



## Diagnosis and treatment of oropharyngeal candidiasis

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*Candida*, a yeast-like fungus, is present in the oral cavity of 40% to 60% of the population [1,2]. *Candida albicans* is the most commonly isolated species [1,2] and is the one most likely to cause disease in humans [3]. Other *Candida* species include *Candida tropicalis*, *Candida krusei*, (both of which are prevalent in immunosuppressed and cancer patients), *Candida guilliermondii*, and *Candida parapsilosis* (of limited pathogenicity but associated with infection of indwelling vascular access devices). The species of colonizing organism is important, because resistance to antifungal agents is more common in some species, including *C. tropicalis* and *C. krusei*. Reports of resistance to systemic agents are increasing.

*Candida* is common in the oral and gastrointestinal flora, and presence in the oral cavity is increased in patients with dentures, individuals who smoke, persons with xerostomia, and patients who use broad-spectrum antibiotics and steroids. The use of immunosuppressive purine analogus (eg, fludarabine, cladribine) and antithymocyte globulin increases risk of invasion. The risk of invasive candidiasis is increased in persons with neutropenia and mucosal injury. The use of growth factors to promote recovery of white cell count in neutropenic patients may reduce the risk of candidiasis and require further study. Age and prior splenectomy increase the risk of infection. Many sedatives, tranquilizers, and some antihypertensive medications may cause dry mouth, which increases the risk of oropharyngeal infection. The use of dentures and tobacco increases the frequency of colonization of the oropharynx and increases the risk of clinical

infection. Cases of superficial and invasive candidiasis are occurring more frequently because of increased use of antibiotics and immunosuppressive agents and advances in medical management, such as chemotherapy, solid organ transplantation and hematopoietic cell transplantation (HCT), parenteral nutrition, and invasive surgical procedures [4]. Candidiasis of the oropharynx and esophagus is associated with HIV infection and is a clinical predictor of disease progression in HIV-infected patients [5,6].

The common portals of entry of *Candida* are the oropharynx and gut, sites that are commonly colonized by the organisms [7]. Invasive fungal infections are one of the major complications in transplant medicine, potentially resulting in mortality [8]. Heart transplant recipients develop fungal infections in approximately 20% of cases [8]. In renal transplant patients, approximately 5% of infections are caused by *Candida* species that present as urinary tract infection and fungemia [8]. Diagnosis of systemic infection is difficult, resulting in limited ability to make an early diagnosis, and invasive infection caused by *Candida* and *Aspergillus* is potentially fatal in neutropenic patients [7]. Higher rates of infection and mortality are seen in patients with hematologic cancer as compared to patients with solid tumors. *Candida* accounts for up to 70% of invasive fungal infections in cancer patients, and a doubling of the rate of fungal infections in all hospitalized patients was reported in the 1980s [7]. *Candida* is the fourth most common pathogen in the blood [7].

Fungal infections, particularly candidiasis and aspergillosis, in HCT are common and result in morbidity and mortality in these high-risk patients [9]. Increasing infections with non-*albicans Candida*

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have been identified and include species such as *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, and *C. krusei*, which show increased resistance to a commonly used antifungal agent, fluconazole. *C. glabrata* and *C. parapsilosis* are more common in patients with solid tumors, and *C. tropicalis* and *C. krusei* are more common in HCT recipients [7]. Intact mucosa serves as a barrier to systemic infection, but cancer therapies may lead to a violation of the barrier, which promotes invasive, systemic infection. Fever caused by fungi typically occurs 7 to 14 days after neutropenia and is the most common cause of fever of unknown origin not responsive to antibiotics [7]. *Aspergillus* tends to occur later, 20 days after HCT, and most patients have nasal or respiratory symptoms, in contrast to invasive candidiasis, which is typical 7 to 10 days after onset of neutropenia [7]. In transplant medicine, the risk for candidiasis also depends on the occurrence of graft-versus-host disease and the use of immunosuppressive therapy for its prevention and management [10]. Gradual restoration of immune function occurs after 3 months of HCT, depending on the discontinuation of immunosuppressive therapy for graft-versus-host disease. The time to engraftment has decreased because of changes in transplantation and use of hematopoietic growth factors, reducing the risk of invasive fungal infection, which occur more commonly during the postengraftment period [10].

“Fungal hypersensitivity syndrome,” a condition promoted by the public media, has been associated with multiple and nonspecific complaints, including fatigue, impaired concentration and memory, respiratory symptoms and asthma, gastrointestinal complaints, muscle and joint pain, and skin and urogenital problems. Recent support for this possible condition was reported in a study in which nystatin capsules to 116 patients were provided in a 4-week randomized controlled trial. The symptoms were assessed by questionnaire, and the results showed nystatin to be superior to placebo in reducing localized and systemic symptoms [11].

