Oral Infections

7

Introduction

Bacterial, fungal, and viral infections are frequently encountered in the oral cavity. The immune system, protective components in saliva, and mucosal integrity are all key elements that work in concert to prevent the development of infection. When any of these are compromised, the resulting imbalance increases the potential for commensal, latent, or invading organisms to cause disease. Behavioral factors, including diet, nutrition, hydration, and oral hygiene, also have a significant influence on an individual's risk. Medications play an important role: immunosuppressive and immunomodulatory agents alter immune function, broad spectrum antibiotics affect the ecological balance of the oral flora, and xerogenic agents impact on the composition and flow of saliva.

There is no single feature characterizing infection in the mouth; findings range from painful swelling to mucosal ulceration to painless papules. The clinical appearance may be similar to that of noninfectious conditions. Therefore, careful history taking and examination, identification of risk factors, and appropriate utilization and interpretation of diagnostic tests (see Chap.3) are critical. The clinical presentation of some infections may be altered in the *immunocompromised* patient: the anatomic distribution of lesions can be quite different, typical signs of infection may be diminished or absent, and standard doses of therapeutic medications may be ineffective. Failure to diagnose and initiate appropriate therapy in these patients can result in needless pain and suffering as well as progression to systemic infection.

Bacterial Infections

Oral bacterial infections are most commonly of dental origin and can progress to abscess formation with potentially significant complications if left untreated. In an otherwise healthy individual, it is exceedingly rare for a nonodontogenic bacterial infection to develop within the oral cavity. Infection rarely occurs following oral surgical procedures (such as tooth extraction and soft tissue biopsy) or minor trauma. Infection of the salivary glands is uncommon and mucosal infection outside of the periodontium (e.g., other than gingivitis and periodonti-

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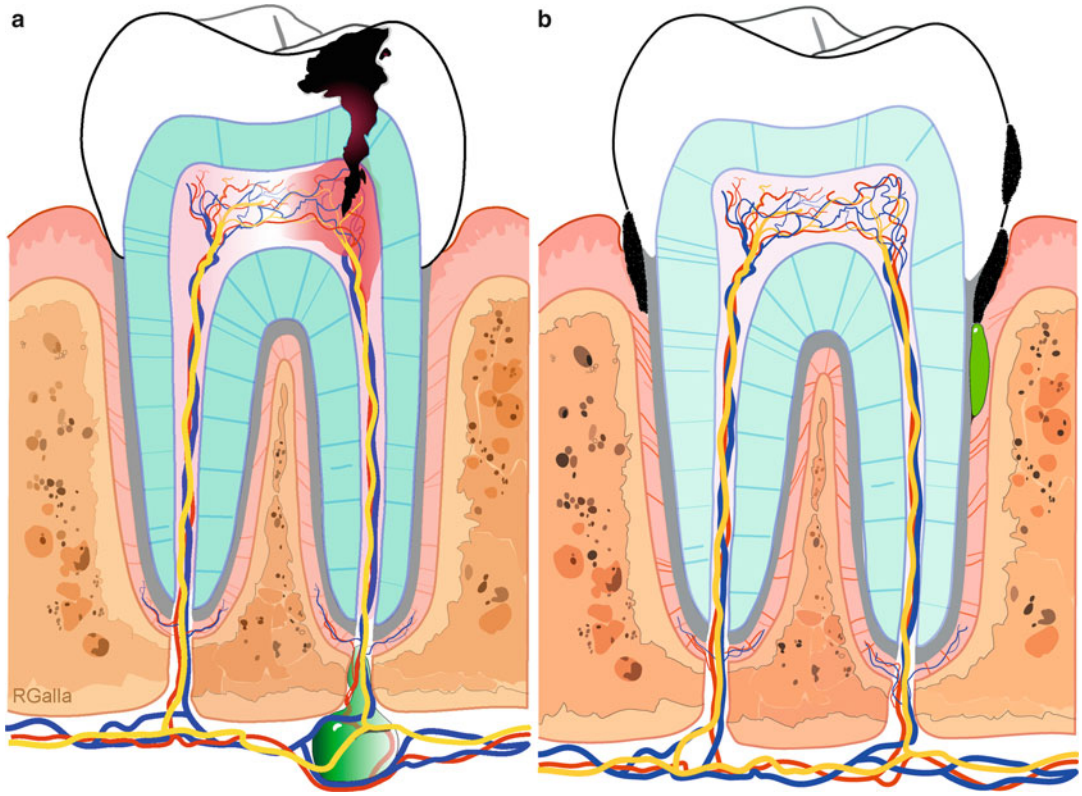

Fig. 7.1 Odontogenic infection. (**a**) Caries is seen extending through the calcified enamel and dentin of the crown with pulpal involvement. A periapical abscess has formed at a root apex (illustrated in *green*) representing extension of necrotic material from the pulp chamber into the alveolar bone through the apical foramen. (**b**) Accumulation of calculus on the crown and root surface (subgingival and supragingival; illustrated in *black*) with deepening of the gingival crevice and formation of a periodontal pocket. Note also how a periodontal abscess (illustrated in *green*) may form in this situation

tis) is generally only encountered in those who are immunosuppressed.

Odontogenic Infections

Odontogenic infections can be broadly classified as either *endodontal*, which are characterized by infection of the dental pulp initiated by dental caries; or *periodontal*, which are characterized by infection of the tooth's supporting structures initiated by accumulation of plaque and calculus (Fig. 7.1). In both cases, the primary risk factors include inadequate oral hygiene with dental plaque accumulation. While the reasons are not entirely clear, many patients with high caries rates often have minimal periodontal disease, whereas patients with advanced periodontal disease often have few caries.

Dental Caries

Caries are caused by the metabolism of sugar in dental plaque by *Streptococcus mutans*, resulting in the production of acid and subsequent demineralization of the protective enamel layer. The destructive process advances inward toward

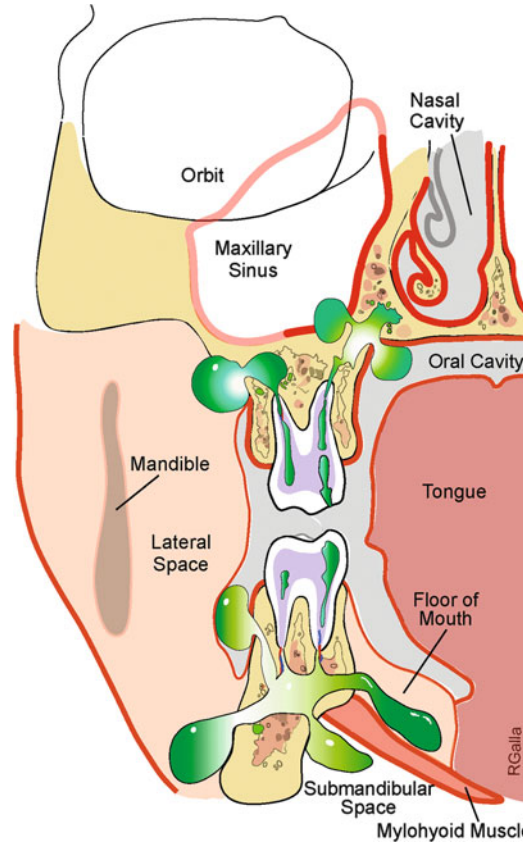

Fig. 7.2 Potential pathways of spread of odontogenic infection illustrated on a coronal diagram. Infection (illustrated in *green*) takes the path of least resistance and can emerge from the alveolar bone into the vestibule, floor of mouth, submandibular space, maxillary sinus, nasal cavity, palate, and lateral muscular space surrounding the mandibular ramus

the pulp, and in the absence of treatment, results in pulpal necrosis and potential abscess formation (Fig. 7.2). Infected material drains from the pulp chamber through the apical foramen into surrounding bone, causing abscess formation at the root apex (*periapical abscess*; Fig. 7.3). From there infection can spread to other parts of the oral cavity, face, or neck and lead to potentially life-threatening soft tissue infections such as Ludwig angina, deep neck abscess, necrotizing fasciitis, and mediastinitis (Figs. 7.4, 7.5, and 7.6). Infection in molars can result in *trismus* (limitation of mouth opening) due to inflammation of the adjacent masticatory muscles (Fig. 7.7).

Decay can form on any tooth surface, but frequently affects the occlusal surfaces of posterior teeth due to the presence of anatomic pits and fissures. The interproximal surfaces are also commonly affected because plaque can be difficult to remove from these areas. The facial surfaces near the gingival margin and exposed root surfaces are particularly susceptible because they are covered with cementum, which is much softer than enamel. Early lesions may show areas of decalcification on the enamel, and are character-

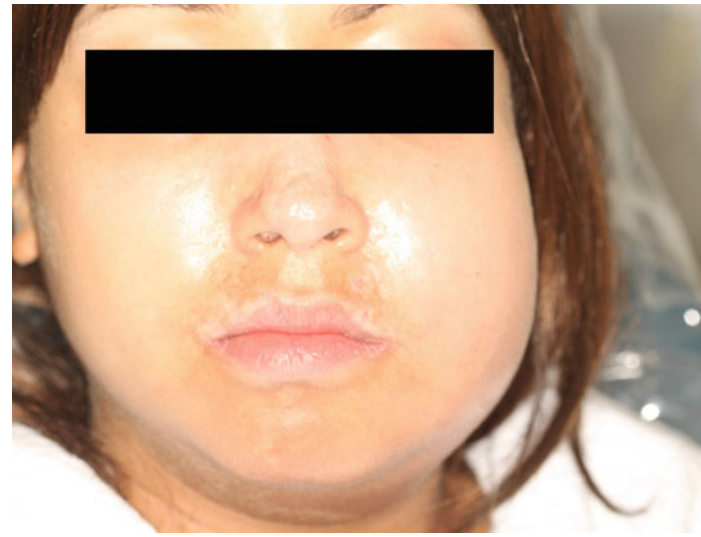

Fig. 7.3 Left facial swelling associated with a decayed and abscessed mandibular molar

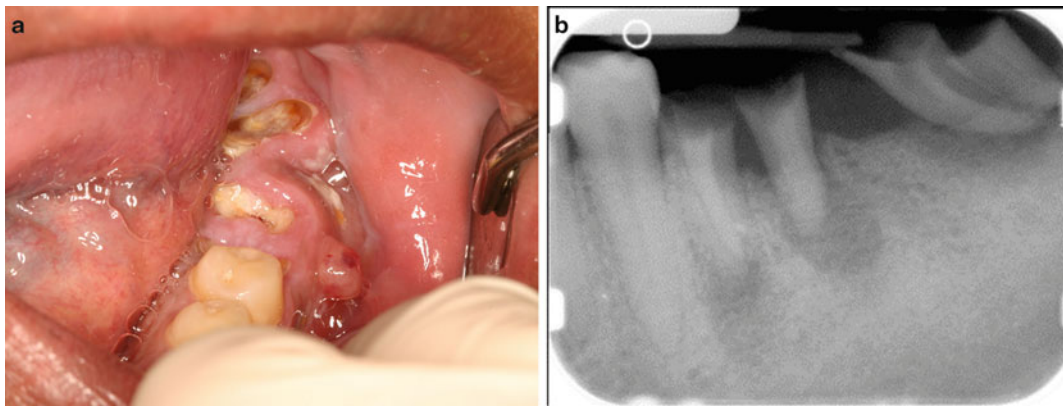

Fig. 7.4 Left mandibular gingival swelling due to a draining abscess (**a**) associated with the remaining decayed and broken down molar roots. (**b**) Periapical radiograph demonstrating periapical radiolucencies associated with the remaining root tips

ized by white spots that may collapse under the pressure of a dental instrument (Fig. 7.8). More advanced lesions demonstrate obvious cavitation with brownish-black discoloration (Figs. 7.9 and 7.10). Entire sections of the tooth may fracture and exposure of the pulp chamber may be evident (Fig. 7.11).

