Oral Fungal Infections
Diagnosis and Management

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KEYWORDS
- Candidiasis • Oral thrush • Oral fungal infection • Mucormycosis • Histoplasmosis
- Blastomycosis • Aspergillosis • Geotrichosis

KEY POINTS
- Most solitary or primary oral fungal infections are rare with the exception of oral candidiasis.
- Candidiasis is the leading infection that most dental practitioners will see in clinical practice.
- Unless diagnosed early and treated aggressively, mucormycosis can be a locally invasive and disfiguring oral and maxillofacial fungal infection.
- This review includes several oral and maxillofacial fungal infections, including mucormycosis, candidiasis, aspergillosis, blastomycosis, histoplasmosis, cryptococcosis, and coccidioidomycosis.

INTRODUCTION

Fungal infections are of great concern in dentistry. Patients may present with infections that can be superficial or indicative of a more serious systemic illness. This article focuses on fungal infections that can range from primary (superficial) to disseminated infections that have a high mortality. Included in the review are the most common oral and maxillofacial fungal infections, route of spread, diagnosis, treatment as well
as prevention. Although uncommon in a dental practice setting, one may encounter fungal infections, such as candidiasis, mucormycosis, histoplasmosis, blastomycosis, aspergillosis, cryptococcosis, geotrichosis and coccidioidomycosis. Table 1 is a broader and comprehensive list of potential oral and maxillofacial fungal infections to serve as reference if one encounters an uncommon organism not covered in this article.

CANDIDIASIS

*Candida* is a dimorphic yeast (fungus) found commonly in the gastrointestinal tract of humans and as normal flora of the skin and mucous membranes. In its normal form, *Candida* is not pathogenic and stays in balance such that it cannot progress to cause infection. Typically, *Candida* infections occur when one of several scenarios happen, including but not limited to, host defenses becoming compromised, a breakdown of the normal skin or mucosal barrier, a disturbance of the host by external factors (such as intake of broad-spectrum antibiotics), or other internal/external risk factors increasing the likelihood of a *Candida* infection. The *Candida* species consists of 2- to 6-μm yeastlike organisms that reproduce through budding. The genus *Candida* includes more than 200 species, most of which are not pathogenic in humans. The most common *Candida* species encountered is *Candida albicans* and accounts for more than 90% of oral cavity isolates. Other common *Candida* species encountered with human pathogenicity include *Candida parapsilosis*, *Candida tropicalis*, *Candida glabrata*, *Candida krusei*, *Candida guilliermondii*, and *Candida lusitaniae*. In healthy individuals, *Candida* spp is reported to be present in 25% to 75% of the population in the absence of any lesion caused by *Candida*.

Candidiasis can present in several forms of infection depending on how deeply the organism has spread, or if host defenses allow for more substantial infections. The most commonly encountered infection from *Candida* is oral thrush, also known as pseudomembranous candidiasis. This type of infection is typically characterized by a white cottage cheese–like film that clinically can be wiped off to reveal a base that

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<td>Candidiasis</td>
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<td>Hyperplastic</td>
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<td>Erythematous</td>
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<td>Pseudomembranous</td>
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<td>Angular cheilitis</td>
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<td><strong>Deep systemic mycoses</strong></td>
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<td>Histoplasmosis</td>
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<td>Cryptococcosis</td>
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<td><strong>Deep opportunistic</strong></td>
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<td>Aspergillosis</td>
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Various potential oral and maxillofacial fungal infections; all bolded are included in the focus of this article.

*Courtesy of D.R. Telles, DDS, Huntington Beach, CA.*
typically is erythematous and at times bleeds. The plaque that can be removed is typi-
cally made up of aggregates of the pseudo-hyphae and hyphae form of the organism
and byproducts of epithelial breakdown. This infection occurs in higher-risk popula-
tions such as neonates, whose host defenses have yet to develop. In a neonate, typi-
cally the transmission can be from either a health care worker or the mother.
Because of not having innate immunodefenses, oral thrush in the first several months
of life can result. In addition to neonates, oral candidiasis increased in the early to
mid-1980s due to the progression of human immunodeficiency virus/acquired immu-
nodeficiency syndrome (HIV/AIDS). During the early years of HIV management, oral
thrush began developing in young individuals and became a red flag of HIV infection.
With the introduction of highly active antiretroviral therapy (HAART), the advances in
management of HIV improved drastically, impacting the incidence of candidiasis and
resulting in a significant reduction of thrush worldwide in HIV patients. However, it is
important to note that oropharyngeal (ie, esophageal) candidiasis is a clinical predictor
of HIV disease progression, and after the initial presentation of oropharyngeal candidi-
asis, AIDS is typically seen within 1 to 3 years. In contrast, because of the overuse/
misuse of oral antibiotics as well as advances in medical management (including organ
transplant, stem cell transplantation, parenteral nutrition, advanced surgical proced-
ures, and chemoradiotherapy), there has been an increase in superficial and invasive
forms of candidiasis.

With disease progression, there are other forms of candidiasis that affect the maxil-
lofacial complex, including angular cheilitis, median rhomboid glossitis, chronic hyper-
plastic, atrophic candidiasis/denture stomatitis, chronic mucocutaneous, and chronic
multifocal candidiasis. In a patient, when encountered with *Candida*, unless host de-
defenses are compromised, it is rare to see the development and progression of candidal
infections. In this article, candidal infections, limited to the oral and maxillofacial com-
plex and the disease progression to deeper or invasive candidiasis, are focused on.

Table 2 shows several different host defenses as well as deficiencies that prevent or
expose the host to the development of a *Candida* infection.

Data from Scully C. Candidosis (candidiasis). In: Oral and maxillofacial medicine—the basis of diag-

| Host defenses and deficiencies preventing or exposing host to *Candida* infection |
|-----------------------------------|-----------------------------------|
| Host defenses | Host deficiencies |
| Skin/mucous membrane barrier | Acquired |
| Salivary nonimmune defenses | HIV/AIDS |
| Lysozyme | Uncontrolled diabetes mellitus or other endocrinopathies |
| Lactoferrin | Broad-spectrum antibiotics |
| Lactoperoxidase | Chemoradiotherapy |
| Histatins | Chronic steroid use |
| Antileukoprotease | Long-term indwelling catheterization |
| Calprotectin | Fluid and electrolyte disorders |
| B-protecin | Organ or bone marrow transplant |
| Histidine-rich polypeptides | Malnutrition with or without chronic alcoholism |
| Oral immune defenses | Congenital |
| T cell–polymorphonuclear cells | Partial or combined immunodeficiencies |
| Phagocytosis | Di George syndrome |
| Augmentation via lymphokines/ interleukins, for example, tumor necrosis factor-α, IL-12 | |
| Salivary IgA | |
Risk Factors

Oral candidiasis and other forms of Candida infections occur more commonly in specific sets of patients most at risk. When encountering a Candida infection, the practitioner should always consider the etiologic reason for the development of a candidiasis because typically there is a condition or comorbidity associated with such infections. Although not all conditions can be changed, when encountering conditions causing a Candida infection, such as hygiene, diabetes, or denture use (Box 1), if these conditions can be modified, then this is the most successful way to both treat the Candida infection and prevent recurrence.