Despite the various topical and systemic agents available to treat patients with oropharyngeal and systemic candidiasis, optimal management can be elusive. Topical therapy is generally effective in uncompromised patients with oropharyngeal candidiasis; however, the optimal treatment for immunocompromised patients and patients with chronic or recurrent infection is not well documented. A general overview of the etiology, pathogenesis, and treatment of candidiasis has been presented [4].

The purpose of this article is to review the local and systemic risk factors for oropharyngeal candidiasis, review the clinical manifestations and diag-

nosis of infection, and discuss current approaches to management.

### Risk factors

Local and systemic risk factors and characteristics of the organisms increase an individual's susceptibility to candidiasis. Host factors include age (ie, neonates and elderly people), diabetes, oral prostheses (particularly acrylic dentures), use of broad-spectrum antibiotics, steroids and other immunosuppressive drugs, hyposalivation, disruption of oral mucosa, dietary factors (eg, high carbohydrate diet, iron deficiency anemia), tobacco use, cancer and cancer therapy, and HIV infection (see Box 1). Patients may have multiple factors that predispose them to candidiasis.

#### Box 1. Risk factors for development of oropharyngeal candidiasis

##### Local factors

Xerostomia (eg, because of radiotherapy, chemotherapy, Sjögren's syndrome, diabetes, medications)

Use of broad-spectrum antibiotics or steroids

High carbohydrate diet

Leukoplakia, oral cancer

Dentures (eg, poor fit, trauma, uncleanness)

Cigarette use

##### Systemic factors

Neonate, advanced age

Diabetes

Nutritional deficiencies (eg, iron, folate or vitamin B<sub>12</sub> deficiency)

Malignancies (eg, leukemia, agranulocytosis)

Immunosuppression (eg, AIDS, steroid use)

### Microbial factors

Factors related to the organism that have been implicated include cell-wall components that enhance adhesion to epithelial cells, hydrophobicity of the organism, germ tube formation, presence of mycelia, ability to persist in epithelial cells, production of enzymes and toxins, induction of tumor necrosis factor, and phenotypic switching [12]. *Candida* is a

dimorphic yeast that demonstrates phenotypic switching from the yeast form to a filamentous form (pseudohyphal), and although the pseudohyphal form has been believed to be more pathogenic, both forms may be associated with clinical infection.

### Systemic risk factors

Neonates are susceptible to oropharyngeal candidiasis because of their immature immune system and exposure to the organism during or shortly after birth [2]. Exposure to *C. albicans* from infected bottle nipples or the hands of nurses or the mother also may lead to oropharyngeal candidiasis [2]. The infection usually can be treated effectively with topical agents [13]. Elderly patients may present with a number of risk factors related to reduced saliva production, denture use, and immune function, which result in increased risk, although age alone does not seem to be a risk factor.

Patients with diabetes are at increased risk of oropharyngeal candidiasis [2]. They are colonized more commonly and with higher than normal numbers of *C. albicans* [5,12]. Elevated glucose levels, reduced chemotactic factor in saliva, altered neutrophil function, and reduced saliva volume may play a role in the pathogenesis of clinical infection [2].

Patients with cancer are at high risk for developing oropharyngeal candidiasis [3,6,14–24]. Oropharyngeal candidiasis is reported in up to one third of patients who receive head and neck radiation therapy, and risk is increased in patients who are colonized before radiation therapy [20]. The presence of clinical oropharyngeal candidiasis may complicate oral mucositis; in patients treated with radiotherapy, risk factors include xerostomia, mucosal damage, the presence of oral prostheses, and continuing tobacco and alcohol use during treatment [20].

In addition to causing mucosal damage, chemotherapy may result in transient xerostomia, which may result in acute oropharyngeal infections. Use of antibiotics may result in overgrowth of fungi [22]. Oropharyngeal candidiasis is reported in up to one third of patients with leukemia [1,3,4,18,20,21]. The intensive radiation and chemotherapy used to treat these patients can disrupt the oral mucosa and cause a shift in the oral flora, thus favoring overgrowth of *Candida* [22]. Frequent treatment with broad-spectrum antibiotics in neutropenic patients also alters the normal oral flora and predisposes to oropharyngeal candidiasis [14]. *Candida* infections, although generally superficial, can become invasive or systemic in these patients and may result in mortality [16,18]. It has been

reported that systemic candidiasis develops more frequently in patients with leukemia who have oropharyngeal candidiasis than in patients who are colonized before treatment, and it is associated with prolonged neutropenia [16,24]. *Candida* is present in approximately 90% of patients with acute leukemia who undergo chemotherapy [24]. Candidiasis in patients with leukemia and patients who undergo HCT causes morbidity (eg, altered taste, oral sensitivity, dysphagia caused by esophagitis, fever) and results in considerable risk of mortality during neutropenia [18,19,21,23]. Systemic candidiasis was shown to be increased in patients with leukemia with ulcerative oral mucositis [18]. Oropharyngeal candidiasis also is associated with long-lasting fever and decreased bone marrow function in patients with leukemia [23].