Intraoral dental radiographs are used to diagnose caries, which appear as distinct areas of radiolucency within the tooth structure (Fig. 7.12). These can also demonstrate the presence of a *periapical radiolucency*, indicative of pulpal pathology (Figs. 7.4, 7.5, and 7.6). Computed tomography (CT) may be indicated if extensive soft tissue swelling is present and there is concern for progression of infection into the deep spaces of the neck (Fig. 7.13). When dental infection is suspected, the patient should be referred to a dentist or other oral health care specialist for further evaluation.

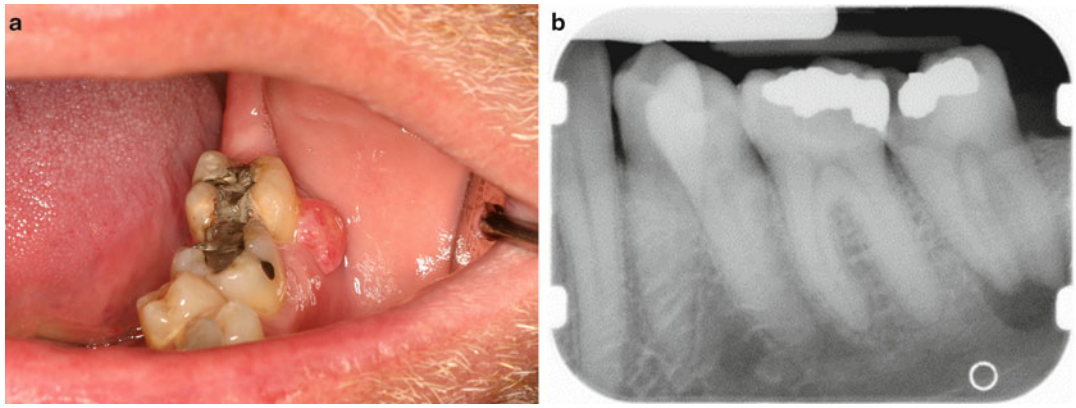

Fig. 7.5 Left mandibular gingival swelling (**a**) associated with abscessed second molar with a fractured amalgam restoration with underlying recurrent caries. (**b**) Periapical radiograph showing dental caries extending into the pulp with well-defined periapical radiolucency

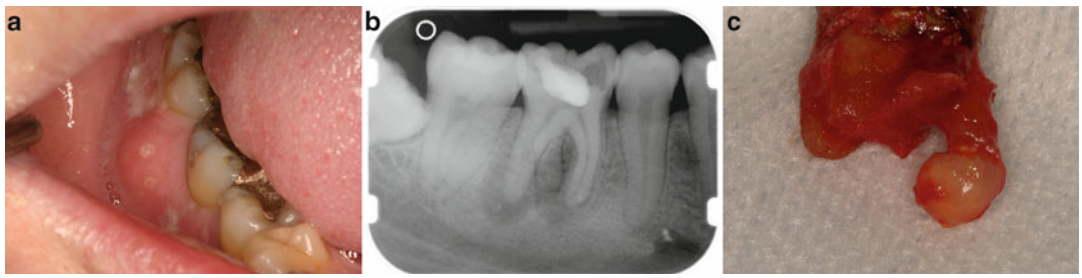

Fig. 7.6 Periapical pathology. (**a**) Abscessed mandibular first molar with adjacent gingival swelling. (**b**) Periapical radiograph (not the same patient) showing caries extending into the pulp chamber and periapical radiolucencies. (**c**) Extracted molar with attached periapical lesion; histopathological evaluation is required to differentiate between a *granuloma* versus *radicular cyst*

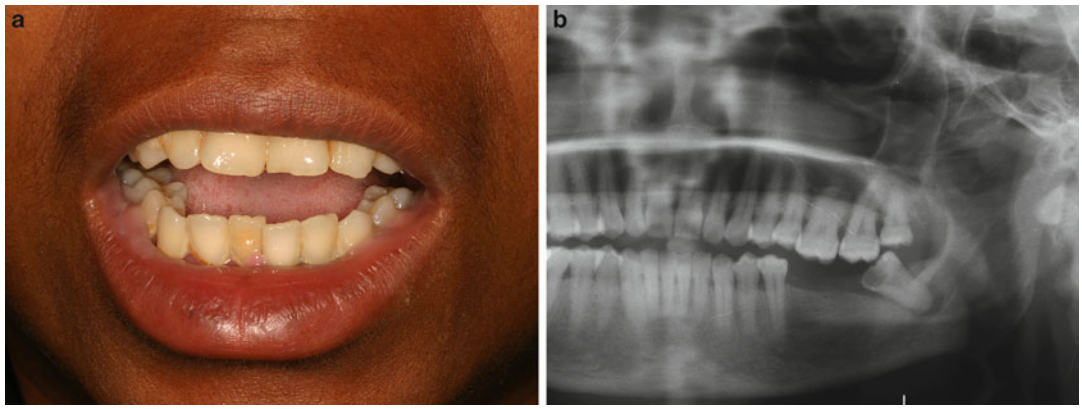

Fig. 7.7 Severe trismus in a patient with an abscessed third molar. (**a**) This is the widest opening that the patient is able to achieve. (**b**) Panoramic radiograph showing the mandibular left third molar with extensive caries and large periapical radiolucency

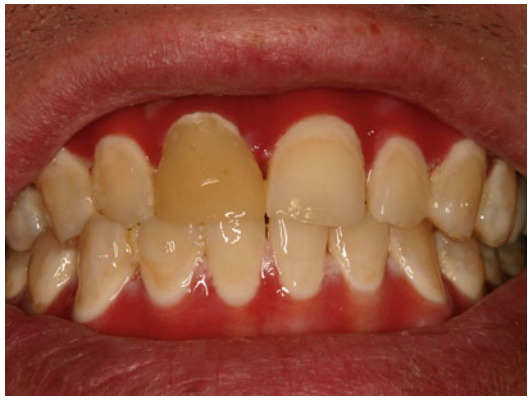

Fig. 7.8 Generalized decalcification or "white spots" along the cervical margins. Caries are most likely already present in many of these areas. The right maxillary central incisor is restored with a temporary crown made of an acrylic material

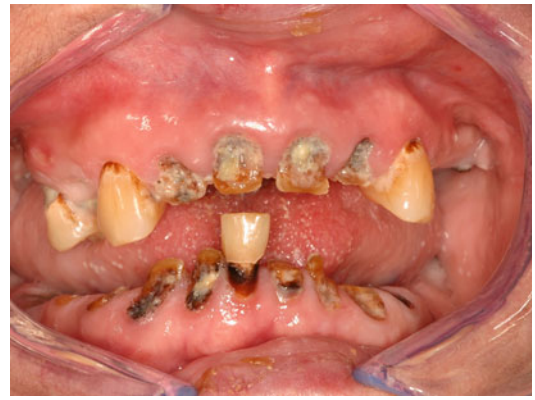

Fig. 7.11 Rampant decay in a patient several years after completion of radiation therapy for head and neck cancer. Numerous teeth are fractured at the cervical margin and the pulp chambers are exposed

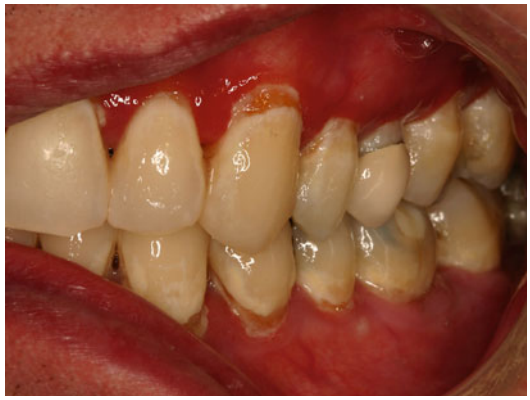

Fig. 7.9 Generalized cervical caries with loss of enamel and brown discoloration. This pattern of dental caries is often seen in patients with salivary gland hypofunction

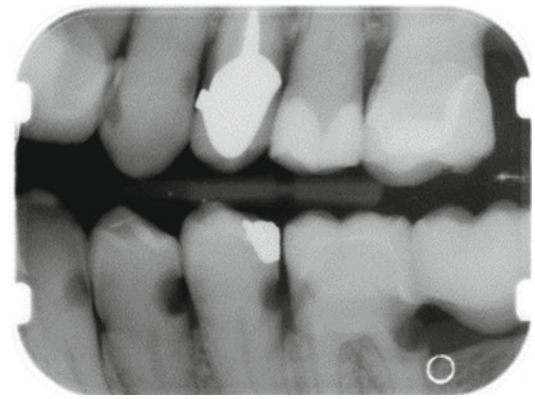

Fig. 7.12 Bitewing radiograph demonstrating interproximal decay on the root surfaces of the posterior maxillary teeth. The areas of decay appear as rounded radiolucent lesions

