Diagnosis and Management of *Candida* and Other Fungal Infections of the Head and Neck

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Fungi are common inhabitants of the oral and nasal mucosa, and therefore the differentiation between colonization and pathogenicity in the setting of upper respiratory tract infection symptoms can be difficult. Fungal head and neck infections occur in both immunocompetent and immunocompromised persons, and patients with neutropenia, diabetes mellitus, corticosteroid use, and HIV infection are particularly susceptible to serious and potentially life-threatening infections. Invasive fungal head and neck infections generally require extensive surgical debridement and prolonged systemic antifungal therapy, and frequently carry a poor prognosis when the underlying immunosuppression cannot be corrected. In contrast, noninvasive fungal head and neck infections often respond to short courses of systemic or topical antifungal therapy, or require limited surgical debridement alone.

Introduction

Fungal infections of the head and neck span the spectrum of disease severity from clinically benign, such as oropharyngeal candidiasis, to aggressive and malignant, such as rhinocerebral mucormycosis. Most fungi are saprophytic rather than pathogenic in the presence of an intact immune system. However, fungi can become invasive and lethal pathogens in the setting of immunosuppression, and even noninvasive fungal head and neck infections can produce significant morbidity. In this article, I review the diagnosis and treatment of upper respiratory tract head and neck infections caused by *Candida* and other fungi, with an emphasis on the two most frequently encountered syndromes in adults, fungal sinusitis and oropharyngeal candidiasis.

Diagnosis and Treatment of Fungal Infections: The Basics

The commensal relationship of many fungi with humans frequently makes the diagnosis of fungal infections a difficult task, since the mere isolation of a fungus from a particular anatomic site does not always indicate pathogenicity. This is particularly true with the respiratory system, because *Candida*, *Aspergillus*, and other fungi frequently colonize the mucosal lining of the upper airway. Therefore, the identification of tissue invasion on histopathology is necessary for the definitive diagnosis of all serious head and neck fungal infections. In the absence of definitive histopathology, clinical examination and history, including travel and exposure history, are important to identify distinct syndromes and make the proper diagnosis of many upper respiratory tract fungal infections. Table 1 lists the geographic features and histologic patterns of the most frequently encountered fungal pathogens in respiratory head and neck infections.

Supportive laboratory studies are available for several fungal infections, but are rarely diagnostic when used alone. Fungi are often difficult to culture within a clinically useful time period. However, because of similar histopathologic appearances, speciation of *Aspergillus* and other hyaline molds often requires the examination of culture morphology in vitro. Serologic tests for most fungal pathogens suffer from low sensitivity or specificity, or are not widely available, and most nucleic acid-based tests are still investigational. Clinically useful advances in noninvasive diagnostic mycology are needed, since the population of immunosuppressed patients susceptible to invasive fungal infections, and yet often unable to tolerate invasive diagnostic procedures, is increasing.

The treatment of fungal head and neck infections is complicated by the small number and often limited activity of currently available antifungal agents (Table 2). In addition, with the notable exception of oropharyngeal candidiasis, optimal therapies for most fungal head and neck infections have not been determined by well-controlled clinical trials, in part due to the lack of previously standardized diagnostic criteria and the few patients at

Table 1. Diagnostic characteristics of commonly encountered fungi in respiratory head and neck infections

Fungi	Geographic distribution	Histopathologic features
Aspergillus, *Fusarium*, *Scedosporium* species	Ubiquitous	Hyaline septate hyphae with acute angular branching
Zygomycetes	Ubiquitous	Irregular, broad hyphae with rare septations
Candida species	Ubiquitous	Oval budding yeast (4–5 μm), pseudohyphae with constrictions at septations (*Candida albicans*)
Histoplasma capsulatum	Ohio and Mississippi River valleys	Intracellular yeast (2–5 μm), with narrow-neck budding and occasional granuloma formation
Blastomyces dermatitidis	Upper midwest, southeast, and south-central United States	Yeast with thick, double-layered cell wall and broad-based budding
Coccidioides immitis	Southwest United States	Large spherules with endospores
Paracoccidioides bransiliensis	South and Central America	Variable size yeast (4–40 μm) with multiple buds ("pilot wheel" cell)

individual institutions. The recent publication of consensus guidelines for the diagnosis of invasive fungal infections in immunocompromised patients for clinical and epidemiologic research [1••], and the formation of multicenter organizations such as the Invasive Fungal Infections Cooperative Group and the NIAID Mycoses Study Group, are important advances, and should lead to improved evidence-based treatment recommendations. In the meantime, uncontrolled trials, anectodal reports, and expert opinions are frequently used to formulate recommendations. Readers are encouraged to review the recently published guidelines by the Infectious Diseases Society of American for the treatment of specific fungal pathogens [2•,3–5,6•].

