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Opportunistic Oral Infections

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INTRODUCTION

An opportunistic infection (OI) is a disease of microbial cause or pathogenesis generally thought to occur in hosts with weakened immunity, altered microbiota, or breached epithelium. As such, OIs can be associated with significant morbidity or mortality.¹ Local or systemic disease ensues during OIs, and, when affecting the oral cavity, disease can be primary or secondary. Oral OIs are initiated by either exogenously acquired pathogens or resident host flora. Indigenous microbes that cause oral OIs can consist of species native to the oral cavity, or arise from niches proximal or distal to the mouth; for example, microorganisms from the skin, gastrointestinal tract, or airway and sinuses.

Numerous pathogens have been associated with oral OIs, including biofilm (sessile) communities and planktonic (free-floating) microorganisms. The specific pathogens implicated in oral OIs are extensive and include various species of bacteria, fungi, viruses, and parasites. Furthermore, parasitic diseases affecting the oral cavity can be caused by helminths, protozoa, or ectoparasites. Ectoparasites can also serve as vectors for prion-related diseases, although oral involvement is a rare finding in prion-mediated diseases and is not a stand-alone feature.^{2,3} Most microbes associated with oral OIs do not cause disease in healthy hosts. Therefore, thorough medical history and knowledge of comorbidities in patients with suspected oral OI is essential for accurate diagnosis. Because treatment of oral OI should be individualized and predicated on a diagnosis and host-pathogen findings, identification of contributory pathogens is important. When indicated, culturing and antimicrobial susceptibility testing can aid in diagnosis and appropriate choice of antimicrobial therapy. In some cases of oral OI, empiric therapy is immediately instituted based on clinical judgment of microbial cause if culture is unavailable, or until culture and

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sensitivity results return from the laboratory. Biofilm-mediated infections may be culture negative and should not rule out the potential for infectious disease when clinical suspicion is high.⁴ In addition, oral OIs can be polymicrobial, which may confound the cause, diagnosis, and treatment.

Oral health care providers should have basic knowledge of the pathogens implicated in oral OIs, how these pathogens are identified, and basic clinicopathologic features, all of which inform accurate clinical diagnosis, management, and prevention strategies. For reference, some of these pathogens and the diseases they cause have already been discussed in detail in other articles presented in this issue. The goal and scope of this article is to provide general practitioners with:

1. Basic knowledge of the pathogens and microbiology of oral OIs
2. The specific types of diseases seen with oral OIs
3. Risk factors for disease development and progression
4. Considerations relevant to diagnosis and patient care in this context

Clinical exemplars are used to clarify key points in the discussion to follow. Importantly, in some cases of oral OI (eg, atypical or challenging cases), a multidisciplinary approach to diagnosis and treatment is required and is beyond the scope of general dental practice, especially when systemic evaluation is necessary. Thus, appropriate specialty referral, such as infectious disease (ID) consultation, should be sought when applicable and on a case-by-case basis.

DISCUSSION

Microbiology

Oral OIs are associated with specific pathogens that include numerous bacteria, yeast, viruses, and parasites, as presented in Table 1. Each of these microorganisms has unique genotypic and phenotypic compositions and virulence factors. Common mechanisms for initiating or propagating disease, or evading host immunity, also exist. When an OI pathogen is acquired or not part of the host indigenous flora, possible modes of transmission, depending on the specific microbe, include sexual; zoonotic; or borne by vector, saliva, blood, food, water, soil, air, or droplets.^{5,6} Moreover, infection via autoinoculation is possible with certain OI pathogens, and this should be taken into consideration for therapeutic decision making.⁷ For example, cryotherapy may be favored rather than laser ablation for the treatment of oral condyloma to reduce the risk of acquiring or spreading human papilloma virus (HPV) in aerosolized plumes.⁸

Further, certain OI pathogens are endemic to specific geographic regions, as are various subtypes within a similar phylogenetic clade.^{9,10} Also, not all microbial species within a similar clade are pathogenic to humans. Some are nonpathogenic, or only pathogenic to nonprimates and seen in veterinary medicine. Therefore, clinicians in different regions should be familiar with the epidemiology of pathogenic strains endemic to their region.