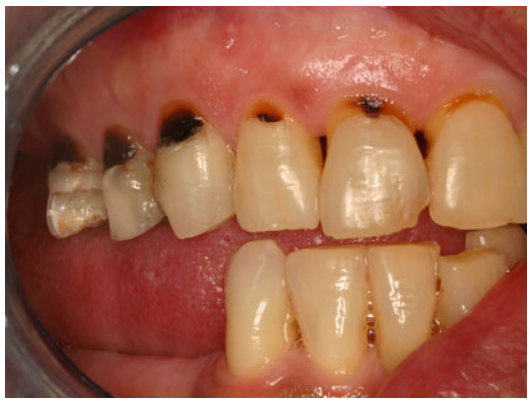

Fig. 7.10 Dark brown cervical caries. Dental caries that are longstanding or "arrested" tend to become darker in appearance over time

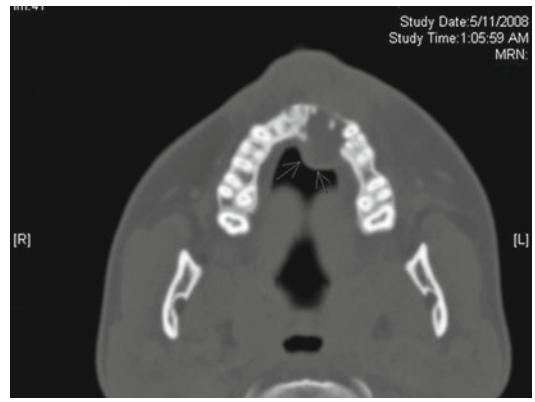

Fig. 7.13 Axial CT scan demonstrating a large abscess associated with the maxillary left lateral incisor with destruction of palatal bone and extensive soft tissue swelling

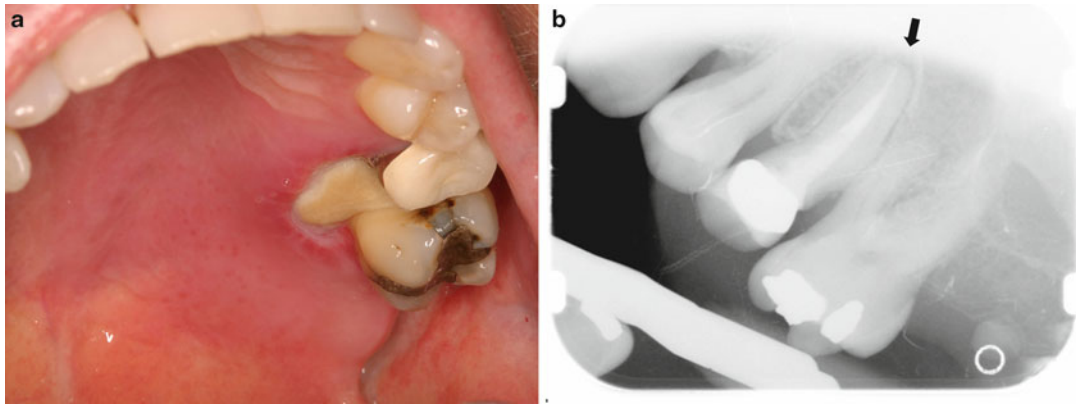

Fig. 7.14 Abscessed premolar in a patient with advanced refractory acute myelogenous leukemia. (**a**) Secondary neutropenic ulceration of the palate due to spread of infection. (**b**) Periapical radiograph showing adequate-appearing endodontic fill with a small periapical radiolucency (arrow)

As long as the pulp chamber has not been breached, caries can be mechanically removed and the tooth can be restored with a variety of dental materials. With pulpal involvement, endodontic therapy (*root canal therapy*) or extraction of the tooth is required. Endodontic treatment involves removal of neurovascular tissue from the pulp chamber and replacement with an inert material such as gutta-percha. In cases of localized intraoral swelling, incision and drainage may also be necessary in conjunction with definitive treatment of the tooth.

The only significant medical risk factor for the development of dental caries is reduced salivary function (see Chap. 8). In patients with profound neutropenia, previously latent or subclinical periapical infections can become acutely active with soft tissue swelling or localized gingival and mucosal necrosis (Fig. 7.14). Antibiotics should be given in these situations, as well as in cases of significant soft tissue swelling. Otherwise, the decision to prescribe antibiotics will depend on the individual clinical situation.

The mainstays of caries prevention involve attention to diet, maintenance of oral hygiene, and use of fluoride. Overall consumption of carbohydrate and frequency of exposure are both important. For example, an individual who ingests snacks or sugary beverages frequently throughout the day is at higher risk for caries than someone who eats only three meals per day and drinks water. Brushing with a soft toothbrush and fluoride toothpaste for 2 min at least twice daily (ideally after every meal) removes dental plaque accumulation and significantly reduces the risk of dental caries. Daily use of dental floss removes plaque from the interproximal regions, which are otherwise difficult areas to clean. Systemic fluoride, usually obtained through fluoridated water, is important during tooth development in children because it incorporates into the developing tooth structure and renders it less susceptible to attack from caries. Prescription topical fluoride preparations are typically reserved for individuals considered to be at high risk for caries.

Dental Caries

	**DIAGNOSTIC TESTS**	Clinical exam and intraoral radiographs.
	**BIOPSY**	No.
	**TREATMENT**	Mechanical removal of decayed tooth structure and restoration of tooth integrity. Endodontic therapy or extraction of tooth is indicated when the pulp is infected. Consider antibiotics depending on clinical presentation, in which case penicillin-group or clindamycin for 7–10 days is generally effective.
	**FOLLOW-UP**	Patients with dental caries should be seen by a dentist regularly following treatment of all active caries to monitor for new or recurrent lesions. High risk patients and those with rampant caries should be prescribed sodium fluoride gel 5,000 parts-per-million which can be applied by toothbrush or in soft custom-fabricated dental trays.

Periodontal Disease

Periodontal disease is caused by the accumulation of plaque and *calculus* (calcified dental plaque also referred to as *tartar*), that leads to chronic inflammation of the adjacent gingiva, periodontal attachment structures, and alveolar bone. Periodontal "pockets" form between the tooth and gingival soft tissues as the infected material migrates apically. As the pockets become deeper and more inflamed, it becomes more difficult to adequately clean these areas. Heavy smoking also contributes to inflammation of the periodontium. Signs of periodontal disease include plaque and calculus accumulation, gingival recession or bleeding, periodontal pocketing, root exposure, and tooth mobility (Figs. 7.15, 7.16, and 7.17). Advanced periodontal disease is often associated with foul smelling breath (halitosis).

The periodontium can become acutely infected with abscess formation and swelling of the adjacent gingiva (Fig. 7.18). This is more likely to develop in areas with deep periodontal pockets and *furcation involvement* (exposure of the space between the roots of multirooted teeth). *Pericoronitis* is a condition in which the gingiva surrounding the crowns of partially erupted molars (usually the third molar or "wisdom tooth") becomes painfully inflamed (Fig. 7.19).

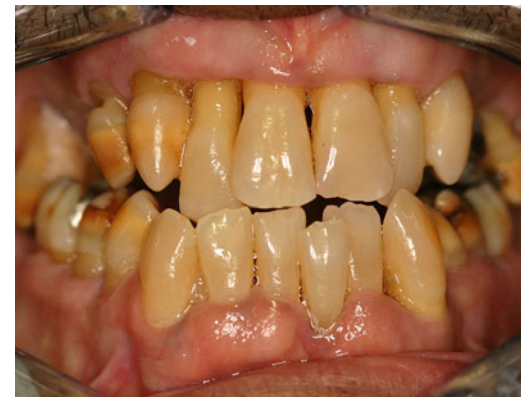

Fig. 7.15 Chronic periodontal disease. There is extensive alveolar bone loss, gingival recession, and blunting of the interdental papillae with subsequent root surface exposure

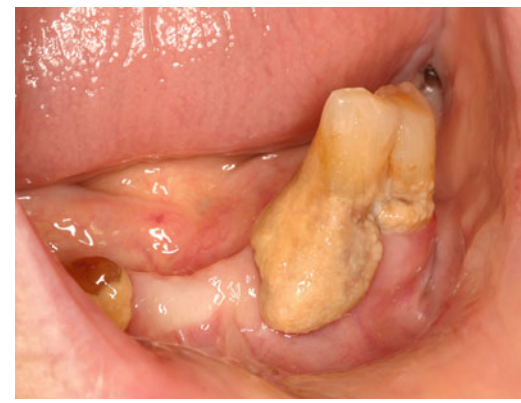

Fig. 7.16 Heavy calculus deposition on the mandibular anterior teeth

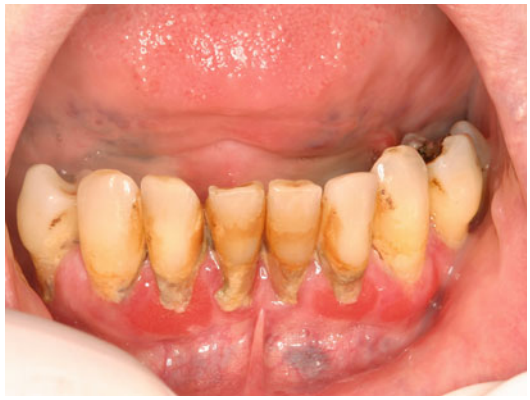

Fig. 7.17 Calculus accumulation on the mandibular anterior dentition with gingival recession and focal areas of severe inflammation

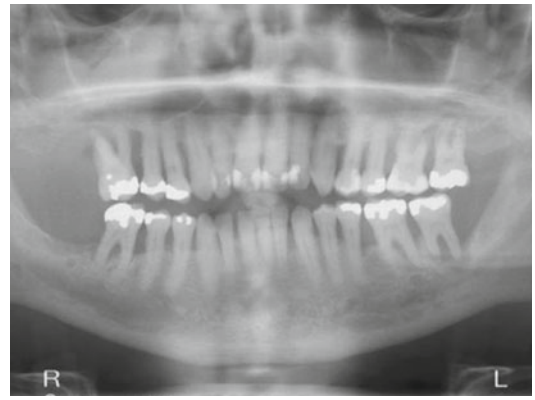

Fig. 7.20 Panoramic radiograph of a patient with advanced periodontal disease. Note advanced alveolar bone loss around the posterior teeth

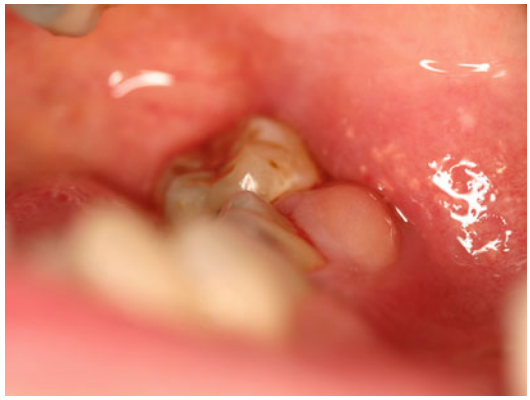

Fig. 7.18 Periodontal abscess formation with firm swelling in the buccal vestibule

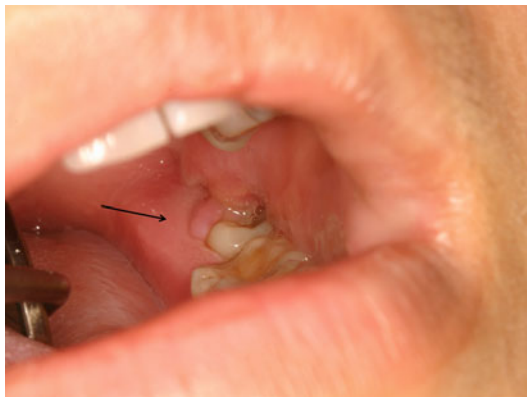

Fig. 7.19 Pericoronitis associated with the mandibular left third molar. Note inflammation and swelling (*arrow*) of the soft tissue as well as limited mouth opening

Radiographic features of periodontal disease include the presence of calculus both above (supragingival) and below (subgingival) the gingival margin, as well as loss of alveolar bone surrounding the teeth (Fig. 7.20). Generalized horizontal bone loss in all four quadrants signifies longstanding inflammation. Localized areas of vertical bony defects represent areas of advanced bone loss and are often associated with tooth mobility and an increased risk for abscess formation.