One area of significant controversy in antifungal therapy is the appropriate use of the lipid-associated amphotericin B formulations [7]. Amphotericin B is a broad-spectrum polyene antifungal agent that is recommended for the treatment of almost all serious fungal infections, but is associated with significant toxicities. The lipid-associated amphotericin B formulations have reduced infusion-related side effects and nephrotoxicity, but at a substantially increased drug cost. Despite their widespread use as initial therapy for invasive fungal infections, there are no prospective controlled treatment trials demonstrating the superiority of lipid-associated amphotericin B over conventional amphotericin B. Therefore, current recommendations are to use the lipid-associated formulations only when patients are refractory to or intolerant of conventional amphotericin B [2•,6•].

Auditory Infections

Fungal infections of the middle ear are rare, and present as chronic or recurrent otitis media with persistent otorrhea [8]. *Candida* species are the most frequently isolated pathogen, and most patients are immunocompetent children, although chronic *Candida albicans* otitis media has been reported in immunosuppressed children [9]. *Candida* otitis media generally responds to oral azole therapy.

Fungal otitis externa, or otomycosis, is a more frequent problem, especially in warm humid climates. *Aspergillus* species are the most common pathogens [10], although *Candida* species have also been implicated [11]. Patients with otomycosis are normally immunocompetent and present with chronic symptoms that resemble bacterial otitis externa, although pruritis can be more prominent than pain [10]. Inflammation, edema, and mycelial debris are often present in the auditory canal, and therapy is surface debridement followed by topical amphotericin B, nystatin, boric acid, clotrimazole, or ketoconazole [6•].

In contrast to otomycosis, malignant fungal otitis externa is a severe necrotizing infection of immunocompromised patients characterized by the invasion of soft tissue and bone adjacent to the auditory canal. Most patients have hematologic malignancies or advanced HIV-infection [12]. *Aspergillus* species are the most common pathogens, and the diagnosis depends on the histopathologic identification of invasive fungal hyphae, because *Aspergillus* is often a saprophyte in the external auditory canal. Treatment is aggressive surgical debridement and systemic amphotericin B therapy [6•,12].

Sinus Infections

Fungal sinusitis can be classified based on clinical and pathologic criteria into four distinct syndromes including acute or fulminant invasive sinusitis, chronic or indolent invasive fungal sinusitis, sinus mycetoma or fungus ball, and allergic or eosinophilic fungal sinusitis (Table 3). Fungal sinusitis is most often due to hyaline and dematiaceous molds, with species of *Aspergillus*, *Rhizopus*, *Alternaria*, *Bipolaris*, and *Curvularia* the most common, although lesser known filamentous fungi are becoming increasing important [13]. *Candida* species and other yeasts are rarely implicated in fungal sinusitis. The potential exception is in critically ill patients, where *Candida* can be frequently isolated from the sinuses of intubated patients [14]. However, the role of *Candida* as a pathogen in ventilator-associated sinusitis is debatable, since this ubiquitous yeast frequently

Table 2. Commonly used antifungal agents for respiratory head and neck fungal infections

Class	Drug name	Available formulations	Spectrum of activity
Polyene	Amphotericin B	IV*, PO	Filamentous fungi (except *Aspergillus terreus*, *Fusarium* species, and *Scedosporium apiospermum*); *Candida* species; endemic dimorphic fungi
	Nystatin†	PO	*Candida* species and dermatophytes
Pyrimidine	Flucytosine	PO	*Candida* species
Azole	Fluconazole	IV, PO	*Candida* species (except *Candida krusei* and some strains of *Candida glabrata*); endemic dimorphic fungi (primary agent for coccidiomycosis)
	Itraconazole	IV, PO	*Aspergillus* and *Candida* species; endemic dimorphic fungi (primary agent for histoplasmosis, blastomycosis, and paracoccidioidomycosis);
	Ketoconazole	PO	*Candida* species; endemic dimorphic fungi (second-line agent)
	Clotrimazole†	PO	*Candida* species
	Voriconazole‡	IV, PO	Filamentous fungi; *Candida* species (including fluconazole-resistant strains); endemic dimorphic fungi
Echinocandin	Caspofungin§	IV	*Candida* and *Aspergillus* species

*Lipid-associated formulations are available; see text for details regarding their indications.
†Topical agent only.
‡Currently under FDA review.
§Recently FDA approved for the treatment of invasive aspergillosis in patients refractory or intolerant to other therapies.
FDA—US Food and Drug Administration; IV—intravenous; PO—oral.

colonizes critically ill hospitalized patients, especially in the setting of broad-spectrum antibacterial therapy.