However, with widespread travel throughout the world, OI cases not usually endemic to a region can also be observed, stressing the importance of travel history in such cases.¹¹

Microbiological diagnosis of OI can be achieved by biological, serologic, histologic, or molecular methods.^{12,13} All have advantages and disadvantages, but sensitivity and specificity are generally high for these modalities and vary based on the specific test, sample, and organism.¹⁴ False-negatives and cross reactivity are possible confounders in any methodology. Therefore, correlation of results with clinical findings, and a combination of tests, usually provides higher accuracy for definitive diagnosis. Parasites can be especially difficult to culture in vitro and time consuming because of the complex life cycle of these organisms and the many variables involved.¹⁵

Contemporary diagnostic microbiology is progressively adopting molecular methods (eg, DNA/RNA-based assays) as first-line tests for a variety of samples.¹⁴ Serologic assessments for circulating antigens or antibodies can be useful for many infections. Molecular methodology includes assays based on polymerase chain reaction, in situ hybridization, immunosorbent techniques, direct and indirect immunofluorescence, next-generation sequencing, and spectroscopy. For dentists in private practice or not in a hospital setting, one challenge in clinical diagnostic microbiology of oral OIs is limited knowledge of commercial laboratories able to perform all needed tests or specific tests, particularly for rare conditions or organisms not routinely investigated in many laboratories, such as certain viral or parasitic pathogens. Additional challenges in diagnostic microbiology include heterogeneity in laboratory methodology, lack of universal standardization or harmonization, and microbial heterogeneity.^{16,17}

Risk Factors

Patients most susceptible to OIs in general are those with compromised immunity.¹⁸ Accordingly, comorbidities such as human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), diabetes, cancer, or neutropenia can play a significant role in susceptibility to oral OI and the course of disease. For example, it has been shown that in transplant patients and hemodialyzed patients (diabetic and nondiabetic), multiorgan disturbances influence both the occurrence of secondary clinical oral manifestations and prevalence and species composition of oral pathogens.¹⁹ Box 1 lists some of the at-risk populations or risk factors associated with oral OIs that have been reported in the literature.^{20–24} Familiarity with comorbidities and factors linked to the development of oral OI proves useful for clinical risk assessment, diagnosis, treatment planning, and prevention. In certain cases of oral OI, treatment of the underlying comorbidity and elimination of risk factors is necessary to achieve clinical resolution of secondary infection.

Diseases

Table 2 lists the various opportunistic IDs that can be encountered clinically in the oral cavity and oropharynx by microbial category. Many of the conditions listed in Table 2 can affect regions other than the oral cavity, and can also be seen in immunocompetent individuals. In contrast, some conditions almost exclusively affect the oral cavity, such as secondary infection or osteomyelitis in medication-related osteonecrosis of the jaw

(MRONJ), as shown in Fig. 1.²⁵ MRONJ is more prevalent and severe in patients with comorbidities such as cancer or immunosuppression, and clinical suppuration and oral trauma have been shown to be independent risk factors for disease onset.²⁶ MRONJ is also known to be associated with bacterial biofilms, making treatment more challenging.^{27,28} In this case, ID consultation was sought, and culture and antibiotic susceptibility testing (AST) was performed from exudate swabs and tissue samples. Gram-staining results were nonspecific and positive for gram-negative pleomorphic rods and white blood cells. Molecular results specifically identified *Serratia marcescens* as the predominant pathogen and AST using Kirby-Bauer methodology revealed sensitivity to ceftriaxone, gentamicin, moxifloxacin, and trimethoprim/sulfamethoxazole (antibiotics not routinely used in dentistry), and resistance to ampicillin, cefazolin, and amoxicillin, which are more commonly used in dentistry. This case of MRONJ shows the importance of familiarity with risk factors for specific oral OIs, such as cancer, chemotherapy, suppuration, and tooth extraction with MRONJ. It also shows how a resident pathogen can become opportunistic in a susceptible patient. It further shows the relevance of sampling and culture for pathogen identification and more targeted therapeutics, and the utility of radiographs to assess hard tissue involvement given the anatomic location of disease. Further, in cases like this, tissue samples for culture may be just as important as, or more relevant than, swab cultures for molecular diagnosis. Microscopic evaluation of tissue in MRONJ cases can also be useful to rule out metastatic cancer to the jaws or other differentials in the clinical diagnosis, and the histopathology in this case was consistent with an osteomyelitis of the jaw, although not specific enough for accurate microbiological diagnosis.