Xerostomia

In the oral cavity, xerostomia can result in several problems with the dentition as well as the risk of developing Candida infections. Stasis of saliva and diminished salivary gland function result in the patient’s inability to produce several defensive antimicrobial mechanisms in the saliva. Saliva contains several defense mechanisms, including “defensins, lactoferrin, sialoperoxidase, lysozyme, histidine-rich polypeptides and anti-Candida antibodies.”11 For example, with respect to lactoferrin, the defense mechanism plays a fungicidal role thatch actively kills Candida before entering the host tissue. Mucosal saliva acts therefore as the first line of defense against Candida, which allows the commensal organisms to stay in balance with other oral biota.

With respect to corticosteroid intake, Alsaeedi and colleagues12 reviewed 9 clinical trials regarding patients with chronic obstructive pulmonary disease from a total patient pool of 3976, which found that the risk for development of Candida infections increased by 2.1 times when taking inhaled forms of corticosteroids. The basis for chronic steroid intake resulting in Candida infection is secondary to the decrease in cellular immunity and phagocytosis.

Box 1

Risk factors for development of oropharyngeal candidiasis

Local Factors
Xerostomia (polypharmacy, Sjogren syndrome, dehydration, radiation)
Broad-spectrum antibiotics or steroid intake
High-carbohydrate diet
Leukoplakia/oral cancer
Denture use
Cigarette use

Systemic Factors
Neonate, advanced age
Diabetes
Nutritional deficiencies
Malignancies
Immunosuppression

Denture Use

Denture stomatitis is the classic representation of Candida infections typically presented as the atrophic variant noted by denuded, erythematous mucosa only at times presenting with a pseudomembrane (Fig. 1). When atrophic candidiasis is seen under a denture, the thought is that this is related to poor denture hygiene, giving C. albicans the ability to adhere to the intaglio surface of the denture acrylic, thus resulting in its colonization. Because of the immobile nature of the mucosa and lack of salivary flow, the environment optimizes the mucosa for infection. The intaglio aspect of the denture contains a plaque, resulting in the formation of a biofilm, which has been well studied and documented as a causative agent of denture stomatitis (atrophic candidiasis).13,14 Based on a review by Arendorf and Walker,15 approximately 67% of existing denture wearers are thought to have Candida-associated denture stomatitis.

Along with denture stomatitis, angular cheilitis (Fig. 2) can also be seen in denture wearers because of collapsed vertical dimension of occlusion resulting in the collapse of the corners of the mouth. Over time, the collapsed areas become moist, harboring an ideal environment for both Candida and Staph infections to develop.16

General hygiene recommendations were published by the American Dental Association in 2011 regarding the proper management of dentures. Among these recommendations was the key recommendation that all denture wearers who are experiencing denture stomatitis remove their dentures at night. The treatment is 2-fold: treating the patient intraorally with topical antifungals as well as properly cleaning their dentures. According to Felton and colleagues,17 the following recommendations should be given to the patient:

1. Dentures should be cleansed daily with a nonabrasive denture cleaner
2. Never soak dentures greater than 10 minutes in a sodium hypochlorite bleach mixture
3. Store dentures overnight in water
4. Ultrasonic cleaning by a licensed dental practitioner is encouraged to reduce biofilm buildup
5. Denture adhesives and other debris should be completely removed from the denture daily
6. Denture checks should be performed by treating dentists at least yearly to check for retention, fit, occlusion, and stability17

Fig. 1. Denture stomatitis. Maxillary removable partial denture with a noted deep red base. The lesions are typically outlined around the denture base. (From Muzyka BC, Epifanio RN. Update on oral fungal infections. Dent Clin North Am 2013;57(4):568; with permission.)
The presentation of *Candida* infections and their associated signs and symptoms vary, depending on which type of infection the host is experiencing. Table 3 includes a breakdown of several forms of *Candida* infections that can occur, with some being more superficial (such as thrush) and requiring less aggressive treatment compared with deeper infections such as candidemia or invasive candidiasis. Typical complaints of superficial infections include itching, burning, easy bleeding, discharge, soreness, and rash. A typical sign that could be picked up with a superficial infection would include a pseudomembrane that would be removable that shows underlying mucosal

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Forms of candidiasis</th>
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<tbody>
<tr>
<td><strong>Various Presentations of Candida Infections in the Body</strong></td>
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<tr>
<td>Oral candidiasis (thrush/pseudomembranous)</td>
<td>Osteoarticular</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>Median rhomboid glossitis</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>Denture stomatitis/erythematous (atrophic) oral candidiasis</td>
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<tr>
<td>Chronic mucocutaneous</td>
<td>Multifocal candidiasis</td>
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<tr>
<td>Esophageal</td>
<td>Urinary tract infection</td>
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<td>Severe forms</td>
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<td>Hyperplastic candidiasis/leukoplakic</td>
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<td>Candidemia</td>
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<tr>
<td>Disseminated (hepatosplenic)</td>
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The infection by *Candida* can appear in several different forms from subtle superficial infections like pseudomembranous candidiasis to invasive endocarditis. Early identification is key for the treatment of more penetrating or deep infections involving *Candida*. For any presentation, a review of the patient's host defenses is necessary.  
**Courtesy of D.R. Telles, DDS, Huntington Beach, CA.**
irritation with edema and erythema. With deeper infections, signs can vary based on the severity of infection, such as hemodynamic instability, shock, positive blood cultures, fever, and tachycardia; in compromised hosts, death can result if diagnosis is delayed.

**Oropharyngeal**

During the early evolvement of the HIV epidemic in the 1980s, oral thrush began appearing in otherwise young healthy men. As seen in Fig. 3, the presentation of oropharyngeal thrush typically presented as a pseudomembranous form. Clinically, the covering over the affected mucosa contains a white plaque, which can be wiped off with gauze to reveal red and at times bleeding mucosa underlying the plaque. In the 1980s, the initiation of thrush became highly suggestive of HIV infection. In contrast, there is an additional form known as atrophic candidiasis in which the mucosa of the tongue, palate, buccal mucosa, or lateral tongue can appear as red and erythematous and commonly presents with pain or a burning sensation.

Invariably, as treatment progressed and antiviral therapies improved, such as the introduction of HAART, oral thrush incidence decreased with the successful treatment of HIV infection. Specifically, Greenspan and colleagues\(^1\) retrospectively studied 1280 HIV patients from 1990 to 1999. The study focused on determining the correlation between antiretroviral therapy (ART) or HAART therapies and the incidence of oral candidiasis, oral hairy leukoplakia, and oral warts (Figs. 4 and 5).

The study concluded that the incidence of oral candidiasis was found to decrease as the ART or HAART therapy advanced with the introduction of protease inhibitors.\(^1\)\(^8\)\(^9\) After adjusting for CD4 count and viral load, the odds of having candidiasis were lower in patients on either ART therapy (odds ratio of 0.32) or HAART therapy (odds ratio of 0.28) compared with patients on neither of these therapies.\(^1\)\(^8\)\(^9\) The mechanism behind the activity of protease inhibitors is activity against a major virulence factor of *C albicans* known as aspartyl proteinase (SAP) enzyme.\(^1\)\(^9\) Cassone and colleagues\(^2\)\(^0\)\(^2\)\(^1\) demonstrated that the use of protease therapy reduced SAP enzyme activity, resulting in decreased candidiasis incidence.