The diagnosis of fungal sinusitis relies on the clinical presentation, imaging studies demonstrating sinus abnormalities, and the appearance and histopathology of tissue obtained by biopsy or during surgery [15]. Fungal cultures are diagnostically unreliable for any form of fungal sinusitis when used in isolation, since fungi can be readily cultured from the sinuses of asymptomatic patients [16•]. Treatment depends on the presence or absence of tissue invasion, and is discussed for individual syndromes below.

Invasive fungal sinusitis

Acute or fulminant invasive fungal sinusitis includes rhinocerebral mucormycosis, a disease caused by the zygomycetes, a group of fungi from the order Mucorales. Rhinocerebral mucormycosis is associated with diabetes mellitus, although it can also occur in severely immunocompromised patients and even rarely in immunocompetent patients [17]. A similar disease caused by *Aspergillus*, *Fusarium*, or *Scedosporium* species is most often associated with advanced HIV infection, systemic lupus erythematosis, malignancy, or bone marrow transplantation [18]. The clinical presentation of acute invasive fungal sinusitis is fever, headache, facial swelling, vision changes, epistaxis, and nasal perforation. Histopathology shows fungal vascular invasion with resulting vasculitis, thrombosis, hemorrhage, and tissue infarction and necrosis. Fungal culture of biopsy or surgical specimens is recommended to differentiate *Aspergillus* from other filamentous fungi [6•]. Aggressive surgical debridement of devitalized tissue and systemic amphotericin B therapy are important to control this rapidly progressive and frequently fatal disease, although the correction of predisposing factors, particularly neutropenia, has the largest impact on outcome [6•]. Lipid-associated amphotericin B formulations and combination antifungal therapy may have improved benefit for acute invasive fungal sinusitis, but comparative clinical trials with these approaches have not been published.

Chronic or indolent invasive fungal sinusitis has been divided into granulomatous and nongranulomatous forms [15], although the clinical significance of this differentiation is unclear [19]. Chronic invasive fungal sinusitis occurs in immunocompetent or immunocompromised patients, most often associated with diabetes mellitus or corticosteroid use, and presents as proptosis or a chronic orbital apex syndrome with decreasing visual acuity and occular immobility. Several filamentous fungi have been implicated as pathogens, but *Aspergillus* species are the most common, especially *Aspergillus flavus* and the granulomatous form of chronic invasive fungal sinusitis [15]. Treatment is primarily surgical debridement and systemic amphotericin B [6•], although prolonged suppressive antifungal therapy to reduce recurrences has also been advocated [19].

Table 3. Clinical characteristics, diagnosis, and treatment of fungal sinusitis syndromes

Syndrome	Host	Clinical features	Histopathology	Treatment
Invasive				
Acute (fulminant) fungal sinusitis	Immunocompromised (diabetes mellitus, malignancy, AIDS)	Fever, headache, epistaxis, facial swelling, nasal perforation, vision and mental status changes	Acute inflammation, fungal invasion of mucosa, submucosa, vasculature, bone	Debridement, systemic amphotericin B
Chronic (indolent) fungal sinusitis	Immunocompetent or immunocompromised (diabetes, corticosteroids)	Orbital apex syndrome, unilateral proptosis	Chronic inflammation, fungal invasion, necrosis, ± granuloma formation	Debridement, systemic amphotericin B, possibly itraconazole
Noninvasive				
Sinus mycetoma	Immunocompetent (nasal polyps)	Unilateral chronic sinusitis, usually maxillary	Dense fungal hyphae in noneosinophilic mucin, no mucosal invasion	Debridement, no antifungals
Allergic (eosinophilic) fungal sinusitis	Immunocompetent (nasal polyps and atopy)	Chronic pansinusitis	Eosinophilic "allergic" mucin, sparse fungal hyphae, no invasion	Debridement, corticosteroids, possibly immunotherapy, no antifungals

Adapted from de Shazo *et al.* [15].

Noninvasive fungal sinusitis

Noninvasive fungal sinusitis occurs in immunocompetent patients, and is frequently associated with a history of allergic rhinitis, asthma, and nasal polyposis. Patients with sinus mycetoma, or fungus ball, have often received multiple unsuccessful courses of antibiotics and present with symptoms of nasal obstruction, chronic unilateral sinusitis, and facial pain. Diagnostic criteria for sinus mycetoma include radiologic studies showing sinus opacification, a mucopurulent discharge with a dense conglomeration of hyphae but no eosinophils, and the absence of fungal invasion on histopathology [20]. Fungal cultures of mycetoma specimens are frequently negative, although *Aspergillus* species and dematiaceous fungi have been implicated as pathogens. Surgical removal of the fungus ball and sinus aeration are usually curative without the need for antifungal therapy [6•,21].