Primary management of periodontal disease includes professional *scaling* and *root planning*, with removal of calculus and inflammatory tissue from around the teeth and along root surfaces in conjunction with attention to improved oral hygiene. In more advanced cases, surgical procedures may be indicated to reduce pocket depth. Antimicrobial therapies include topical rinses, such as chlorhexidine gluconate; locally delivered antibiotics, such as minocycline injected subgingivally; and systemic antibiotics.

Periodontal Disease

	**DIAGNOSTIC TESTS**	Clinical exam and intraoral radiographs.
	**BIOPSY**	No.
	**TREATMENT**	Scaling and root planing and education regarding improved oral home care. In some cases antimicrobial and/or surgical therapy may be indicated. Pericoronitis should be initially managed with broad spectrum antibiotics (e.g., amoxicillin/clavulanic acid) and warm salt water rinses; extraction of the associated tooth is necessary in recurrent cases.
	**FOLLOW-UP**	Patients with periodontal disease may require professional dental cleaning three to four times annually. The patient is frequently managed in conjunction with a periodontist. Home oral hygiene instruction is important. Smoking cessation should be discussed and encouraged.

Inflammatory Gingival Hyperplasia

Although uncommon, the gingiva can become markedly enlarged in response to localized inflammation. This can be observed in the context of periodontal disease or in response to certain medications. Associated medications include calcium channel blockers (such as nifedipine), calcineurin inhibitors (cyclosporine), and anticonvulsants (phenytoin). In all cases, poor oral hygiene is believed to be a significant contributing factor. The underlying mechanism is thought to be related to calcium regulation of collagen degradation in fibroblasts resulting in increased production of dense connective tissue. Unlike the gingival enlargement that can be seen with leukemic infiltration (see Chap. 11), these lesions are generally firm and of a normal pink color without significant associated bleeding (Figs. 7.21, 7.22, and 7.23). Treatment includes gross debridement of plaque and calculus, which often results in partial or complete resolution. If associated with a medication, discontinuation or substitution is indicated and often effective in reducing progression of gingival enlargement. If this does not result in significant improvement, gingivectomy, usually performed by a periodontist, is indicated.

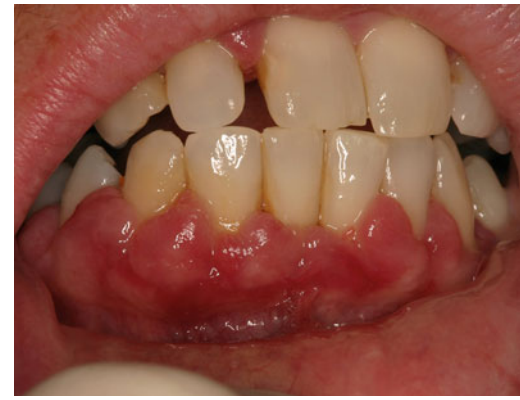

Fig. 7.21 Inflammatory gingival hyperplasia secondary to chronic periodontal disease

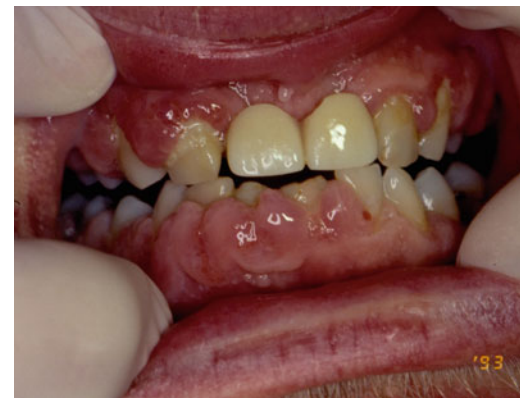

Fig. 7.22 Calcium channel blocker and calcineurin inhibitor associated gingival hyperplasia in a solid organ transplant recipient. There is considerable erythema in areas of heavy plaque accumulation. Photograph courtesy of Sook-Bin Woo, D.M.D., M.M.Sc., Boston, MA

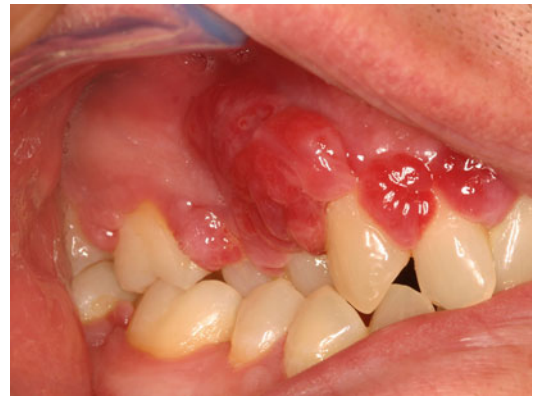

Fig. 7.23 Severe inflammatory gingival hyperplasia secondary to chronic periodontal disease with spontaneous bleeding

Inflammatory Gingival Hyperplasia

	**DIAGNOSTIC TESTS**	None.
	**BIOPSY**	May be necessary for definitive diagnosis and to exclude malignancy, especially in cases where there are localized areas of prominent gingival enlargement.
	**TREATMENT**	Scaling and root planing as primary therapy; patients must also maintain strict oral hygiene practices. Discontinuation of any potentially causative medication if appropriate. For lesions that do not resolve following conservative therapy, referral to a periodontist for gingivectomy is indicated.
	**FOLLOW-UP**	None specifically indicated.

Acute Necrotizing Stomatitis

Previously referred to as "trench mouth" described in soldiers fighting on the front lines in World War I, *acute necrotizing stomatitis* is seen mainly in patients with severe malnutrition and very poor oral hygiene. It has also been observed disproportionately in patients with HIV disease. This aggressive and painful periodontal infection is caused by the convergence of poor oral hygiene, immune suppression, and inadequate nutrition. When localized to the gingiva, the condition is called *acute necrotizing gingivitis*; if it progresses to involve the periodontium, it is referred to as *acute necrotizing periodontitis*. Rarely, this develops into a destructive and devastating infection of the hard and soft orofacial tissues resulting in a disfiguring condition termed *noma*, which is seen almost exclusively in developing countries.

Clinical features of necrotizing stomatitis include severe gingival inflammation with edema, bleeding, blunting of tissue contours, and "punched out" appearing interdental defects with varying areas of ulceration (Fig. 7.24). Necrotic alveolar bone may be evident, and heavy plaque and calculus accumulations are generally present. Intraoral radiographs demonstrate advanced bone loss with vertical defects

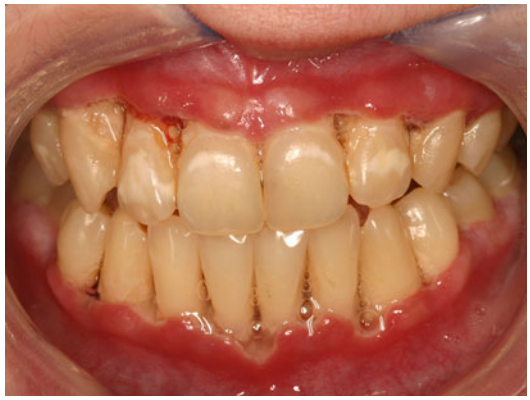

Fig. 7.24 Acute necrotizing ulcerative periodontitis in a 16-year-old female with AIDS. There is marginal ulceration of the gingiva, gingival recession with loss of attachment, and crater-like interdental defects ("punched-out papillae")

that often correspond to areas of extensive soft tissue destruction. This condition is associated with a very foul odor, reflective of the extent of infection and tissue necrosis.

Treatment includes aggressive debridement and administration of antibiotics. Due to the extent and depth of infection, local anesthesia is often required for adequate removal of all plaque and calculus deposits. In addition, daily rinses with chlorhexidine gluconate provide a topical effect, and this medication is continued indefinitely after systemic antibiotics are completed. Following initial therapy, home oral care maintenance is critical to prevent recurrence. Underlying factors such as poor nutrition and immunosuppression must also be addressed.

Acute Necrotizing Stomatitis

	DIAGNOSTIC TESTS	None.
	BIOPSY	No.
	TREATMENT	Gross periodontal debridement followed by thorough scaling and root planing. A 7–10-day course of amoxicillin/clavulanic acid (250/125 mg) and metronidazole (250 mg) should be prescribed in conjunction with daily chlorhexidine gluconate rinses. Medication for pain management may be necessary.
	FOLLOW-UP	Close follow-up with regularly scheduled professional dental cleanings and assessment of oral home care.

Parotitis

Bacterial parotitis is characterized by painful acute swelling of the parotid gland, commonly on one side (Fig. 7.25). Risk factors include dehydration, salivary gland hypofunction, and sialolithiasis. In the setting of diminished salivary outflow, commensal bacteria ascend the duct in a retrograde fashion resulting in infection within the parenchyma of the gland. It is usually caused by *Staphylococcus aureus*. Extraoral examination demonstrates visible fullness of the gland, often with erythema of the overlying skin and outward displacement of the ear. Palpation of the gland elicits discomfort, and intraoral examination may show swelling and erythema in the region of the duct orifice. Purulent discharge may be visible as well. Bacterial infections also affect the submandibular gland in a similar fashion.