In an HIV individual, the highest-risk patients typically have a CD4 T-cell count of less than 200, which by definition is the onset of AIDS. Patients with CD4 counts between 350 and 500 rarely exhibit clinical findings of immunosuppression and those with CD4 counts between 200 and 350 typically present with illnesses such as candidiasis (oral thrush), mucosal infections, or herpes zoster.\(^1\)\(^9\) In 2000, Patton\(^2\)\(^2\) at the University of North Carolina at Chapel Hill studied 606 adults (455 men and 151

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**Fig. 3.** Oral thrush (pseudomembranous candidiasis of the oral cavity). (Courtesy of M.W. Marshall, DDS, Huntington Beach, CA.)
women) infected with HIV who self-identified as HIV positive. The study concluded that certain common oral lesions, including pseudomembranous candidiasis, are strong indicators of immune suppression and thus serve as potential clinical markers of HIV. In an earlier study, Patton and colleagues found in a sample of 250 individuals through a bivariate analysis, that HIV-infected individuals with oral lesions, including Fig. 4. Changes in prevalence of oral lesions. During the early 1990s, ART and HAART therapies did not include protease inhibitors. Notable was the decrease in oral candidiasis after the introduction of protease inhibitors from 1996 to 1999. (From Greenspan D, Canchola AJ, MacPhail LA, et al. Effect of highly active antiretroviral therapy on frequency of oral warts. Lancet 2001;357(9266):1411; with permission.)

Fig. 5. Oral lesions and use of ART, 1996 to 1999. Decreases are noted in the incidence of oral candidosis (candidiasis) when taking either ART or HAART therapies versus not taking any treatment. (From Greenspan D, Canchola AJ, MacPhail LA, et al. Effect of highly active antiretroviral therapy on frequency of oral warts. Lancet 2001;357(9266):1411; with permission.)
hairy leukoplakia or oral candidiasis, were 1.8 times more likely to have a plasma HIV viral load of 20,000 copies/mL or higher than individuals without lesions.

Other typical causes of oral thrush can include the administration of broad-spectrum antibiotic, immunocompromised status, cancer, extremities of life (newborn or elderly), inhaled corticosteroids, and xerostomia. The intraoral locations of thrush can vary from patient to patient but typically involve the tongue, buccal mucosa, palate, and gingiva.

Median rhomboid glossitis (central papillary atrophy) is a variation in atrophic candidiasis that can present as a dorsal midline red lesion on the tongue (Fig. 6). The surface is typically de-papillated, but when biopsied with either brush or incisional, renders Candida infection. Fig. 6 shows an example of the appearance of the lesion that typically affects men 3 times as often as women, according to Muzyka and Epifanio.24

Hyperplastic Candidiasis

With hyperplastic candidiasis, the provider is alerted that the patient has some form of leukoplakia/dysplasia or a verrucous variant of mucosal changes. As seen in the 3 photographs in Fig. 7, this patient has a white mottled-appearing lesion on the left buccal mucosa. Hyperplastic lesions have the tendency to extend into the lip commissure, similar to the lesions shown in the 3 photographs in Fig. 7. In addition, the lesions can appear nodular or speckled. Other areas that can present with this unique form of Candida include the lateral border of the tongue and palate.25 This form of Candida has an increased risk for developing dysplasia or malignancies and therefore should be closely followed.26 Fortunately, this form of oral pharyngeal candidiasis is rare.

Fig. 6. Median rhomboid glossitis. (From Muzyka BC, Epifanio RN. Update on oral fungal infections. Dent Clin North Am 2013;57(4):568; with permission.)
Esophageal candidiasis can result from swallowing Candida when a host already has an active oral fungal infection. When the passage of saliva includes infected tissues and food, the yeast can result in adherence to the esophageal lining. If esophageal candidiasis progresses, it can result in the following symptoms: scarring, obstructions, esophageal stricture, substernal discomfort or chest pain, nausea, and vomiting. Clearly, one of the first signs of Candida spreading presents as dysphagia or odynophagia.\textsuperscript{27,28} In some cases, oral infection of candidiasis may not precede the development, and therefore, other causes must be explored. Esophagitis is associated with cancer, organ transplantation, proton pump inhibitors, progressive HIV infection to AIDS, or primary chronic mucocutaneous disorders. When symptoms of esophageal candidiasis are present, the gold standard is for direct endoscopy, and if patches or lesion are observed, then direct brush or incisional biopsy is indicated. Radiographic evaluation of the esophagus will also aid in the diagnosis of obstruction, fistula, bleeding, perforation, or stricture, which may require endoscopic dilation.\textsuperscript{29} Medical management via antifungals, in conjunction with urgent referral to a gastrointestinal specialist, is indicated when suspicious of esophageal candidiasis. Respiratory infections can also develop, including involvement of the larynx, pharynx, bronchi, or pulmonary circuit. Candida has been well documented to have the ability to infect anywhere along the respiratory tract and has the potential to cause bronchitis or pneumonia. Typical presenting clinical manifestations include cough, tachypnea, dyspnea, tachycardia, and fever. In some cases, empyema and abscesses can result in lung

\textbf{Esophagitis, Pneumonia, Bronchi}

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\begin{figure}[h]
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\caption{Hyperplastic candidiasis. As shown in these 3 photographs (A–C), the presentation of nonwipeable plaques appear as white and red patches. When biopsied, this specimen rendered Candida infection with hyphae and pseudohyphae present on the H&E stain (hematoxylin-eosin, original magnification $\times XX$). The patient was treated with Ketoconazole successfully. (Courtesy of M.W. Marshall, DDS, Huntington Beach, CA.)}
\end{figure}
damage and scarring. In addition to altered pulmonary functions tests, a clinical presentation of a patient with chronic pneumonia could include clubbing of the fingers due to chronic hypoxemia. Primary *Candida* pneumonia is a rare condition resulting from the aspiration of oropharyngeal contents into the respiratory tract. Secondary *Candida* pneumonia results from seeding of *Candida* in an individual with candidemia (blood infected with *Candida*). There is a small subset of patients in the pediatric population who are also at risk for developing *Candida* allergic reactions resulting in respiratory symptoms. Treatment of all pneumonias is similar to the treatment of candidemia, which is discussed in the treatment section in later discussion.

**Chronic Mucocutaneous**

In contrast to isolated *Candida* infections, chronic mucocutaneous candidiasis can occur as a result of impaired immune function (acquired) or related primary T-cell immune deficiencies. Patients with either condition may have chronic recurrent *Candida* infections that can affect one or several areas of the body, including the skin, mouth, nails, eyes, and other mucous membranes. In primary immune deficiencies, patients with high susceptibility to chronic mucocutaneous candidiasis have deficiencies or impairment of the T-cell–mediated interleukin-17 (IL-17)–dependent T-cell immunity. This disorder is also seen in patients with endocrinopathies or autoimmune diseases, such as hypothyroidism and hypoparathyroidism, according to Coleman and Hay. This condition is considered an autosomal-dominant disorder in which patients rarely develop disseminated or invasive candidiasis.