Allergic or eosinophilic fungal sinusitis should be suspected in patients with a history of atopy, nasal polyposis, and chronic pansinusitis. This syndrome likely represents an immunologic rather than infectious disease, and shares clinical features with allergic bronchopulmonary aspergillosis [22•]. The reported incidence of allergic fungal sinusitis varies widely. Some studies indicate that 5% to 10% of patients with chronic rhinosinusitis have allergic fungal sinusitis [23], whereas other studies suggest a much higher percentage [16•]. The true incidence probably varies with climate, as geographic "hot spots," such as the southwestern United States, have been described [24]. *Bipolaris spicifera* and other dematiaceous fungi are most often associated with allergic fungal sinusitis, and the underlying pathophysiology is hypothesized to represent a cyclic inflammatory cascade amplified by fungal antigens [22•,25].

The diagnosis of allergic fungal sinusitis has several criteria, including an immunocompetent patient with radiologically confirmed sinusitis, the presence within the sinus of "allergic" mucin containing eosinophils and fungal hyphae, and the absence of fungal invasion on histopathology [26]. The optimal treatment for allergic fungal sinusitis involves a combined medical and surgical approach, since surgical debridement alone is associated with a high recurrence rate [27]. Postoperative oral corticosteroids have been shown to reduce recurrences in one retrospective study [28], and prospective studies have demonstrated that fungal antigen immunotherapy improves patient outcomes when used as a component of the overall treatment strategy [29,30]. In contrast, antifungal agents have no role in the routine treatment of allergic fungal sinusitis, as systemic agents have frequent toxic side effects, and clinical trials showing efficacy with either topical or systemic antifungals agents have not been published [27].

Oropharyngeal Infections

Candida

Oropharyngeal candidiasis is one of the most common fungal head and neck infections and has been classified into four clinical varieties [31]. Acute pseudomembranous candidiasis, or thrush, is the most frequent form of

oropharyngeal candidiasis and is characterized by the presence of white curdlike lesions in the oropharynx that are easily dislodged by gentle scraping. Erythematous candidiasis is also referred to as chronic atrophic candidiasis or denture stomatitis and is characterized by the presence of red atrophic lesions, usually at sites of mucosal contact with poorly fitting dentures. Chronic hyperplastic candidiasis resembles clinical leukoplakia and must be differentiated from dysplastic or malignant lesions with a similar appearance. Angular chelosis, or perleche, is a candidal infection of the labial commisures, and is characterized by erythema or fissuring at the corners of the mouth.

Oropharyngeal candidiasis can occur in immunocompetent patients, usually associated with antibiotic use, inhaled corticosteroids, pregnancy, diabetes mellitus, hypoparathyroidism, or malnutrition [32], but is a much more frequent problem in immunosuppressed patients. In particular, oropharyngeal candidiasis is a common opportunistic infection in patients with both acute and chronic HIV infection [33]. Accordingly, patients with oropharyngeal candidiasis should be thoroughly questioned regarding HIV risk factors and tested if appropriate.

Oropharyngeal candidiasis is normally diagnosed by the clinical history and physical examination, and can be either asymptomatic or associated with oral pain and halitosis. The presence of severe odynophagia, dysphagia, or retrosternal chest pain suggests more extensive disease with esophageal involvement. Atypical cases and those refractory to empiric antifungal therapy may require laboratory confirmation of the diagnosis, either through culture or microscopic examination of oral scrapings. However, culture and histology results must be correlated with the clinical presentation, since *Candida* is a frequent component of the normal oral flora [34]. The most common *Candida* species associated with oropharyngeal candidiasis is *C. albicans* [35], although unusual species such as *Candida dubliniensis* are being isolated from HIV-infected patients with increasing frequency [36].