When dealing with potential OI, ID paradigms apply given the context of communicable disease, and infection control measures and universal precautions should be used. In some cases, the presence and identification of an oral OI, or multiple lesions of oral OI in the same patient, may raise clinical suspicion for undiagnosed immunosuppression. In such cases, systemic evaluation and ID consultation should be sought because further laboratory and medical investigations may be warranted to assess systemic health and immune status, as shown in Fig. 2. In the context of HIV, early diagnosis of infection and immunosuppression, along with access to medical care and antiretroviral therapy, plays an important role in HIV-related oral disease prevention.²⁹ Vaccination for HIV-related IDs is also a consideration in patients with HIV to prevent specific OIs.³⁰ This case also shows that not just rare pathogens but common organisms, such as *Candida* spp, can be opportunistic or more virulent in immunocompromised patients. Furthermore, less common *Candida* species may be seen in immunocompromised hosts, such as *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, *Candida dubliniensis*, or *Candida geotrichum*. This finding reinforces the need in some cases for culture and molecular diagnostics for more definitive subtyping. Overall, there has been a reduction in HIV-related oral OIs, except for an increase in HPV-related lesions in the era since highly active and combined antiretroviral therapy.^{31,32}

Clinicopathologic Considerations

The clinical presentation of oral OIs is diverse. Tissue damage can occur as a direct result of invading pathogens, or secondary to host immune responses. Systemic findings, if present,

may include fever, malaise, fatigue, malnutrition, or lesions analogous to or different from those found in the oral cavity. Lymphadenopathy may or may not be a feature with oral OIs. In some cases of oral OI, serologic studies may reveal increased levels of nonspecific inflammatory markers such as C-reactive protein, or an increased erythrocyte sedimentation rate. Determining microbial etiopathogenesis (ie, bacterial, fungal, viral, or parasitic) based on clinical features, history, and signs and symptoms can be helpful for informing initial empiric pharmacotherapy until further testing and results.

Oral lesions associated with OIs can present with a broad range of morphologies, including ulcer, plaque, cyst, wart, erosion, granuloma, nodule, sequestrum, or abscess. None of these are pathognomonic for a specific disease, but can aid in identifying causes and guide further testing for a more definitive diagnosis, such as culture or biopsy. For example, an oral abscess would be more appropriate for swab culture, as opposed to solid warts (Fig. 3) or nodules, which would be more suitable to biopsy and histopathologic evaluation for definitive diagnosis. Molecular confirmation with in situ hybridization is useful for diagnosis in oral condyloma acuminatum, as in this case.

When a nonhealing oral lesion is available for biopsy, results can be informative for diagnosis or further testing. For example, Fig. 4 shows histopathologic findings for a patient with a nonhealing area of necrotizing ulcerative gingivitis clinically that was nonresponsive to local therapy and antibiotics. Biopsy was performed and suggestive of histoplasmosis fungal infection with associated inflammatory response. Without biopsy these organisms and diagnosis could easily have been missed, and even with biopsy the diagnosis is challenging. Parasitic protozoa that cause diseases like leishmania and Chagas disease have similar histopathologic findings to histoplasmosis because all are intracellular parasites.

Histoplasma organisms are uniform in size and morphology, with a characteristic clear halo encompassing the cell wall, whereas protozoa may be of various sizes and morphologies without a clear halo. However, diagnosis can be difficult on histopathology alone, especially when organisms are not readily identifiable on hematoxylin-eosin sections, requiring further testing or special stains. Periodic acid-Schiff or silver-based stains are useful for identifying structures with high carbohydrate content, such as the cell wall of fungi, aiding in discrimination from protozoa. Other fungi and fungal diseases in the differential diagnosis of histoplasmosis, such as *Cryptococcus*, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and mucormycosis have different histomorphologic features (eg, hyphae or sporulation) from histoplasmosis and are usually geographically specific. This case also shows how clinical and epidemiologic correlation and additional testing or stains are warranted for definitive diagnosis, and ID specialty referral is essential after oral diagnosis to rule out pulmonary, pericardial, meningeal/cerebrospinal fluid, or other systemic involvement that can be seen with histoplasmosis, and also to assess immune status and provide appropriate systemic antifungal therapy. ID consultation can also be useful when intravenous antimicrobials are indicated for treatment.

Histopathology is also useful for identifying infections associated with granulomatous inflammation, but is limited for definitive diagnosis. In granulomatous cases, additional stains include Gomori methenamine silver, Giemsa, periodic acid-Schiff, and Ziehl-Neelson.

³³ In addition, the histopathology of an oral OI caused by a parasitic helminth is shown in

Fig. 5 from a patient with an enlarging oral submucosal mass. A larval form of a parasite was identified in the biopsy specimen, warranting ID consultation for blood, urine, and fecal testing for systemic molecular diagnosis. Advanced imaging studies such as computed tomography scans or MRI can also be useful in such cases for systemic evaluation.