**Diagnosis**

Typically, when *Candida* is seen in the superficial form, such as pseudomembranous, angular cheilitis, or other forms of mucocutaneous candidiasis, a presumptive diagnosis can be made with a trial of topical antifungal agents such as nystatin or clotrimazole. When superficial infections or lesions resolve, the proof is determined by the response of therapy. Laboratory testing for *Candida* infections can include incisional biopsy of a suspected lesion or brush biopsy (exfoliative cytology) followed by Gram staining or placement into a potassium hydroxide (KOH) preparation or periodic acid-Schiff. Histologically, the classic appearance of *Candida* hyphae will appear as clear tubes, whereas with Gram staining, the hyphae and yeast appear dark blue. In the PAS stain, the organism will appear red to purple. It is important to remember, as stated previously, that *Candida* is a common organism found in the oral cavity, and therefore, the simple presence of *Candida* does not prove that the lesion is associated with a *Candida* infection. Therefore, quantitative culture counts have been recommended as guidelines to prove candidiasis in a respective culture taken. In some cases, biopsy may be necessary, which includes variations in the presentation of *Candida* infections, such as leukoplakic candidiasis (hyperplastic candidiasis), invasive candidiasis, and mucocutaneous lesions, which are stored in 10% formalin in order to rule out dysplasia or other malignant conditions.

**Treatment**

Various systemic and nonsystemic (topical) agents are available for treating oropharyngeal candidiasis. Topical agents have served as the preferred therapy, particularly in uncomplicated cases. If possible, topical preparations should be used before systemic antifungal drugs. Topical agents are not absorbed systemically and thus lack the drug interactions and systemic adverse effects found with some systemic agents. Topical agents are commercially obtainable in a variety of formulations, including
troches, oral rinses, vaginal tablets, powders, and creams. Systemic agents are preferred when topical agents are ineffective or not tolerated in cases such as immunocompromised HIV or patients with cancer.

Treatment of oral candidiasis available currently is summarized in Table 4 for topical treatments and Table 5 for systemic treatments of oral candidiasis (typical if refractory to topical treatment or recurrent).

**Topical Therapy**

**Gentian Violet**

Until the 1950s and the advent of the polyene-antifungals, Gentian Violet was classically used to treat oral candidiasis. To date, Gentian Violet is used in underserved or underdeveloped countries because of its cost-effectiveness and availability. This agent has particular side effects, including mucosa staining and mucosa irritation. The dosage recommendations for this are 1.5 mL of a 0.5% solution administered twice daily until the lesions resolve, and the treatment typically is extended 5 to 7 days after the lesions have disappeared. This agent is not commonly used in the United States due to the increased efficacy of polyene alternatives.

**Polyenes**

Approximately 87 polyenes have been investigated; however, only 3 are commercially available, including nystatin, amphotericin B, and natamycin. Nystatin oral suspension remains the most commonly used polyene for the initial treatment of oral candidiasis. The drug is available as an oral suspension, lozenge, or cream. The typical formulation of a troche includes 100,000 units of nystatin, given 2 to 5 times daily for 7 to 14 days. It is important to ensure treatment extends several days after the lesions disappear in order to lower the rate or risk of recurrence of candidiasis. The general recommendation is to extend therapy 48 hours beyond resolution of perioral symptoms. Nystatin is not absorbed systemically and therefore lacks serious toxicity. Adverse effects most often involve the gastrointestinal tract (ie, nausea, vomiting, and diarrhea). Although Nystatin is often used as prophylaxis for, or treatment of, oropharyngeal candidiasis in patients with cancer or patients with AIDS, several reports have cited disappointing findings, including frequent treatment failures and early relapses.

Both Nystatin and amphotericin B are produced by *Streptomyces* species and act by binding to ergosterol and possibly to sterols in the cell membrane of fungi, altering cell membrane permeability by causing formation of aqueous pores or channels that leak cellular components and resulting in destruction of the *Candida* organism.

**Azoles**

The azoles are fungistatic, interfering with ergosterol synthesis, causing a change in the permeability of the cell membrane, leakage of cellular contents, and cell death. Clotrimazole, an imidazole, was the first broad-spectrum antifungal of its class. Clotrimazole has been reported to be effective for prophylaxis and treatment of oropharyngeal candidiasis in patients with cancer, in whom it may prevent the development of esophagitis. However, it appears to be less effective than fluconazole in treating HIV-infected patients with oropharyngeal candidiasis. Miconazole has also been shown to be effective in patients with oropharyngeal and esophageal candidiasis.

When topical treatment does not effectively control oropharyngeal candidiasis, combining a topical agent with a systemic agent may successfully eradicate infection. In addition, combining topical and systemic agents may be beneficial by permitting the use of lower dosages and shorter courses compared with a single agent.
### Table 4
Topical therapeutic options for the treatment of oral candidiasis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Vehicle or Form</th>
<th>Dose and Frequency</th>
<th>Side Effects and Special Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentian Violet</td>
<td>Solution</td>
<td>1.5 mL of 0.5% solution twice daily</td>
<td>Skin irritation, Oral ulcers, Purple staining of clothes and skin</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Cream, Ointment, Suspension, Lozenge, Tablet (vaginal)</td>
<td></td>
<td>Nausea and vomiting, Skin irritation</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Cream, Ointment, Lotion, Suspension</td>
<td>Cream, ointment, lotion: 3 to 4 times daily for a maximum of 14 d, Suspension: 100 mg/mL</td>
<td>Not absorbed from the gut</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Cream, Ointment, Gel, Lacquer</td>
<td>2% Cream and ointment: Twice daily for 2–3 wk, 2% Gel: 3 to 4 times daily for 2–3 wk, Lacquer: 1 g applied once weekly to dentures for 3 wk</td>
<td>Skin irritation, Burning sensation, Maceration</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Cream</td>
<td>2% cream 2 to 3 times daily for 14–28 d</td>
<td>Skin irritation, Headache</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>Cream, Solution, Troche</td>
<td>1% cream twice daily to 3 times daily for 3–4 wk, 1% solution 3 to 4 times daily for 2–3 wk, 10 mg troche 5 times daily for 2 wk</td>
<td>Skin irritation, Nausea and vomiting</td>
</tr>
</tbody>
</table>

**Systemic therapy**

Systemic therapy may be required in a patient with oropharyngeal candidiasis if the patient is refractory to topical treatment, cannot tolerate topical agents, and/or is at high risk for systemic infection. According to Pappas and colleagues, for patients diagnosed with invasive forms of candidiasis or candidemia, the general recommendation is to extend drug treatment for a period of 14 days after the first negative culture. The invasive forms of candidiasis and their respective recommended treatment regimens are listed in Table 6.

**Amphotericin B**

Amphotericin B is another polyene antifungal, which is effective if given intravenously (IV) to patients having severe oropharyngeal candidiasis or patients with infections refractory to other agents. For invasive candidiasis, Amphotericin B is usually prescribed at 0.5 to 0.7 mg/kg daily and as high as 1 mg/kg for more resistant species.