Treatment includes broad spectrum systemic antibiotics, hydration to enhance salivary flow, and pain management. Drainage of the gland can

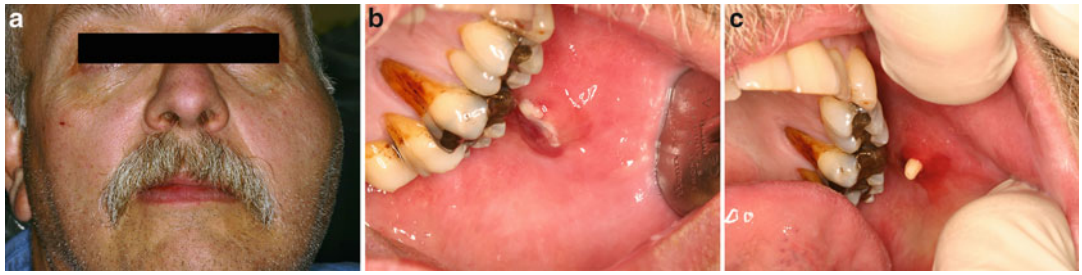

Fig. 7.25 Bacterial parotitis secondary to sialolith obstruction of Stenson duct. (**a**) Acutely painful left-sided facial swelling. (**b**) Purulent discharge at the parotid papilla. (**c**) Delivery and removal of the sialolith. The patient felt immediate relief following stone removal

be enhanced by "milking" it with gentle but steady pressure applied extraorally, which generally also improves pain. Use of sialogogues, such as sour lemon, stimulates salivary flow and helps flush out the gland. Purulent discharge should be collected for aerobic and anaerobic bacterial cultures, especially if the patient has already been treated with antibiotics without clinical improvement. Salivary stones (see Chap. 8), when present, should be removed if possible to prevent recurrence (Fig. 7.25c).

Viral salivary gland infections are characterized by nonsuppurative swelling that may or may not be painful and are usually bilateral. *Mumps* is the most common cause of viral parotitis, mediated by paramyxovirus. Given the widespread use of the MMR (measles/mumps/rubella) vaccine, this condition is encountered infrequently in most developed countries. Other viruses known to infect the salivary glands are cytomegalovirus (CMV), Epstein-Barr virus (EBV), and HIV.

Parotitis

	DIAGNOSTIC TESTS	Culture and sensitivity of purulent discharge, especially if nonresponsive to antibiotics. CT may be ordered to evaluate for the presence of salivary calcifications or abscess.
	BIOPSY	No.
	TREATMENT	Manual compression of gland to facilitate drainage of purulence via Stenson duct in conjunction with sialogogues and hydration. Broad spectrum antibiotics such as amoxicillin/clavulanic acid 875/125 twice daily for 2 weeks or until complete resolution of swelling and symptoms. Pain medication as needed. If a sialolith is identified clinically or radiographically, removal of the stone is indicated (see Chap. 8).
	FOLLOW-UP	Until condition resolves.

Fungal Infections

The vast majority of oral fungal infections are caused by *Candida albicans*, which is considered a component of the normal oral flora. Deep fungal infections are in comparison exceedingly rare and are generally only encountered in immunocompromised individuals; these will only be discussed briefly.

Oral Candidiasis

As candida species make up part of the commensal oral flora in most individuals, it is a change in the normal oral environment rather than actual exposure or "infection" per se, that results in clinical infection (*candidiasis* or *thrush*). This can be precipitated by reduced salivary flow (see Chap. 8), immunosuppression (including poorly controlled diabetes mellitus), and use of antibiotics or steroid medications. Oral candidiasis can be encountered in any age group; organisms colonize the mucosa resulting in a superficial infection that typically causes symptoms of soreness and burning. It is not uncommon for patients to also describe discomfort in the throat with swallowing, indicating the presence of oropharyngeal or esophageal involvement.

The most common clinical presentation is generalized patchy white to yellow spots or plaques that have a "cottage cheese" like appearance, referred to as *pseudomembranous candidiasis* (Figs. 7.26, 7.27, and 7.28). These can be easily wiped away with gauze leaving an erythematous base with minimal bleeding. Lesions can be seen anywhere but are frequently located on the tongue, buccal mucosa, and palate. Much less frequently, candidiasis can present with a purely erythematous macular lesion, and is termed *erythematous candidiasis* (Fig. 7.29). Very rarely, candidiasis can present as a white plaque that does not rub away and looks clinically identical to leukoplakia (see Chap. 9); this is referred to as *hyperplastic candidiasis*. The presence of oral lesions is frequently associated with infection of the corners of the mouth,

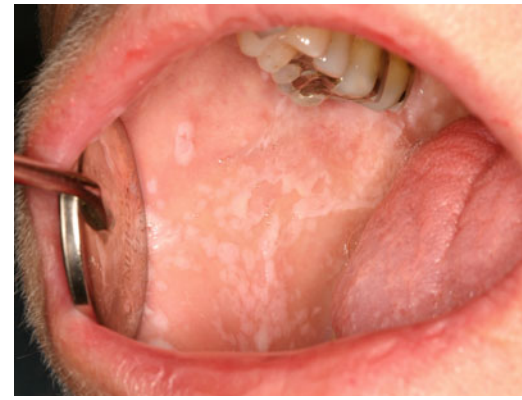

Fig. 7.26 Pseudomembranous candidiasis of the right buccal mucosa with white patches

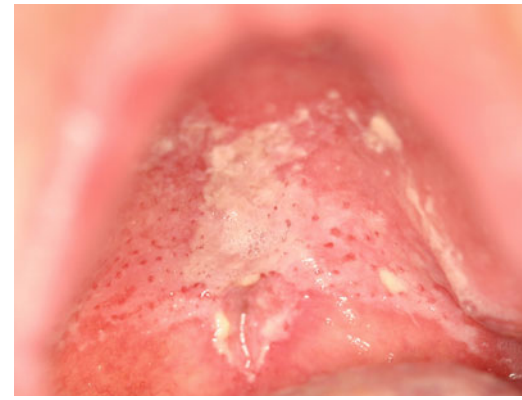

Fig. 7.27 Plaque-like pseudomembranous candidiasis of the palate in an edentulous patient whose denture hygiene was poor

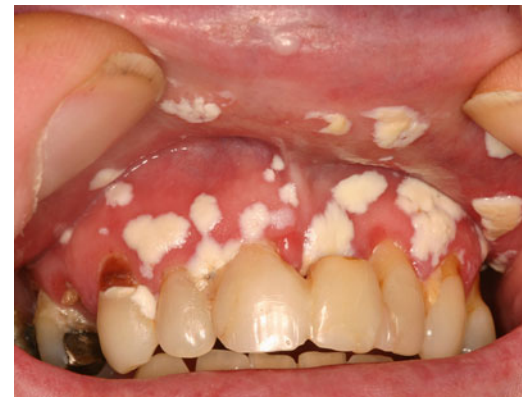

Fig. 7.28 Cottage cheese-like pseudomembranous candidiasis of the gingiva and labial mucosa

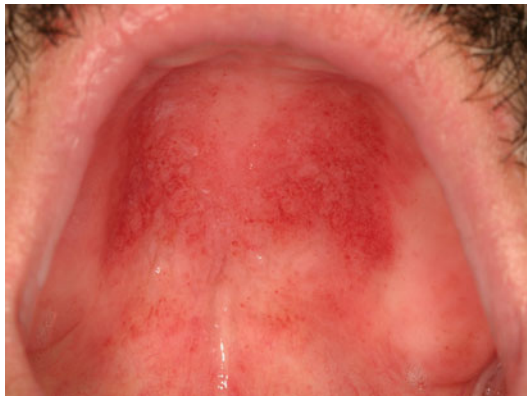

Fig. 7.29 Erythematous candidiasis of the palate in a patient that wears a full upper denture

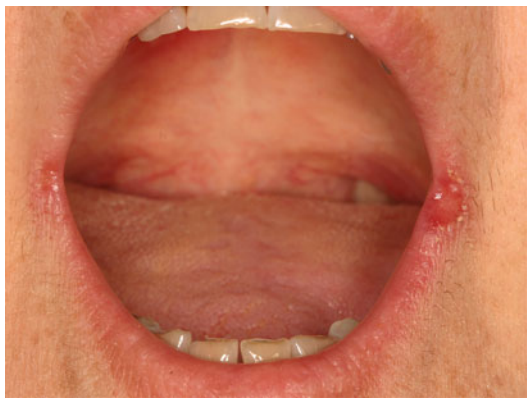

Fig. 7.30 Angular cheilitis. The commissures are fissured and erythematous

resulting in painful erythematous raw and cracked skin known as *angular cheilitis*. This is seen more frequently in edentulous patients with overclosure (collapse of jaws) and in individuals with a lip licking habit (Fig. 7.30).

Diagnosis of candidiasis can typically be made by clinical features alone. As the *hyperplastic* form cannot be distinguished clinically from leukoplakia, an incisional biopsy is required for diagnosis. Fungal culture should be reserved for lesions that are not responsive to empiric therapy. In such cases, sensitivity testing should also be requested. Clinical response to empirical antifungal therapy, with complete resolution of signs and symptoms, confirms the diagnosis.

Primary management of oral candidiasis is with topical and systemic antifungal agents (Table 7.1). The most commonly utilized topical agents include nystatin suspension and clotrimazole troches. While both can be effective, there is greater evidence to support the use of clotrimazole troches, although some cases may not respond even with adequate dosing. Systemic therapy using fluconazole is usually highly effective. If applicable, removable dentures should also be treated, as these are frequently colonized and will continue to reinfect the underlying soft tissue. Preparations for denture disinfection are commercially available; however, a simple and inexpensive alternative is to soak the prosthesis (if it does not contain metal) overnight in a 1:10 dilution of household bleach. Angular cheilitis is effectively managed with topical nystatin/triamcinolone cream.

Management of any underlying contributing factors is important in preventing recurrence. Long-term prophylaxis should be prescribed in cases of chronic recurrent disease. Topical agents may be effective; however, systemic treatment is often easier for the patient to manage due to more convenient dosing schedules. In most cases, fluconazole given once or twice weekly is highly effective at preventing recurrent infection.

Oral Candidiasis

	**DIAGNOSTIC TESTS**	Not generally indicated unless poorly responsive to empiric therapy, in which case fungal culture with sensitivity testing should be performed.
	**BIOPSY**	When the clinical diagnosis is uncertain, as with hyperplastic candidiasis.
	**TREATMENT**	See Table 7.1. Patients with recurrent candidiasis should be treated with a prophylactic regimen.
	**FOLLOW-UP**	Close follow-up during treatment of active infection; as needed for chronic conditions.