In general, treatment of oral OIs is based on clinical presentation, causative pathogens, anatomic involvement, and also management of any underlying comorbidities. Current reference materials can provide up-to-date approaches to treatment of most oral OIs and specific causative pathogens (eg, antibiotic, antifungal, antiviral, or antiparasitic drugs), but again this first requires an accurate diagnosis and knowledge of causal pathogens.

The information and cases presented herein show the heterogeneity in clinical presentations and manifestations of oral OIs. Case exemplars from each causal category (bacterial, fungal, viral, and parasitic) are presented in this article to highlight microbiological and clinicopathologic considerations relevant to practice. Importantly, some oral OIs may be associated with an increased risk for cancer development in affected patients and require long-term follow-up and surveillance. Examples include Kaposi sarcoma in patients with HIV/AIDS, or the increase in oropharyngeal cancers in younger patients caused by high-risk HPV subtypes.³⁴ Therefore, clinical risk assessment and history with review of systems, and again accurate diagnosis, treatment, and follow-up, are essential in cases of oral OI for improved patient outcomes. Because many of the pathogens associated with oral OIs are transmissible or communicable, infectious disease paradigms apply and ID consultation may be appropriate in some cases as this article has shown. Further, the oral cavity with its robust microbiota can act as a source of pathogens to induce clinically significant OIs, particularly in immunosuppressed individuals. Thus, evaluation of the oral cavity in patient populations susceptible to OIs in general is highly recommended.

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KEY POINTS

- An oral opportunistic infection (OI) is initiated by either exogenously acquired pathogens or resident host flora, and usually occurs in hosts with weakened immunity or known risk factors.
- Specific pathogens implicated in oral OIs include various species of bacteria, fungi, virus, and parasites, and infectious disease paradigms apply given the context of communicable disease.
- Microbiological diagnosis of oral OI can be achieved by biological, serologic, histologic, or molecular methods.
- Treatment of oral OIs is based on clinical presentation, causative pathogens, anatomic involvement, and also management of any underlying comorbidities.

Box 1**Risk factors for oral opportunistic infections**

Age

Chemotherapy

Chronic steroid therapy (local or systemic)

Diabetes (uncontrolled)

Drugs/medications

Genotype

Geography

Head and neck radiotherapy

HIV/AIDS

Hospitalization/nosocomial

Leukopenia/lymphopenia/neutropenia

Poor oral hygiene

Pregnancy

Sexual exposure

Smoking

Surgery

Syndromes

Transplant-associated immunosuppression

Trauma

Vector transmission

Xerostomia

Zoonosis

Fig. 1.

A 71-year-old man with advanced-stage prostate cancer who was undergoing active chemotherapy (monthly intravenous zoledronate) and developed an oral OI of MRONJ. (A) Copious purulence is seen (*arrows*) extruding from the interdental space of the jaw, which was painful, and teeth tested nonvital. (B) A large area of exposed sequestrum is observed (*arrow*) at the nonhealing site following tooth extractions. (C) Gross specimen debrided from the infection for culture and histopathologic evaluation. (D) Radiograph of the jawbone showing ill-defined osteolysis around the anterior mandibular teeth with loss of lamina dura. (*Courtesy of Allan C. Jones DDS, MS, Torrance, CA.*)

Fig. 2.

An man with several types of OI in the oral cavity. (A) Central papillary atrophy (*black arrow*) of the tongue and a wart or papilloma (*green arrow*) of the lateral tongue is seen. (B) The palate shows evidence of pseudomembranous (*black arrow*) and erythematous (*green arrow*) candidiasis. (C) A Sabouraud dextrose agar slant from clinical swab for fungal culture is strongly positive and fungal colony-forming units (*black arrows*) can be seen. These combined findings should raise suspicion for immunosuppression and HIV, which was subsequently confirmed with additional testing and serology.

Fig. 3.

(A) Labial mucosa at commissure shows wartlike growths. (B) Histopathologic examination of biopsy reveals koilocytosis (*black arrows*), which represents squamous cells with large and irregular, well-defined perinuclear halos and cytoplasmic thickening; nuclear irregularity and variation in size is also observed (hematoxylin-eosin 100, original magnification $\times 40$). (C) Digoxigenin-labeled probe counterstained with nuclear red (original magnification $\times 10$).

Fig. 4.