Amphotericin B’s principal use is in patients at risk for progressive and potentially fatal fungal infections. Its routine use is for oropharyngeal candidiasis, but it has been limited due to its toxic side effects. Notable toxic side effects include fever, chills, gastrointestinal effects, cardiovascular toxicity, pulmonary toxicity, and renal

<table>
<thead>
<tr>
<th>Agent</th>
<th>Vehicle or Form</th>
<th>Dose and Frequency</th>
<th>Side Effects and Special Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Tablet</td>
<td>200 mg daily or twice daily for 2 wk</td>
<td>US Food and Drug Administration does not advise use of oral ketoconazole</td>
</tr>
<tr>
<td>Flucanazole</td>
<td>Capsule</td>
<td>Initial loading dose of 250 mg; 50–200 mg daily thereafter for 7–14 d</td>
<td>Nausea and emesis</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Capsule</td>
<td>100–200 mg daily for 14 d</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Oral solution</td>
<td>For severe recalcitrant cases, loading dose of 200 mg 3 times daily for 3 d</td>
<td>Pregnancy risk category C</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Suspension</td>
<td>100 mg twice daily on day 1, then 100 mg daily for 13 d</td>
<td>Interactions with other medications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For refractory cases: 400 mg twice daily for 3 d, then 400 mg daily to twice daily for 25–28 d</td>
<td>Potential negative effects on male fertility</td>
</tr>
</tbody>
</table>

toxicity. However, despite such devastating side effects, amphotericin is considered a gold-standard treatment therapy for advanced *Candida* infections such as treatment of candidemia, meningitis, endocarditis, and so forth.

More recently, amphotericin is available as a nonsystemic oral rinse (topical treatment) for patients with oropharyngeal candidiasis. Amphotericin B lozenges are effective in patients susceptible to *Candida* infection. Lozenges provide delivery of a long-lasting concentration of the drug in the saliva. Unlike numerous other antifungal agents, resistance to Amphotericin B rarely occurs during therapy. In addition, the oral form of amphotericin lacks the ability to be absorbed; thus, toxic side effects are not evident.

Currently, there are 2 lipid forms of amphotericin B (LFAmB):

- Amphotericin B lipid complex
- Liposomal amphotericin B

When comparing LFAmB with Amphotericin B, LFAmB (typical dosage was 3–5 mg/kg per day), infusion-related reactions resulting in nephrotoxicity are diminished 6.6-fold compared with classic amphotericin B. Therefore, many clinicians have moved to using LFAmB for severe forms of *Candida* infections, especially in the intensive care unit setting.

**Azoles (imidazoles and triazoles)**

Azoles are recommended to treat patients with either systemic or superficial fungal infections. Azoles are broken up into 2 categories: Imidazoles (Clotrimazole, Ketoconazole, Miconazole) and Triazoles (Fluconazole, Itraconazole, Posaconazole, Voriconazole). Oral azole drugs are effective against *C. albicans*; however, they show limited use in resistant *C. krusei* and *C. glabrata*.39

Clotrimazole, when compared with historical treatment of oral candidiasis using nystatin rinses or troches, has shown superior efficacy in alleviating and preventing oral candidiasis. Clotrimazole is available in both creams and troches for treating all forms of oral candidiasis, including angular cheilitis. Based on the experience of the authors, it is their recommendation that first-line therapy start with 10 mg troches 5 times a day for a 14-day period. However, if patient compliance for this frequency of Clotrimazole presents a clinical dilemma, an effective alternative may include Miconazole 50 mg buccal tablet once daily placed daily for 14 days. Compliance with first-line therapy tends to present an inversely proportional variable in clinical efficacy based on the required amount of times an agent is to be taken per day.

Ketoconazole was the first imidazole found to have systemic activity. The typical dosage ranges from 200 to 400 mg orally daily. Although ketoconazole has been effective in treating oropharyngeal candidiasis, in patients with HIV infections and cancer, several studies have shown ketoconazole to be less effective than fluconazole in those patients with HIV infections. The most common adverse events reported for ketoconazole include nausea, vomiting, abdominal pain, and itching. However, the adverse event of greatest concern is hepatotoxicity; therefore, long prophylactic courses should be avoided. Asymptomatic increases in transaminase levels in serum have been reported in 2% to 10% of patients, with spontaneous resolution during therapy or resolution after discontinuation of therapy. When prescribing this medication, note that it must be taken with food and may not be adequately absorbed by patients having reduced gastric acidity.39 For hepatitis with jaundice, although rare, hepatic failure has occurred in patients receiving systemic ketoconazole.

Two triazoles, fluconazole and itraconazole, are the newest azoles to become commercially available. Fluconazole is particularly useful for treating patients...
<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary</th>
<th>Alternative</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Candidemia</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nonneutropenic adults</td>
<td>Caspo 70 mg loading then 50 mg/d; Mica 100 mg/d; or Anid 200 mg loading, then 100 mg/d</td>
<td>Flu 800 mg/d loading, then 400 mg/d</td>
<td>14 d after last positive blood culture and resolution of signs and symptoms</td>
<td>Remove all intravascular catheters, if possible</td>
</tr>
<tr>
<td>Neonates</td>
<td>AmB 1.0 mg/kg/d IV; or Flu 12 mg/kg/d IV</td>
<td>LFAmB 3–5 mg/kg/d</td>
<td>14–21 d after resolution of signs and symptoms and negative repeat blood cultures</td>
<td>Occult central nervous system and other organ involvement must be ruled out; use LFAmB with caution if urinary involvement suspected</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Caspo 70 mg loading, then 50 mg/d; Mica 100 mg/d; or Anid 200 mg loading, then 100 mg/d</td>
<td>LFAmB 3–5 mg/kg/d or Flu 800 mg loading, then 400 mg/d</td>
<td>14 d after last positive blood culture and resolution of signs and symptoms and resolved neutropenia</td>
<td>Removal of all intravascular catheters is controversial in neutropenic patients; gastrointestinal source is common</td>
</tr>
<tr>
<td>Chronic disseminated candidiasis</td>
<td>LFAmB 3–5 mg/kg/d; or Caspo 70 mg loading, then 50 mg/d; or Mica 100 mg/d; or Anid 200 mg loading, then 100 mg/d</td>
<td>Flu, 6 mg/kg/d</td>
<td>3–6 mo and resolution or calcification of radiologic lesions</td>
<td>Flu may be given after 1–2 wk of LFAmB or an echinocandin if clinically stable or improved; steroids may be beneficial in those with persistent fever</td>
</tr>
<tr>
<td>Condition</td>
<td>Treatment</td>
<td>Duration</td>
<td>Notes</td>
<td></td>
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<tr>
<td>Endocarditis</td>
<td>LFAmB 3–5 mg/kg/d ± 5-FC 25 mg/kg orally 4 times a day; or Caspo 150 mg/d; Mica 150 mg/d; Anid 200 mg/d</td>
<td>Flu 6–12 mg/kg/d IV/orally</td>
<td>At least 6 wk after valve replacement; Valve replacement is almost always necessary; long-term suppression with Flu has been successful among selected patients who cannot undergo valve replacement. Consider step down to Vori or Posa for susceptible, Flu-resistant isolates.</td>
<td></td>
</tr>
<tr>
<td>Osteoarticular</td>
<td>Flu 400 mg/d or Caspo 50 mg/d; Mica 100 mg/d or Anid 100 mg/d</td>
<td>LFAmB 3–5 mg/kg/d 6–12 mo ± surgery</td>
<td>Step down therapy to Flu after at least 2-wk induction with an echinocandin or LFAmB</td>
<td></td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>Flu 800 mg loading, then 400 mg/d; or Vori 400 mg × 2 loading, then 300 mg twice a day; or LFAmB 3–5 mg/kg/d</td>
<td>Intravitreal AmB 5–10 μg or Vori 100 μg</td>
<td>4–6 wk at least after surgery; Vitrectomy is usually performed when vitreitis is present</td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td>Flu 200 mg/d; or 5-FC 25 mg/kg 4 times a day for Flu-resistant isolates</td>
<td>AmB 0.3–0.6 mg/kg/d</td>
<td>1–2 wk; Echinocandins have minimal role in cystitis; for upper tract disease, treat as for candidemia</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** 5-FC, 5-fluorocytosine; AmB, amphotericin B; Anid, anidulafungin; Caspo, caspofungin; Flu, fluconazole; Mica, micafungin; Posa, posaconazole; Vori, voriconazole.