Table 7.1 Management of oral fungal infections

Antifungal agent	Class	How supplied	Dispensation instructions	Regimen	Notes
Topical					
Nystatin	Polyene	100,000 U/mL suspension	One bottle (473 mL)	Swish and spit (or swallow if esophageal lesions) for 1–2 min two to three times/day. Continue until lesions resolved	Efficacy varies. If lesions do not respond, treat with systemic agent
Clotrimazole	Azole	10 mg troche	One bottle (70 or 140 troches)	Let one troche dissolve fully in the mouth, four times/day	Troches will not dissolve in patients with significant dry mouth
Nystatin/triamcinolone acetonide	Polyene and corticosteroid	Cream	One tube (15, 30, or 60 g)	Apply a small amount to the corners of the mouth twice daily	Signs and symptoms generally respond within 2–3 days
Systemic					
Fluconazole	Azole	Tablet (100, 150, and 200 mg) oral suspension (40 mg/mL)	One month supply (30 tablets). While a full 30-day regimen is rarely required, this ensures sufficient medication in the event of recurrence or difficult-to-treat cases	Take one tablet once daily. A 7-day course is generally sufficient for complete clearing of candidiasis. In patients with recurrent infection (e.g., use of oral topical steroid, salivary gland hypofunction) treatment with one 100 mg tablet once or twice weekly is in most cases highly effective	True resistance to fluconazole is exceedingly rare. In the event of poor response, culture with sensitivity testing and empirically increase dose (e.g., from 100 to 200 mg). Oral suspension is useful for patients with difficulty swallowing pills. There is no evidence that topical fluconazole is any more effective than nystatin or clotrimazole

Deep Fungal Infections

Non-candidal oral fungal infections are rare and are seen almost exclusively in immunosuppressed individuals. Infections include *aspergillosis*, *cryptococcosis*, *blastomycosis*, *histoplasmosis*, *paracoccidioidomycosis*, and *mucormycosis*. Lesions typically present as deep necrotic ulcerations that can lead to localized destruction and tissue invasion as well as systemic dissemination (Fig. 7.31). Oral lesions are often accompanied by lesions within the respiratory tract, such as the lungs or sinuses, and diagnosis requires biopsy. Imaging studies should be ordered to evaluate the extent of underlying tissue involvement. Management includes aggressive systemic antifungal therapy in conjunction with surgical debridement. Despite aggressive therapy, these infections are associated with high rates of morbidity and mortality.

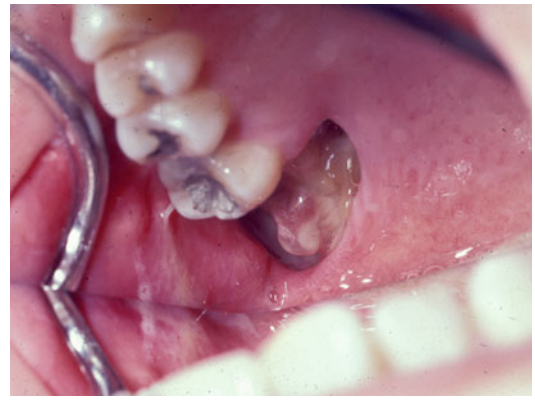

Fig. 7.31 Aspergillus infection of the maxillary sinus with invasive ulceration and necrosis of the posterior maxilla in an immunosuppressed patient following hematopoietic stem cell transplantation. Photograph courtesy of Mark Schubert, D.D.S., M.S.D., Seattle, WA

Deep Fungal Infections

	**DIAGNOSTIC TESTS**	Chest radiograph and advanced imaging of the head and neck (CT or MRI) to evaluate extent of involvement. Superficial cultures or swabs are of no diagnostic utility.
	**BIOPSY**	Yes; half of the specimen should be submitted in formalin and half fresh for tissue culture and advanced staining techniques.
	**TREATMENT**	Antifungal therapy and surgery.
	**FOLLOW-UP**	Close follow-up until condition resolves.

Viral Infections

A wide variety of viral infections affect the oral cavity (Table 7.2). These include members of the human herpes virus family (herpes simplex 1&2, varicella zoster virus [VZV], CMV, and EBV), human papillomaviruses, and enteroviruses. Some infections are common in normal health, while others are seen only in immunocompromised individuals. Clinical appearances are often very similar to noninfectious oral conditions and certain infections may present quite differently between the immunocompetent versus immunocompromised states. Accurate and prompt diagnosis is necessary, as the choice of appropriate management will depend on the specific organism involved, and can vary from palliative treatment alone to antiviral therapy or surgery.

Herpes Simplex Virus

Herpes simplex virus (HSV) is a ubiquitous virus to which the majority of humans are exposed at some point during their lifetime, usually by the teenage years but occasionally later in adulthood. The virus is transmitted through saliva by direct contact, and becomes latent in the trigeminal nerve ganglion following primary infection.

Table 7.2 Viral infections that are known to cause oral lesions

Type of virus		Mode of transmission	Oral lesions	Diagnosis	Management
Herpes family viruses					
Herpes simplex virus (HHV1, HHV2)	DNA	Saliva, genital secretions	Primary:	Clinical primarily	Primary:
			• Primary herpetic gingivostomatitis	Viral culture	Acyclovir 200 mg five times/day for 7 days
				PCR	Valacyclovir 2 g once daily for 7 days
				Cytology	
			Secondary:	Direct fluorescence assay (DFA)	Supportive care including pain control, nutritional support, and adequate hydration
			• Perioral crusted blistering lesions (cold sores)	Serology	Secondary:
			• Intraoral irregular shallow ulcers affecting the keratinized mucosa		Same as primary regimen, need to begin treatment at the earliest onset of prodrome symptoms
					Suppression: Acyclovir 400 mg twice daily
					Valacyclovir 500 mg or 1 g once daily
Varicella Zoster virus (HHV3)	DNA	Saliva, airborne droplets	Primary:	Clinical primarily	Acyclovir 800 mg five times/day for 7–10 days
			• *Varicella* or "*chicken pox*", may present with oral ulcers	Viral culture	Valacyclovir 1000 mg three times/day for 7–10 days
				PCR	
				Cytology	
			Secondary:	DFA biopsy	Famciclovir 500 mg three times/day for 7–10 days
			• *Herpes zoster* or "*shingles*", unilateral intraoral ulcers identical to those caused by HSV, when cranial nerve V involved		
Epstein-Barr virus (HHV4)	DNA	Saliva	Oral hairy leukoplakia (OHL)	Biopsy	No specific treatment necessary. May respond to acyclovir or valacyclovir therapy
Cytomegalovirus (HHV5)	DNA	Bodily fluids, including saliva	Oral ulcers, typically solitary and deep, in immunocompromised patients	Biopsy	Valganciclovir 900 mg twice a day until healed
					Ganciclovir 1 g three times a day until healed
Human papilloma virus	DNA	Direct contact, however, lesions do not have to be present	Benign epithelial proliferations	Biopsy; HPV subtype analysis as clinically indicated	Surgical excision
			Squamous cell carcinoma of the oropharynx		If cancer diagnosed, referral to a cancer center
Enterovirus	RNA	Fecal/oral	Multiple aphthous-like ulcers, on the soft palate in particular	Clinical	Supportive care only
				PCR	
		Respiratory/oral		Serology	

Once present, the virus remains dormant and has the potential to reactivate throughout the lifetime of the individual. Subclinical viral shedding in the saliva is common even in the absence of clinically evident lesions, likely explaining to some extent the widespread prevalence of this infection in the human population. Although HSV-1 was historically considered specific to the oral cavity and HSV-2 was considered specific to the anogenital region, either subtype can cause oral infections. Other than minor molecular differences between HSV-1 and HSV-2 strains, the resultant infection, natural course of disease, and treatment are exactly the same.

Primary HSV is characterized by flu-like symptoms that typically precede onset of oral lesions by 2–3 days and severe oral ulcerations that can affect both the keratinized and nonkeratinized mucosa (Fig. 7.32). The gingiva is typically very painful and fiery red in appearance. Ulcerative lesions begin as small vesicles that often develop in clusters and eventually break down to form coalescing, shallow, irregularly shaped ulcerations. The pain associated with these lesions is severe. In the absence of antiviral therapy, the clinical course of primary HSV is typically no more than 14 days with complete resolution of all signs and symptoms. There is a wide range of clinical presentations, however, and many primary infections are probably never diagnosed. A history of intimate physical contact within 1 week of developing signs and symptoms of primary HSV infection should be sought.

Diagnosis can often be made by history and clinical examination alone, and treatment should be initiated immediately. Viral culture, PCR or direct fluorescent antibody (DFA) testing of ulcerative lesions can confirm the diagnosis. Positive serology for HSV IgM antibodies signifies primary infection, but the presence of IgG antibodies can only confirm prior exposure. Although primary HSV is a self-limiting infection, early treatment with antiviral medication can reduce the severity and length of illness but will not prevent the establishment of latency. Most important is symptomatic and supportive care, as oral intake can be severely limited during primary infection due to pain. Use of systemic and topical analgesics in conjunction with hydration and nutritional support are critical aspects of management, especially in young children. Management of primary and secondary HSV infection is summarized in Table 7.2.