Patients with depletion of CD4+ lymphocytes because of HIV infection are at high risk for oropharyngeal candidiasis. Oropharyngeal candidiasis is the most prevalent opportunistic oral infection in AIDS, and it occurs in as many as 95% of patients [5,6,17,24–27]. The development of candidiasis in HIV-infected patients suggests progression of immunosuppression [5,6], and in patients in whom candidiasis has been controlled with therapy, progression or recurrence of the candidiasis is commonly seen in advancing disease.

The clinical manifestations of oropharyngeal candidiasis in AIDS patients include the pseudomembranous and erythematous forms and angular cheilitis [5,26]. Pain and change in taste that often accompany this infection can result in poor appetite, which leads to weight loss [17]. Oropharyngeal candidiasis can extend into the esophagus and cause gastrointestinal bleeding and severe regional and systemic infection [17,25,28,29]. Therapy should consider an altered host response to help combat the infection, frequent relapses, persistent infection that requires prolonged treatment, potential antifungal drug resistance, and adverse drug effects [6].

Broad-spectrum antibiotics create a favorable environment for the proliferation of *Candida* species by altering the oral flora [30]. Use of corticosteroids also places patients at increased risk [30]. Xerostomia-inducing medications may place the patient at risk of infection by affecting saliva.

### Local and oral factors

Impaired salivary gland function increases the risk of oropharyngeal candidiasis [1,12,30] Because of the decreased saliva secretion and low pH. Saliva protects against candidiasis by diluting and moving organisms

from mucosal surfaces. Antimicrobial proteins in the saliva, including defensins, lactoferrin, sialoperoxidase, lysozyme, histidine-rich polypeptides, and specific anti-*Candida* antibodies, interact with the organism [4]. Lactoferrin, a nonspecific defense factor in saliva and mucosal secretions, seems to have fungicidal activity against *Candida* species.

Drugs that cause hyposalivation predispose patients to oropharyngeal candidiasis. Patients with head and neck cancer treated with radiation to the head and neck develop disturbances of the salivary glands that may be permanent [12]. HCT recipients and patients who receive chemotherapy also can experience salivary gland dysfunction [7].

Oropharyngeal candidiasis is reported in up to 65% of older patients who wear full upper dentures [3]. Increased susceptibility to oropharyngeal candidiasis in denture wearers may be caused by enhanced adherence of *Candida* to acrylic, reduced saliva flow under the denture, poorly fitted dentures, or poor oral hygiene [1,2].

The risk for oropharyngeal candidiasis is increased when there is disruption of the oral mucosa [1,12]. The oral epithelium is a physical barrier that prevents invasion of microorganisms, and epithelial turnover helps clear adherent organisms from the mouth. Patients who receive chemotherapy have an altered rate of mucosal regeneration, which may result in increased vulnerability to infection [12]. Patients with mucositis, especially individuals with an immunocompromised system, are at high risk for invasive candidiasis [9,10,17–19].

Local use of antimicrobial products and anti-inflammatory agents (steroids) increases the risk for colonization and infection [31]. Other studies have shown that chronic use of oral topical steroids and steroid inhalers also increases the risk of oropharyngeal candidiasis, possibly by suppressing cellular immunity and inhibiting phagocytosis [2,30,31].

Tobacco use represents a local factor that is associated with increased risk of colonization and clinical infection [20,30].

### Clinical presentation

Symptoms that may be associated with *Candida* infection include oral and pharyngeal burning, sensitivity, altered taste, and change in the sense of smell. If involvement extends to the oropharynx, dysphagia and odynophagia may occur. Oropharyngeal candidiasis can be classified clinically in several ways (see Box 2) [3,30,32]. The use of “acute” and “chronic” descriptors of candidiasis should be avoided, particularly in

individuals with chronic immunosuppression, because oropharyngeal manifestations can persist for extended periods regardless of the clinical findings.