requiring prolonged antifungal therapy because it is taken only once a day and is relatively well tolerated. Typical dosing of fluconazole varies (depending on specific infections) but ranges from 100 to 400 mg orally/IV. In one study comparing Fluconazole 100 mg daily dose orally with topically administered Clotrimazole troches (10 mg 5 times daily for 14 days), oral candidiasis was found to have a longer relapse time. Both fluconazole and itraconazole have been shown to be effective in treating oropharyngeal candidiasis in patients with HIV infection and cancer. They are widely used in these patients. Further studies are needed to establish optimal doses in patients with HIV infection, different types of oropharyngeal candidiasis, and leukemia and bone marrow transplant patients.

**ECHINOCANDINS (ANIDULAFUNGIN, CASPOFUNGIN, MICAFUNGIN)**

The Echinocandins are antifungals with their own drug class. These agents act through the action against the β-(1,3)-D-glucan synthase enzyme complex, hence acting to inhibit the synthesis of fungal cell wall. Caspofungin and micafungin are indicated in the treatment of refractory or invasive/disseminated candidiasis. Anidulafungin indications include candidemia, the treatment of esophageal candidiasis, as well as a prophylaxis for stem cell recipients. According to McCarty and colleagues, echinocandins have been shown to be effective antifungal agents in 70% to 75% of Candida in randomized, comparative clinical trials. However, despite this drug class being available only as parenteral preparations, the few reported drug interactions, high clinical efficacy, and progressive concerns over fluconazole-resistant strains of Candida, more physicians have turned to echinocandins as a first-line therapy for patients with candidemia. Typical dosing for these agents include the following:

- Caspofungin: loading dose of 70 mg followed by 50 mg daily;
- Anidulafungin: loading dose 200 mg and then 100 mg daily;
- Micafungin: 100 mg daily.

Seemingly, despite the high efficacy against candidemia, some C glabrata isolates have been shown to be resistant to echinocandins.

**Pyrimidines (Flucytosine)**

Flucytosine, a pyrimidine analogue, acts to disrupt RNA synthesis and hence protein and DNA syntheses and is a known fungicidal agent. When used as monotherapy, resistance to this agent develops quickly. Typically, flucytosine is used as a combination therapy with Amphotericin B, fluconazole, or itraconazole. Dosing of Flucytosine comes in either an oral solution of 10 mg/mL or 250 mg oral capsule with a recommended dose of 50 to 150 mg/kg per day given every 6 hours.

**Resistance to Treatment**

Resistance of Candida to polyene agents is virtually unknown despite many years of clinical use. However, reports of resistance to azoles, particularly among patients with AIDS, are appearing with increasing frequency. In many situations, resistance appears to develop in those patients with advanced HIV disease or after repeated or long-term therapy.

It must be emphasized that all the azoles, particularly ketoconazole, can interact with many other agents, including antacids, histamine 2 antagonists, rifampin, omeprazole, phenytoin, astemizole, insulin, cyclosporine, oral anticoagulants, and corticosteroids. Such interaction may result in either decreased or increased blood levels of these antifungal agents, thus altering their potential efficacy or toxicity.
MUCORMYCOSIS

Zygomycosis is a term that was classically used to describe fungal infections that are caused by Zygomycetes, which consist of aseptate or septate irregular ribbonlike hyphae that have the capability of reproducing sexually through zygospores. The main ways in which humans acquire mucormycosis is via inhalation of fungal spores or via direct penetration through the skin. The most common fungal organisms associated with mucormycosis are shown in Fig. 8.

Risk factors for the development mucormycosis include uncontrolled diabetes (especially with concurrent ketoacidosis), IV drug use, chelation therapy, high-dose glucocorticoids, penetrating trauma/burns, concurrent hemodialysis (especially when using the chelating agent desferrioxamine), use of occlusive dressings/boards, tongue blades, blast injury, malt/lumbar industrial workers, construction workers, malnutrition, and poor wound care. Other than direct penetration with Mucorales, the most common mode of transmission is through inhalation of fungal spores that can result in sinus, orbital, rhino, central nervous system, or pulmonary infections. Diabetics carry a particularly high risk of developing this infection, because when the disease is uncontrolled, this results in impairment of neutrophil function, phagocytosis, and oxidative reactions as well as increases free iron, which acts as a substrate, which enhances mucormycosis growth.

In the oral and maxillofacial region, typical lesions that can be encountered include cutaneous (either primary or secondary to disseminated disease) or sinus mucormycosis. Primary penetration of fungal spores through breach of the skin barrier is the most common cause of cutaneous mucormycosis.

The presentation of oral and maxillofacial involvement including the face, nose, or palate is seen in 50% of cases but has been noted to be early diagnostic signs. An example of the eschar from mucormycosis is seen in Fig. 9 extending from

Fig. 8. The hierarchy of mucormycoses isolates. (Data from Farmakiotis D, Kontoyiannis D. Mucormycoses. Infectious Dis Clin N America 2016;30(1):143–63.)
rhinosinusitis. If left untreated, extension into the orbit can lead to orbital cellulitis, corneal anesthesia, facial anhidrosis, proptosis, diplopia, loss of vision, ophthalmoplegia, or trigeminal/facial/orbital/optic nerve involvement.

Treatment of Mucormycosis

First-line treatment of mucormycosis is Amphotericin B. In a study by Chamilos and colleagues, if initial Amphotericin B treatment is delayed, it is associated with significant increase in overall mortalities. Establishing an early diagnosis is essential and can be accomplished by doing a direct biopsy in conjunction with radiographic examination with either a computed tomographic scan or an MRI. As an alternative to Amphotericin B, posaconazole (an antifungal triazole) has shown a clinical efficacy in the treatment of refractory cases initially treated with Amphotericin B (known as salvage therapy). Currently, hyperbaric oxygen (HBO) therapy has been used by some clinicians in combination with traditional antifungal and surgical therapies. HBO therapy typically comprises pressured dives in an HBO chamber typically at 2 to 2.5 atm. HBO therapy has long been used as an adjunct to surgery when wound healing presents issues. The therapy provides reduction in tissue hypoxia and acidosis and provides high oxygen concentrations that are considered fungistatic, resulting in wound healing while enhancing neutrophilic action. However, further studies are required in order to establish this as a standard adjunct for the treatment of mucormycosis.