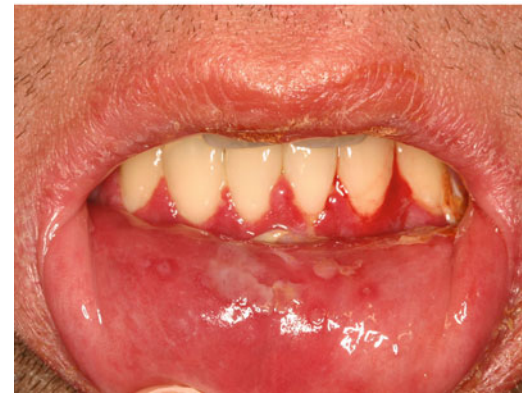

Fig. 7.32 Primary herpes simplex virus infection. There are freshly collapsed vesicles, irregularly shaped shallow ulcerations, and desquamation and erythema of the gingiva

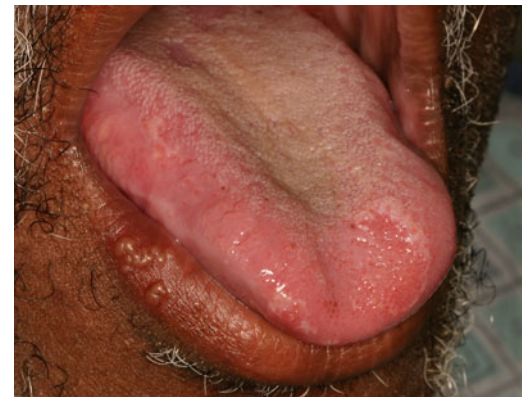

Fig. 7.33 Recrudescent herpes simplex virus infection in a patient following cardiac surgery. Note crop of intact vesicles on the lower right lip and coalescent ulceration of the anterior right tongue

Once infected, the virus becomes latent in the trigeminal ganglion with the potential for reactivation or recrudescence. Well-known triggers include stress, hormonal changes, sun exposure, and trauma. Lesions are typically preceded by a prodrome, which is characterized by tingling, itching, or a painful sensation in the area where the lesion will appear. The majority of secondary lesions occur on and around the lips and nostrils and present initially with multiple small vesicles that break down and form a painful, crusted, ulceration (Fig. 7.33). Much less frequently,

lesions develop intraorally, where they are limited to the keratinized mucosa. Intraoral lesions look identical to those of primary infection but are generally unilateral and limited to one specific anatomic site (e.g., tongue, gingiva, lip, and hard palate). In immunocompromised patients lesions may develop extraorally as well as intraorally, and lesions can be much more extensive; multiple areas may be affected, including both the keratinized and nonkeratinized mucosa (Fig. 7.34). Patients are highly infectious during the period of active lesions; however, viral shedding can occur at any time regardless of the presence of lesions.

While the diagnosis of recrudescent HSV infection can be made by viral culture, this is rarely necessary except for atypical cases. Treatment at the initial onset of prodromal symptoms can effectively suppress vesicle formation or reduce the severity and length of the outbreak. Topical antiviral therapy can be effective if applied frequently throughout the day, but systemic therapy is generally preferable due to better compliance and efficacy.

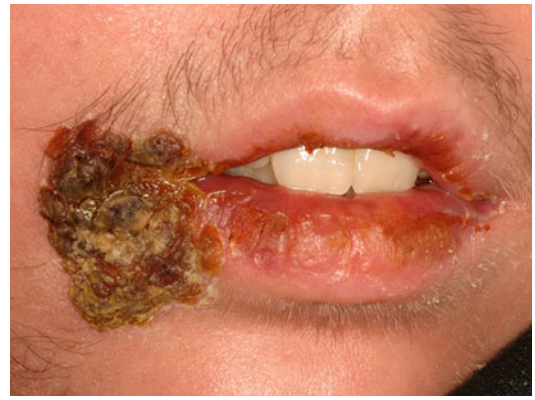

Fig. 7.34 Recrudescent herpes simplex virus infection in an immunosuppressed patient following allogeneic hematopoietic cell transplantation. The patient also had multiple ulcers of the right lateral tongue

Antiviral therapy is of limited utility following appearance of vesicles; lesions will heal completely within 7–10 days. For those with frequent recurrent herpes labialis, prophylactic suppressive antiviral therapy is safe and effective.

Herpes Simplex Virus

	**DIAGNOSTIC TESTS**	Viral culture, PCR, cytology, or DFA for definitive diagnosis. Empiric therapy should be initiated promptly when findings are clinically consistent with HSV.
	**BIOPSY**	No.
	**TREATMENT**	Antiviral therapy and appropriate supportive care when indicated; see Table 7.2.
	**FOLLOW-UP**	As needed.

Varicella Zoster Virus

Primary infection with VZV results in chicken pox, following which the virus becomes latent in the spinal dorsal root ganglia. While reactivation (*herpes zoster*; "shingles") can develop at any time, this occurs at a much higher frequency in adults over 60 years of age, and is thought to be related to immunosenescence to VZV. With the introduction of the VZV vaccine, the epidemiology of herpes zoster infection appears to be changing; the frequency of primary infection in children is reduced; and vaccination of older adults results in a lower risk of reactivation. A rare but significant complication of herpes zoster infection is *postherpetic neuralgia* (PHN), which is characterized by burning neuropathic pain in the area of previous lesions.

Similar to recrudescent HSV infection, herpes zoster lesions are preceded by a prodrome, typically characterized by a tingling or stabbing

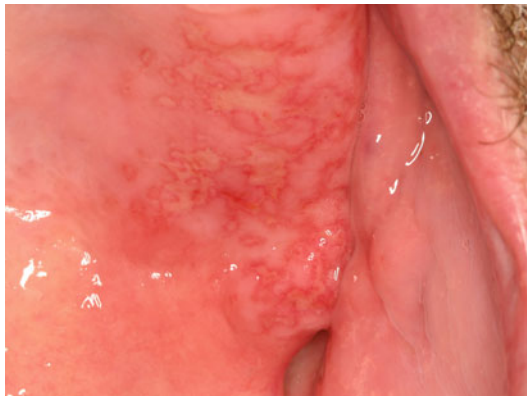

Fig. 7.35 Herpes zoster infection of the left palate. The pattern of shallow coalescing crop-like ulcers appears to follow the anatomy of the palatine nerve branches

sensation. The trigeminal nerve is involved in approximately 20 % of cases and most commonly affects the ophthalmic division (V1). Lesions are characteristically unilateral and appear identical clinically to those of HSV (Fig. 7.35). The distribution of lesions follows the dermatome of the affected nerve. Diagnosis is generally made on clinical findings alone, although viral culture and DFA testing can provide confirmation. When the second or third divisions of the trigeminal nerve are affected (V2, V3), lesions may present both extraorally and intraorally. Prior to the appearance of vesicles and ulcers, intraoral herpes zoster may initially present with severe pain that can easily be confused with odontogenic infection, sinusitis, or myofascial pain dysfunction. When cranial nerves VII and VIII are involved, facial nerve paralysis and hearing loss can occur (known as *Ramsay Hunt syndrome* or *herpes zoster oticus*). In immunocompromised patients, multiple dermatomes may be affected, lesions may present bilaterally, and disseminated zoster can develop resulting in visceral pain, organ involvement, and death.

Antiviral therapy with acyclovir, valacyclovir, or famciclovir for 7–10 days within 48–72 h following appearance of lesions can be effective in reducing pain, promoting healing, and preventing or reducing the severity of PHN. While combined treatment of antiviral medication with high-dose corticosteroids has been evaluated to reduce the risk of developing PHN, its efficacy and clinical utility remain controversial. PHN can be managed with topical and systemic agents similar to other neuropathic pain conditions (see Chap. 10).

Varicella Zoster Virus

	**DIAGNOSTIC TESTS**	Viral culture, PCR, cytology, or DFA to confirm diagnosis. Serological testing is of limited utility.
	**BIOPSY**	No.
	**TREATMENT**	Antiviral therapy with acyclovir, valacyclovir, or famciclovir at the earliest suspicion of reactivation. Topical and systemic pain management as indicated.
	**FOLLOW-UP**	PHN is rare but should be considered when pain persists in the area of lesions after resolution of lesions.

Cytomegalovirus

Most individuals are infected with CMV at some point during their lifetime. Initial infection is usually asymptomatic but may present as a mild flu-like illness or mononucleosis-like syndrome that is clinically identical to that caused by EBV (see below). The salivary glands become infected and provide a source of constant viral shedding. Clinically significant disease, such as pneumonia, gastroenteritis, and retinitis, due to reactivation only occurs in immunocompromised individuals. Blood tests used to evaluate CMV disease activity include antibody testing, antigen testing, shell

vial assay, and qualitative and quantitative PCR. Results from these tests may support a diagnosis, or be used as an indication to begin antiviral therapy in immunocompromised patients; however, no specific findings define infection.

Nonspecific painful oral ulcerations resembling *major aphthous* (see Chap. 5) may develop in immunocompromised patients, and CMV involvement can only be diagnosed by biopsy (Fig. 7.36). Histopathology demonstrates enlarged cells within the vascular endothelial cells in the connective tissue with intranuclear inclusions that have a classic "owl's eye" appearance; immunohistochemistry and in situ hybridization for CMV antigens are both useful tests for confirmation of the diagnosis. Treatment with ganciclovir and valganciclovir are both highly effective in managing CMV disease.

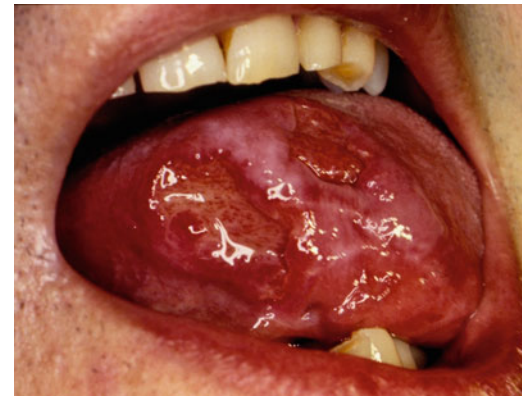

Fig. 7.36 Cytomegalovirus infection of the tongue in an HIV-positive patient with multiple large, penetrating ulcers. Incisional biopsy demonstrated cytopathological changes and immunohistochemistry confirmed presence of the virus. Photograph courtesy of Sook-Bin Woo, D.M.D., M.M.Sc., Boston, MA

Cytomegalovirus

	**DIAGNOSTIC TESTS**	Quantitative CMV viral load testing may help support a diagnosis of CMV induced oral ulcerations. The relationship is unclear and results must be interpreted carefully. Surface cultures, as are used for the diagnosis of HSV, are ineffective given the location of CMV deep in the connective tissue. Consider obtaining a complete blood count in the rare event of secondary pancytopenia.
	**BIOPSY**	Yes, for unexplained oral ulcers in immunocompromised patients. A sample should also be submitted fresh in viral culture medium.
	**TREATMENT**	Ganciclovir or valganciclovir.
	**FOLLOW-UP**	Patients should be followed carefully to assess for healing of oral lesions.

Epstein-Barr Virus

Similar to CMV, most humans are exposed to EBV. Primary infection (*acute infectious mononucleosis*) is most commonly seen in adolescents and young adults; when symptomatic, it is characterized by sore throat, fever, and lymphadenopathy. Diagnosis includes (a) lymphocytosis, (b) atypical lymphocytes on peripheral smear, and (c) positive EBV serology. The salivary glands and oropharyngeal lymphoid tissues become infected and are responsible for constant shedding in saliva during latency, which is most commonly responsible for viral transmission.