#### Box 2. Classification of oropharyngeal candidiasis

- Pseudomembranous (thrush)
- Erythematous
- Denture stomatitis (atrophic)
- Angular cheilitis
- Leukoplakia caused by hyperplastic candidiasis
- Candidal ulceration

The classic form of candidiasis is the pseudomembranous form (thrush), which is characterized by soft, yellowish-white plaques on the oral mucosa that can be removed with vigorous rubbing and may leave red or bleeding sites after removal [3,32]. The erythematous form of candidiasis frequently develops in patients who take antibiotics or use steroid inhalers and in patients with HIV [3,30]. This form of candidiasis is characterized by sensitive and painful erythematous mucosa with few, if any, white plaques. The dorsal aspect of the tongue and the palate is generally involved, and the patient presents with red mucosa with loss of papillae on the tongue and patchy red changes in the palate, although any portion of the oral mucosa can be affected [30].

In denture stomatitis, or denture sore mouth (atrophic candidiasis), the palatal mucosa in contact with the denture is affected and is chronically erythematous and edematous. A hyperplastic response may be seen, although patients generally experience no symptoms [3]. Treatment includes correction of denture faults, careful cleaning of dentures, and antifungal therapy [33]. Angular cheilitis, an inflammatory reaction at one or both corners of the mouth, is characterized by painful red fissures. *C. albicans* is a common pathogen, and infection is frequently accompanied by *Staphylococcus aureus* infection [3]. Denture wearers and patients with HIV are predisposed to this type of presentation. Although denture stomatitis and angular cheilitis usually do not indicate serious disease, severe infections may occur in immunocompromised individuals [4].

Leukoplakia caused by hyperplastic candidiasis may represent a precancerous condition that presents as unilateral or bilateral, elevated, white mucosal lesions on the buccal mucosa, tongue, lips, and floor of the mouth [3,29]. *Candida* species are present in

the tissue, can be identified on biopsy, and may be cultured from the mouth. They may not be the cause of the lesions, however, and may be merely secondary invaders [3]. Clinical signs and symptoms range from painless plaque-like white patches to nodular erythroplakic lesions that cause the patient discomfort. Smoking seems to be a risk factor for development of hyperplastic candidiasis.

### Systemic infection

Systemic *Candida* infection is usually caused by *C. albicans* and less frequently by *C. krusei* and *C. tropicalis* in immunosuppressed patients. Patients with neutropenia caused by leukemia or from treatment of their malignancy, patients with indwelling intravascular lines, and patients who receive antibiotics or parenteral nutrition are at risk for *Candida* septicemia. *Candida* endocarditis is related to intravascular trauma (eg, cardiac catheterization, surgery) and is more common on prosthetic valves, where it can become a life-threatening infection. Candidiasis that involves the esophagus, trachea, bronchi, or lungs is an AIDS-defining condition [28].

All forms of systemic disease are serious and cause morbidity and risk of mortality. Intravenous amphotericin B is the treatment of choice, although ketoconazole or fluconazole is preferred for chronic mucocutaneous candidiasis [34].

### Diagnosis

The diagnosis of candidiasis is based on clinical signs and symptoms, laboratory testing, and the response to antifungal treatment. Laboratory tests include smears from the lesions using Gram's stain or a potassium hydroxide preparation or cultures from the skin, mouth, vagina, urine, sputum, or stool [5,35]. A culture is obtained if identification of the species or strain is desired. One must remember, however, that the diagnosis of oropharyngeal candidiasis cannot be based solely on the presence of *Candida* species because the organism is a common commensal in the oral flora [4]. Studies have shown that high colony counts of *Candida* species in saliva collections correlate with the presence of clinical infection, and quantitative counts may be used in diagnosis [36]. Occasionally, histologic evidence is necessary, specifically in cases of hyperplastic candidiasis (candidal leukoplakia), mucocutaneous candidiasis, and invasive candida ulceration in immunosuppressed patients.

### Treatment

#### *Susceptibility testing: identification of species and resistant strains*

Susceptibility testing of fungi to antifungal agents is not as standardized as that of bacteria but is evolving, and guidelines are being developed by the National Committee for Clinical Laboratory Standards [37]. The current applicability of in vitro antifungal susceptibility tests is limited by poor standardization and insufficient correlation of in vitro test results with clinical outcome [38–41]. Antifungal susceptibility studies may help clarify which strains are likely to develop resistance during long-term therapy [42].

#### *History of treatment*

Gentian violet, an aniline dye, was used for topical treatment until the first topical polyene antibiotic, nystatin, became available in 1951 [43]. The first systemic antifungal agent, amphotericin B, was reported in 1956 and is the standard against which newer systemic therapies are compared.