HISTOPLASMOSIS

Histoplasmosis is an endemic fungal infection caused by the saprophytic and dimorphic fungus *Histoplasma capsulatum*. The spore form is found most commonly in moist, warm soil areas in the central and eastern United States, especially around the Mississippi and the Ohio River Valley and particularly in areas of exposure to excretions of bats and birds. In the United States, incidence of histoplasmosis in adults 65 and older was found to be 3.4 cases per 100,000 population, with rates highest in the Midwest at 6.1 cases per 100,000. There are approximately 500,000 cases of Histoplasmosis annually in the United States.
Transmission

Transmission and infection is through aerosolization and inhalation of spores into the lungs.

Diagnosis

A new blood culture test is now available that uses a lysis-centrifugation blood culture technique that can rapidly detect organisms in patients with disseminated histoplasmosis. Biopsy and culture of tissue from biopsy, body fluids, and secretions are also used. Histoplasma antigen can also be detected in the urine.

Oral Manifestations

Oral manifestations of a histoplasma infection can present in all types of histoplasmosis (acute, chronic, and disseminated), but with variable occurrence. In one review of 78 patients with histoplasmosis, oral manifestations were found in 19% of acute cases, 31% of subacute cases, and 66% in disseminated cases.

The mucocutaneous presentation can be quite variable as well. These lesions can often appear similar in appearance to squamous cell carcinomas with a firm base, necrotic center, and rolled borders. Fig. 10 shows that the most common locations intraorally are the tongue, buccal mucosa, and palate. It is very rare for mucocutaneous lesions to be the only or primary finding, thus reinforcing the necessity of a complete and thorough health and travel history, clinical examination, and radiographic examination, if indicated. Biopsy of oral lesions is needed to confirm the diagnosis.

Fig. 10. (A–C) Histoplasma infections demonstrating ulcerated, granulomatous lesions with an inflamed base and firm rolled borders on the lateral and dorsal surface of the tongue. (From de Paulo LFB, Rosa RR, Durighetto AF. Primary localized histoplasmosis: oral manifestations in immunocompetent patients. Int J Infect Dis 2013;17(2):e139; with permission.)
Treatment

For most patients, a histoplasma infection is self-limiting and will resolve without treatment. However, if symptoms persist or worsen, antifungal therapy will be needed. Itraconazole is a commonly used antifungal agent and may be needed for 3 to 12 months.

BLASTOMYCOSIS

Blastomycosis infections are caused by the soil saprophyte *Blastomyces dermatitidis*, which flourishes in moist soils, or by decomposing matter such as dead leaves and wood. The endemic areas for *Blastomyces* in the United States include the Midwestern, south-central, and southeastern states with the highest concentration in the Ohio and Mississippi River valleys, the Great Lakes, and Saint Lawrence River. This rare fungal infection has a yearly incident rate of 1 to 2 cases per 100,000 in the United States. Wisconsin has the highest rate with 10 to 40 cases per 100,000. Oral lesions are rare. Most oral lesions are ulcerative, but there may be verrucous lesions, granulomas, sessile-based projections, abscess in the mandible with radiographic bone loss, and mobile teeth.

CRYPTOCOCCOSIS

*Cryptococcus* is an encapsulated yeast that is often a cause of an invasive and opportunistic mycoses affecting different organ systems. More than 50 species of *Cryptococcus* have been identified, but only 2 species are known to cause human disease, namely, *Cryptococcus neoformans* and *Cryptococcus gattii*.

*C. neoformans* generally affects immunocompromised patients, with the highest-risk patients being patients with advanced AIDS. Only 11% to 14% of cases of disseminated infection occur in patients without AIDS.

Oral lesions are encountered rarely, and there have only been a handful of reported cases, most being in the HIV population. Annie and colleagues described a case of multiple facial Cryptococcal lesions in a patient with AIDS with disseminated disease. Oral Cryptococcosis can manifest as superficial ulcers, violaceous nodules, granuloma, cancerous looking lesions, or draining sinuses (Fig. 11).

Diagnosis of Cryptococcosis depends on isolation of the organism in culture from the involved site, including skin and oral lesions, blood, cerebrospinal fluid, and bronchoalveolar lavage.

Treatment

Management of Cryptococcosis depends on the site of involvement and the immune status of the patient. Clinical Practice Guidelines by the Infectious Diseases Society of America recommends treatment based on 3 risk groups: HIV-infected individuals, organ-transplant recipients, and non-HIV–infected and non-transplant patients. The primary antifungal therapies used for management of Cryptococcosis include intravenous amphotericin B or its lipid formulation, oral flucytosine and oral fluconazole.

ASPERGILLOSIS

Aspergillosis is caused by *Aspergillus* species, which is a mold with hyaline hyphae. It is considered the second most common opportunistic fungal infection after the *Candida* species. There are more than 800 species, out of which only a few can produce a spectrum of diseases, especially in immunocompromised patients, ranging
from noninvasive allergic forms to invasive disease. Aspergillus fumigatus is the most frequently isolated species in invasive disease. In recent years, mortality from invasive candidiasis has been on a decline, while an overall increase in deaths from invasive Aspergillosis and other molds has been noted.

Aspergillus species are ubiquitous in the environment and are found in soil, water, air, and organic decaying vegetation. The most common portal of entry is by inhalation of fungal spores into the sinuses and the respiratory tract. Once inhaled, in the absence of appropriate host defenses, the spores enlarge, germinate, and disseminate hematogenously by vascular invasion.

Individuals with a normal host defense rarely develop invasive disease. Defects in ciliary clearance in the airways, compromised innate and adaptive defense against Aspergillus, predispose an individual to develop disease.

In the oral and maxillary region, rhinosinusitis is the most common manifestation, either invasive, destructive invasive, or allergic form. Less commonly, the oral cavity, larynx, trachea, and ear are involved.

Invasive rhinosinusitis often occurs in association with invasive pulmonary Aspergillosis. Spores occasionally get introduced to the antrum via an oroantral communication during a dental procedure, such as a root canal perforation or a dental extraction, and become pathogenic. The maxillary sinus is the most common sinus to be affected. Invasive fungal sinusitis can have an acute and fulminant course with a
high mortality occurring predominantly in the immunocompromised patient, or a chronic indolent, granulomatous form with progression through the sinus mucosa, underlying bone and tissue. Clinically, Aspergillus rhinosinusitis can present with headache, fever, nasal congestion, facial swelling, purulent or bloody nasal discharge. It should be suspected in a patient with recurrent or refractory sinusitis not responding to antibiotic therapy.

Oral lesions associated with Aspergillosis and other systemic mycoses usually occur as a part of a disseminated disease from the lungs, but occasionally can reflect extension from a contiguous structure such as the maxillary sinus or a primary infection of the oral mucosa. Perioral Aspergillosis can have a broad spectrum of clinical presentations. Necrotic ulcers are one of the most frequently encountered lesions, as shown in Figs. 12 and 13. Oral lesions show 3 distinctive clinicopathologic stages. The early stages are characterized by isolated areas of violaceous marginal growth consisting of degenerated epithelium and fungal hyphae infiltrating connective tissue. In the advanced stage, these lesions transform into gray necrotic lesions extending into the attached gingiva with ulceration and pseudomembrane. Vascular invasion is found at the bases of the ulcers. In the late stage, progressive destruction of alveolar bone and surrounding facial muscles is noted, with histopathologic evidence of infiltration of fungal hyphae into the tissues. The presence of deep perioral ulceration in an immunocompromised patient should raise suspicion for fungal infection, including Aspergillosis.