B lymphocytes are also an important site of infection and latency. EBV is associated with endemic Burkitt lymphoma, nasopharyngeal carcinoma, and non-Hodgkin lymphoma, including posttransplant lymphoproliferative disease. The only oral condition that is specifically attributed to EBV is *oral hairy leukoplakia* (OHL), a benign condition characterized by painless white plaques on the ventrolateral tongue (see Chaps. 4 and 11). OHL is only seen in immunosuppressed individuals and has primarily been reported in association with HIV disease. Biopsy shows classic EBV-associated viral cytopathic changes in the superficial epithelium characterized by nuclear

clearing and peripheral margination of chromatin (nuclear beading) caused by EBV viral replication. In situ hybridization can further confirm the presence of EBV in the tissue. Once diagnosed, specific treatment is not necessary; however, antiviral therapy with acyclovir can be effective for clinical resolution of lesions. This should not be confused with *leukoplakia*, which is not EBV associated and is considered a potentially malignant lesion (see Chap. 9).

Epstein-Barr Virus

	**DIAGNOSTIC TESTS**	EBV serology and CBC for diagnosis of primary infectious mononucleosis. HIV testing indicated if OHL suspected.
	**BIOPSY**	Yes, for OHL.
	**TREATMENT**	Acyclovir can be effective for OHL.
	**FOLLOW-UP**	None specific for OHL; the patient's underlying medical condition should be followed carefully.

Human Papilloma Virus

Human papilloma virus (HPV) is a ubiquitous virus with over 100 identified subtypes. It is associated with both benign and malignant epithelial growths of the aerodigestive and anogenital mucosa. Transmission is by direct contact and prevalence in the population is estimated to be at least 50 %. The most common subtypes associated with benign mucosal proliferative lesions are 2, 4, 6, 11, 13, and 32. Subtypes 16 and 18 have been associated with oropharyngeal *squamous cell carcinoma* as well as cancer of the cervix (see Chap. 9). HPV vaccine is now available for both women and men and is considered protective against cervical cancer, anogenital warts, and anal cancer. It has not been evaluated with respect to prevention of oropharyngeal carcinoma. The association of various sexual behaviors with primary infection, mechanisms of latency, and risk factors for the development of oral lesions are unclear.

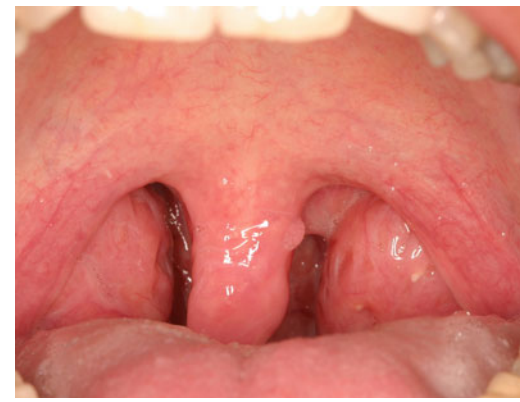

Fig. 7.37 Squamous papilloma on the lateral aspect of the uvula. The lesion is well-defined with a characteristic "papillary" or pebbly texture and normal pink color

Oral lesions caused by HPV infection include *squamous papilloma*, *verruca vulgaris*, *condyloma acuminatum*, and *focal epithelial hyperplasia* (or *Heck disease*; Figs. 7.37, 7.38, 7.39, and 7.40). While differences exist clinically between these lesions, they are all characterized

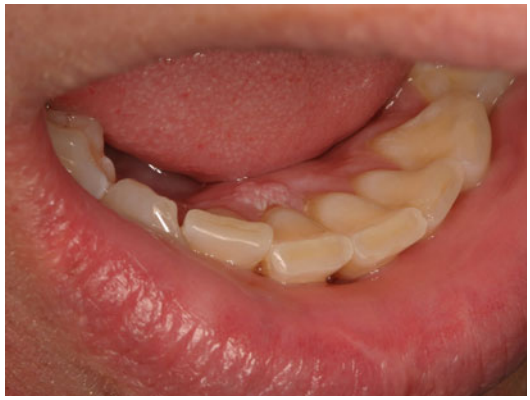

Fig. 7.38 Verruca vulgaris of the anterior lingual gingiva. The lesion is whiter than the surrounding tissue with prominent hair-like projections

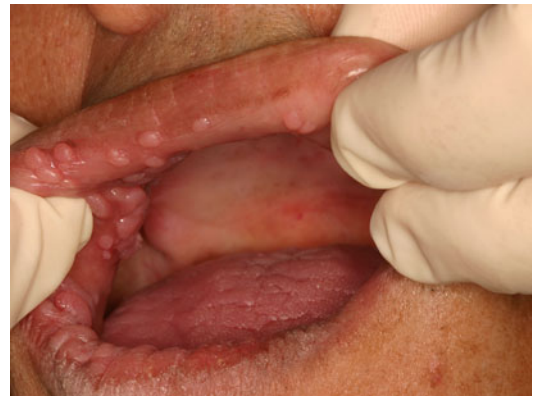

Fig. 7.41 Papillomatosis with numerous clustered lesions of the anterior oral cavity in an HIV-positive patient

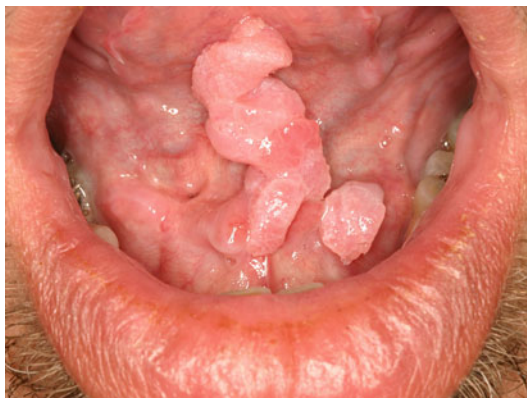

Fig. 7.39 Large condyloma acuminatum of the ventral tongue

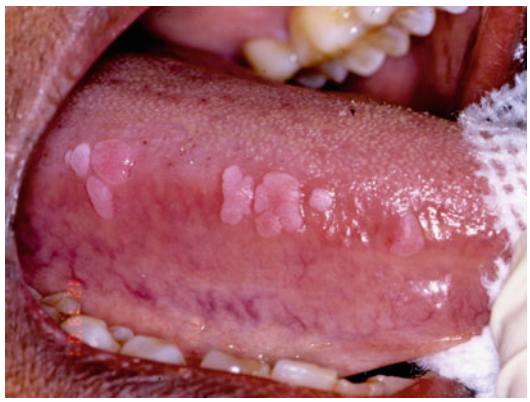

Fig. 7.40 Focal epithelial hyperplasia with multiple flat pink papillary lesions on the lateral tongue. Photograph courtesy of Sook-Bin Woo, D.M.D., M.M.Sc., Boston, MA

by well-defined epithelial proliferations that are pink to white in color, ranging from 1.0 mm to 1.0 cm in diameter, often with a pebbly or "wart-like" surface. Lesions, although painless, may be subject to trauma from the dentition, can be annoying, and may have cosmetic consequences when located on the lips or tongue. In immunocompromised patients, in particular those with HIV infection, multiple lesions may occur resulting in a condition called *papillomatosis* (Fig. 7.41). None of these benign lesions are considered to have any malignant potential.

Diagnosis is primarily based on clinical appearance; however, lesions may need to be biopsied to rule out dysplasia or malignancy, especially in patients who are at increased risk for oral cancer. Lesions are characterized histopathologically by marked epithelial hyperplasia and koilocytosis. Management of solitary lesions is by simple surgical excision. Treatment of multiple lesions can be more challenging and approaches include surgery, cryotherapy, laser ablation, and intralesional interferon alpha therapy; unfortunately recurrence is common in these cases. Lesions on the lip and vermillion border (but not intraoral mucosa) may be treated with topical immunomodulatory (imiquimod) or antineoplastic (5-fluorouracil) agents, although results are variable.

Human Papilloma Virus

	DIAGNOSTIC TESTS	None.
	BIOPSY	Yes, to rule out malignancy. HPV typing can be performed if clinically indicated.
	TREATMENT	Surgical excision.
	FOLLOW-UP	As needed.

Enterovirus

Enteroviruses belong to the Picornaviridae (small RNA virus) family of viruses and include, among many others, coxsackievirus. *Herpangina* and *hand-foot-and-mouth disease* are mediated by coxsackievirus and are both characterized by painful oropharyngeal ulcers (Fig. 7.42). Enteroviruses are transmitted primarily by the fecal–oral route, but may be transmitted by aerosolized saliva droplets as well during the acute phase of infection. Outbreaks tend to occur during the summer and fall, but in temperate climates can occur year round. Regular hand washing is the most effective preventive measure. The incubation period is 3–7 days, followed by acute onset of variable flu-like symptoms (sore throat, dysphagia, fever, and malaise), although in many cases infection is entirely subclinical. While more common in children, enterovirus infection can present at any time during life.

Herpangina is characterized by multiple small vesicles on the soft palate and tonsillar pillars that rapidly break down to form aphthous-like ulcers. Oral lesions may be more widespread in *hand-foot-and-mouth disease* and are accompanied by cutaneous vesicles. The infection is self-limiting, with systemic symptoms typically resolving within several days and oral lesions healing within 7–10 days. In most cases diagnosis is made by clinical findings alone, although various tests are available for atypical cases or for epidemiological purposes (e.g., culture, serology, and PCR). There is no specific antiviral therapy for enterovirus infection; supportive care including pain management, hydration, and soft diet should be provided until lesions and symptoms resolve.

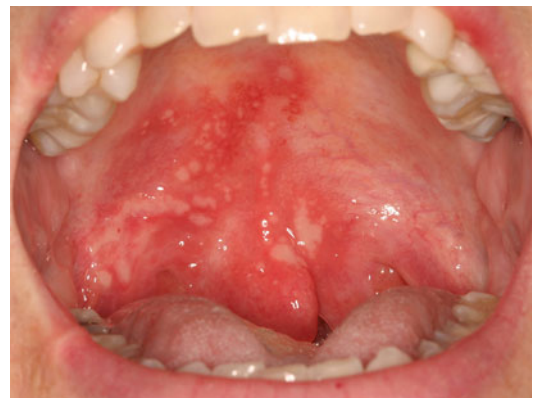

Fig. 7.42 Coxsackie virus infection with multiple shallow minor aphthous-like ulcers of the posterior soft palate and uvula with associated erythema

Enterovirus

	**DIAGNOSTIC TESTS**	None; diagnosis is made based on characteristic clinical features in most cases. PCR and serologic testing are available for complex presentations.
	**BIOPSY**	No.
	**TREATMENT**	Supportive care measures.
	**FOLLOW-UP**	Condition is self-limiting; follow-up as clinically indicated.

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