy to achieve remission of disease. Detailed discussion on management of specific ulcer subsets is beyond the scope of this article.

Summary

In general, a detailed history and examination of the patient provides sufficient information for diagnosis. The pattern, frequency, and natural history of ulcer episodes are helpful. The presence or absence of associated features and the site of oral involvement guides most physicians accurately in the diagnosis. Additional investigations, including blood tests, and occasionally the use of oral cultures or biopsy, are needed to make a definitive diagnosis. A multispecialty approach is often necessary to evaluate patients with other systemic features.

Most acute oral ulcers heal spontaneously without specific therapy being necessary, but an understanding of the cause of the ulcer is reassuring to the patient and guides the clinician in management to prevent recurrent episodes of oral ulceration, or chronicity of ulcers.

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