Multiple antifungal agents and preparations have been used to treat oropharyngeal candidiasis, including amphotericin B, nystatin, fluconazole, itraconazole, ketoconazole, clotrimazole, and caspofungin. Two extensive reviews of clinical trials on the treatment and prophylaxis of oropharyngeal candidiasis in HIV-infected patients have recently been published [37••,38]. Oral systemic azoles are the most efficacious, with clinical response rates of 87% to 100% for fluconazole when used at 100 mg/d for 1 to 2 weeks. Itraconazole solution has similar efficacy, whereas ketoconazole is slightly less efficacious with response rates of 43% to 81%. The topical agents, clotrimazole troches and nystatin suspension, are also slightly inferior to fluconazole and itraconazole in direct comparative trials, although most patients will initially respond to topical agents. Current recommendations for the initial treatment of oropharyngeal candidiasis are clotrimazole troches, nystatin suspension or pastilles, oral fluconazole, or itraconazole solution [2•], although some authors recommend reserving systemic azole therapy for patients initially unresponsive to topical therapy or for patients with esophageal involvement [38]. Fluconazole-refractory patients can be treated with itraconazole solution [39], oral amphotericin B [40], or systemic amphotericin B in severe cases. Similar to other opportunistic infections in HIV-infected patients, the improvement of immune system function with highly active antiretroviral therapy reduces the rates of oropharyngeal candidiasis and the appearance of fluconazole-resistant *Candida* [41].

Repeated episodes of oropharyngeal candidiasis are common in HIV-infected patients, and both the number of recurrences and duration of fluconazole therapy influence the appearance of fluconazole-resistant *Candida* [35]. Despite the frequent occurrence of primary oropharyngeal candidiasis and the high recurrence rate in HIV-infected patients, routine antifungal prophylaxis is not recommended by the United States Public Health Service or the Infectious Diseases Society of America [2•,42••]. This decision has been based on the therapeutic effectiveness of antifungal agents; the low mortality associated with acute oropharyngeal candidiasis; the risk of selecting resistant organisms; and the cost, side-effects, and drug interactions of the currently available azole antifungal agents. However, in patients with severe or frequent recurrences, prophylactic oral fluconazole is effective when given at doses of 50 to 100 mg/d and 150 to 200 mg/wk [37••]. The decision to initiate prophylaxis must take into account patients' quality of life, need for prophylaxis against other fungal infections, cost, toxicity including drug interactions, and the potential for inducing fluconazole resistance [42••].

Endemic dimorphic fungi

Oral lesions commonly occur during chronic infections with the endemic mycoses and are frequently the sole manifestation of disseminated disease. Travel and exposure history are essential for suspecting the diagnosis. Oral lesions occur in approximately 50% of patients with chronic, progressive, disseminated histoplasmosis, and are painful, indurated, ulcerative lesions with heaped-up margins located anywhere on the oral mucosa [43]. Paracoccidioidomycosis, the most common endemic fungal infection in Latin and South America, is associated with oral lesions on the alveolar processes and gingiva that frequently have a "mulberry-like" appearance [44]. The diagnosis must be suspected based on the history and clinical presentation, and is confirmed by culture and the presence of characteristic histopathology on biopsy specimens (Table 1). In contrast to most other fungal infections, a highly sensitive and specific antigen test for *Histoplasma capsulatum* is available to support the diagnosis of disseminated histoplasmosis. Treatment is systemic itraconazole or amphotericin B, depending on the severity of disseminated disease [4].

Filamentous fungi

Aspergillus and other filamentous fungi are uncommon causes of isolated oral lesions and occur almost exclusively in profoundly neutropenic patients [45], similar to invasive aspergillosis at other anatomic sites [46]. Treatment is systemic amphotericin B, and prognosis depends on correction of the underlying immunosuppression, particularly neutrophil recovery.

Tracheobronchial and Laryngeal Infections

Fungal infections of the trachea, bronchi, and larynx are uncommon. *Aspergillus* tracheobronchitis has been reported in severely immunocompromised patients and can present with mucoid impaction, pseudomembrane formation, or ulcerative and invasive disease [47]. Fever, cough, and dyspnea are common symptoms. Treatment with systemic amphotericin B, itraconazole, and inhaled amphotericin B have all been reported with variable success, but prognosis depends primarily on the reversal of immunosuppression [6•]. Laryngeal lesions have also been reported with disseminated blastomycosis [48], coccidioidomycosis [49], and paracoccidioidomycosis [50], and often present with chronic dysphagia, pain, and hoarseness. Biopsy and histopathology are necessary to differentiate the ulcerative lesions caused by the endemic mycoses from squamous cell carcinoma, and treatment is systemic amphotericin B or the appropriate azole (Table 2).

Conclusions

Fungi are important pathogens in upper respiratory tract head and neck infections. The recognition of distinct clinical syndromes often suggests the diagnosis, and an empiric trial of antifungal therapy for the noninvasive syndromes is often diagnostic and therapeutic. Histopathologic examination of tissue remains the definitive diagnostic test for most fungal head and neck infections, particularly with invasive diseases in the immunocompromised host. Prognosis and treatment depends on the pathogen, degree of invasiveness, and competence of the host immune system.

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