The top image shows a hematoxylin-eosin-stained section from a necrotizing ulcerative gingivitis biopsy. Histopathologic evidence of acute inflammation or neutrophils (*blue arrows*) is seen in a background of chronic inflammation comprising macrophages and histiocytes. Vague granulomas (*top left*) were also observed. Intracellular microbes consistent with histoplasmosis could be seen (*red arrows*) in a granular cytoplasm within phagocytic cells. The bottom image shows a periodic acid-Schiff stain, which highlights fungal cell walls and more readily shows tissue pathogens (*red arrows*). Top-(20 × original

magnification), Bottom-(10 × original magnification). (*Courtesy of Audrey Boros, MSc, DDS, Los Angeles, CA.*)

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Fig. 5. Oral submucosal mass consistent with helminth larvae (red *arrows*) at a cross section of the parasite's digestive tract. (*Courtesy of Yeshwant Rawal, BDS, MDS, MS, Seattle, WA.*)

Table 1

Representative pathogens by microbial category that can be encountered in patients with oral opportunistic infections

Bacteria	Fungi	Virus	Parasites
<i>Actinomyces</i>	<i>Aspergillus</i>	Bunyaviridae	<i>Balantidium</i>
<i>Aggregatibacter</i>	<i>Candida</i>	Cytomegalovirus	<i>Calliphora</i>
<i>Bacteroides</i>	<i>Cryptococcus</i>	Coxsackievirus	Cestodes
<i>Bartonella</i>	<i>Geotrichum</i>	Echovirus	<i>Chrysomya</i>
<i>Brucella</i>	<i>Histoplasma</i>	Epstein-Barr virus	Ciliophora
<i>Campylobacter</i>	Mucoraceae	Herpes simplex virus	<i>Cochliomyia</i>
<i>Capnocytophaga</i>	<i>Paracoccidioides</i>	Human papillomavirus	<i>Cordylobia</i>
<i>Corynebacterium</i>	<i>Penicillium</i>	Kaposi sarcoma virus	<i>Cryptosporidium</i>
<i>Coxiella</i>	<i>Sporothrix</i>	Paramyxovirus	<i>Demodex</i>
<i>Dialister</i>	<i>Trichophyton</i>	Poxvirus	<i>Dermatobia</i>
<i>Eikenella</i>		Roseolovirus	<i>Entamoeba</i>
<i>Enterobacter</i>		Togavirus	<i>Giardia</i>
<i>Escherichia</i>		Varicella zoster virus	<i>Hypoderma</i>
<i>Francisella</i>			Larvae forms
<i>Fusobacterium</i>			<i>Lucilia</i>
<i>Haemophilus</i>			<i>Musca</i>
<i>Klebsiella</i>			Nematodes
<i>Micrococcus</i>			<i>Oestrus</i>
<i>Micromonas</i>			<i>Plasmodium</i>
<i>Mycobacteria</i>			<i>Rhinosporidium</i>
<i>Peptostreptococcus</i>			Trematodes
<i>Porphyromonas</i>			<i>Trichomonas</i>
<i>Prevotella</i>			Trypanosomes
<i>Propionibacterium</i>			<i>Wohlfahrtia</i>
<i>Pseudomonas</i>			
<i>Salmonella</i>			
<i>Serratia</i>			
Staphylococci			
<i>Streptococcus</i>			
<i>Tannerella</i>			
<i>Treponema</i>			
<i>Veillonella</i>			
<i>Yersinia</i>			

Table 2

Opportunistic infections that can affect the oral cavity by microbial category

Bacterial	Fungal	Viral	Parasitic
Actinomycosis	Aspergillosis	Aggressive periodontitis	Amebiasis
Bacillary angiomatosis	Blastomycosis	Condyloma acuminatum	Chagas disease
Cat-scratch disease	Candidiasis	Hand-foot-and-mouth disease	Cysticercosis
Cellulitis	Coccidioidomycosis		Dirofilariasis
Leprosy	Cryptococcosis	Heck disease	Filariasis
Linear gingival erythema	Histoplasmosis	Herpes zoster	Leishmaniasis
	Mucormycosis	Infectious mononucleosis	Mesomycetozoa
Mucositis	Paracoccidioidomycosis	Kaposi sarcoma	Myiasis
Necrotizing ulcerative gingivitis	Penicilliosis	Mucocutaneous ulcers	Toxoplasmosis
	Phycomycosis	Molluscum contagiosum	
Necrotizing ulcerative periodontitis	Sporotrichosis	Oral hairy leukoplakia	
		Papillomas	
Necrotizing ulcerative stomatitis		Papillomatosis	
		Parotitis	
Oral syphilis		Recurrent herpes	
Oral tuberculosis			
Osteomyelitis			
Osteonecrosis			
Parotitis			