Orofacial osteomyelitis, including of the paranasal sinuses, jaw, and skull base, has been reported. Gabrielli and colleagues reviewed 310 cases of osteomyelitis caused by Aspergillus species and found 18% of the cases involved the maxillofacial area.

Diagnosis of aspergillosis requires a histopathologic examination and culture of affected tissue and fluid. The fungi appear with septate hyphae with dichotomous branching at acute angles. Angioinvasion is characteristic of Aspergillus along with tissue and bone necrosis.

Fig. 12. Diffuse edematous swelling of the palatal mucosa (bottom arrows) with focal ulceration (top arrow). (From Syed A, Panta P, Shahid I, et al. Invasive aspergillosis associated with a foreign body. Case Rep Pathol 2015;2015:2; with permission.)
The management of invasive Aspergillosis is usually multidisciplinary and involves using antifungal agents, with surgical debridement as indicated (local disease), and reduction of immunosuppression if feasible.68

COCCIDIOIDOMYCOSIS

Coccidioidomycosis or valley fever, commonly referred to as the “great imitator,”72 is an endemic mycosis caused by the dimorphic fungi Coccidioides immitis and Coccidioides posadasii.73 It was reclassified as a fungus in 1900 after being incorrectly identified as a protozoan in 1892.74,75 It is endemic to the Southwestern United States such as Arizona and California, along with Central and South America. In Southern California, as much as 75% of the population is found to have immunity to the organism.76 Patients from outside of these areas may acquire the disease by traveling to the endemic regions or by reactivation of latent disease during periods of immunosuppression.77

The usual acquisition of Coccidioidomycosis is via inhalation of soil dust containing infectious spores. Cutaneous involvement is the most frequent extrapulmonary manifestation, especially of the face and the extremities. On the face, it has a predilection for the nasolabial fold. Tongue and lip ulcers comprise almost 20% of the lesions.78 Underlying skeletal and bone involvement can also occur.79

Diagnosis is based on histopathologic examination of tissue and fluid samples, culture, serology, polymerase chain reaction (not widely used), and imaging of the affected area. Serum antibodies immunoglobulin M (IgM) and IgG are the most frequently used diagnostic tests. IgM can be detected early in the disease (1–3 weeks), whereas IgG levels are raised after 8 to 10 weeks of symptom presentation.80

Because most of the patients who present with early infection will achieve resolution without treatment, specific antifungal therapy is not used in most cases. However, appropriate follow-up every 3 to 6 months should be performed in these patients until radiographic resolution is achieved.77

GEOTRICHOSIS

Geotrichosis is opportunistic mycoses most commonly caused by the yeast Geotrichum candidum. It is an infrequently encountered infection. However, many suggest
that it may be underdiagnosed or misdiagnosed due to its close resemblance to diseases cause by Candida sp, particularly of the oral cavity.\textsuperscript{81} Geotrichum species are ubiquitous yeasts and have been isolated in soil, plants, fruits, and vegetables. G candidum is considered a resident flora in humans and has been isolated from multiple sources, including the mouth, respiratory tract, gastrointestinal tract, skin, and vagina.\textsuperscript{82}

Usually considered nonpathogenic in immunocompetent hosts, G candidum can cause invasive infection in the immunocompromised patient, especially patients with diabetes mellitus, HIV/AIDS, hematologic malignancies including leukemia and lymphoma, and patients on immunosuppressive agents (eg, steroids).\textsuperscript{83,84} It has also been reported in patients on long-term antibiotic treatment.\textsuperscript{85} Invasive disease has been associated with a high mortality, exceeding 50\%.\textsuperscript{86} Women and older patients are more susceptible.

Oral geotrichosis clinically resembles oral candidiasis. Bonifaz and colleagues\textsuperscript{84} reported a total of 12 cases of oral geotrichosis and found 3 clinical varieties, with pseudomembranous being the most common type (75\%), followed by hyperplastic and palatine ulcer. Pseudomembranous geotrichosis appears as white plaques on an erythematous background, which can be easily scraped off, and can be mistaken for candidiasis very easily. It mainly involves the tongue (glossitis) along with the buccal mucosa, soft palate, and rarely, the pharynx. It has also been associated with angular cheilitis.\textsuperscript{84} Patients tend to present with burning and difficulty swallowing. Because treatment for oral geotrichosis is similar to treatment of candidiasis (ie, responds to typical anti-candidal drugs), it is thought that many cases are misdiagnosed. The villous manifestations of geotrichosis comparably resemble candidiasis as well as some viral infections. On the other hand, palatine ulcers are deeper and appear similar to other mold infections, such as mucormycosis or aspergillosis, which can be very aggressive with cerebral extension and carry a poor prognosis.

Diagnosis is based on microscopic examination of sample from lesions, prepared with 10\% KOH and stained with methyl blue (cotton blue), showing hyphal septation with arthroconidia (Fig. 14). The hyphae may, however, be confused easily with pseudohyphae and blastoconidia of Candida. Cultures in Sabouraud glucose agar followed

![Fig. 14. Direct KOH wet mount of ocular fluid showing brown granular material and hyphae measuring 6 to 8 μM in width and chains of arthroconidia (arrows). (From Myint T, Dykhuizen MJ, McDonald CH, et al. Post operative fungal endophthalmitis due to Geotrichum candidum. Med Mycol Case Rep 2015;10:5; with permission.)](image)
by biochemical tests are therefore needed for confirmation. Molecular biology is the most accurate technique and can identify different species.

Treatment of oral lesions consists of topical antifungals, such as nystatin or Gentian Violet 1%. Variable and limited data exist on Geotrichum species susceptibility for antifungals. Voriconazole has the lowest MIC (minimum inhibitory concentration) for azoles (Zaragoza), whereas Amphotericin is the most widely used antifungal in deep seated and disseminated infections. Duration of treatment is not clearly defined as it depends on site and extent of disease process.

SUMMARY

Oral and maxillofacial fungal infections are rare. When a host has an intact immune system, most fungal exposure should not progress into infection. When encountering fungal infections such as candidiasis, a thorough patient history is necessary, including any risk factors, partner history, familial history of diseases that can impact the immune system (eg, diabetes, immunosuppression, asthma, autoimmune disorders), smoking history, and hygiene regimens. It is imperative when encountering any oral fungal infections to explore the possibility of an underlying impairment; hence, it is warranted to involve the primary care physician early. An in-depth review of the patient may include a complete blood count, urine analysis, white blood cell count, sputum culture/Gram strain, glycosylated hemoglobin (HBA1c), HIV levels, CD4 count, albumin/prealbumin, brush biopsy/smear, incisional biopsy, and possibly fungal or blood cultures. In patients suspect for esophageal fungal infections, endoscopy or bronchoscopy with bronchial alveolar lavage may help to diagnose fungal infections. Molecular assays and DNA probes for identifying species that cause specific fungal infections still require additional research to validate use as a standard diagnostic tool. As a dental practitioner, early detection and diagnosis for most oral and maxillofacial fungal infections lead to decreased morbidity and mortality, especially with locally invasive infections such as Mucormycosis and Aspergillosis.

REFERENCES