The azoles include the imidazoles and the triazoles. The first azole, benzimidazole, was discovered in 1944 [43]. Miconazole and clotrimazole (both identified in 1969) and ketoconazole (1977) are imidazoles. The antifungal activity of the triazoles, including fluconazole and itraconazole, was reported in the mid-1980s.

#### *Treatment approach*

Underlying risk factors for colonization and infection should be managed whenever possible. For example, in patients with hyposalivation, treatment with sialagogues should be considered. Oral prostheses should be disinfected or topical antifungal agents should be applied to impact colonization of the acrylic surface, and instructions in denture use should be provided. If tobacco use is identified as a risk factor, tobacco cessation should be encouraged. In patients with diabetes, improved glucose control may reduce oral candidiasis. In patients with neutropenia, use of hematopoietic growth factors may speed recovery of blood counts, which reduces risk of local and systemic *Candida* infection. Changes in use of medications that increase the risk of *Candida* colonization and infection should be considered (eg, it may be possible to replace topical steroid use with the use of other topical immunosuppressive medications).

Various systemic and topical agents are available to treat oropharyngeal candidiasis (Table 1) [4,44].

Table 1  
Routes of action of antifungal agents for the treatment of oropharyngeal candidiasis

Class and agent	Route of action	
	Topical	Systemic
Polyenes		
Nystatin	X	
Amphotericin B	X	X
Imidazoles		
Clotrimazole	X	
Miconazole	X	
Ketoconazole		X
Triazoles		
Fluconazole		X
Itraconazole		X
Other		
Chlorhexidine gluconate 0.2% (antiseptic for denture disinfection)	X	
Denture cleansers	X	

Topical agents have been the mainstay of therapy, particularly in uncomplicated cases. If possible, topical preparations should be used before systemic antifungal drugs [45] because they are not absorbed systemically and lack adverse systemic effects and the possible drug interactions of systemic agents. Salivary action may dilute and rapidly eliminate topical drugs from the oral cavity, however, which reduces their effectiveness [46], and compliance with required repeated topical application impacts efficacy. Topical agents are available in various formulations, including oral rinses, troches, powders, and vaginal tablets and creams. Systemic agents are used when topical therapy has been ineffective or not tolerated, primarily in immunocompromised patients with cancer or HIV infection. Topical and systemic medications are used to attempt prophylaxis in patients who receive HCT.

#### Topical therapy

The medication chosen should be appropriate for the conditions in the oral cavity, and cost should be considered. The taste and texture should be considered when selecting a medication and formulation. Unfortunately, many of the oral products include high concentrations of sucrose and have a high cariogenic potential, which is a particularly important consideration in dentate patients with dry mouth. In patients with dry mouth, oral rinses should be used because tablets not only may dissolve poorly but also may become rough with use, which results in physical irritation of the oral tissue. Antifungal creams may be readily applied to the surface of dentures, but their

taste and texture may not be tolerated if they are applied without an occlusive appliance. Creams are easily applied to the corners of the mouth. A single-dose trial of an antifungal agent provides guidance on product acceptability by the patient.

Gentian violet was commonly used to treat oropharyngeal candidiasis until the advent of polyene antifungal medications [30] and was replaced quickly by the polyenes because of emerging resistance and local side effects, such as staining and irritation of the oral mucosa [43,47]. Three polyenes—nystatin, amphotericin B, and natamycin (used only for ocular infection)—are available. These agents act by binding to ergosterol in the cell membrane of fungi, altering cell-membrane permeability, and causing pores and leakage of cellular components, which leads to microbial death [43,48].

Nystatin is the most widely used agent for the initial treatment of patients with oropharyngeal candidiasis [1,2]. It is available in oral rinse, topical cream, oral pastille, and vaginal tablet and powder [1,2,5]. Nystatin is not absorbed systemically and lacks serious toxicity. Adverse effects include nausea, vomiting, and diarrhea [43], which can be problematic for cancer patients who are already nauseated from chemotherapy. The oral rinse is heavily sweetened with sucrose, which increases the risk of caries formation. If chosen, nystatin suspension should be used with precautions to reduce caries risk. The oral rinse may be useful for edentulous patients, but the tablets may not dissolve well in the mouth and may be irritating to the mucosa, particularly if it is friable or damaged [1]. Although nystatin is commonly used as prophylaxis for treatment of oropharyngeal candidiasis in AIDS and cancer patients, several reports have cited disappointing results in these patients, with frequent treatment failure and early relapse [6,15,16,19].

Antiseptic agents have been assessed for antifungal effect. An in vitro study of antifungal effects of Listerine® and chlorhexidine (0.12% and 0.2%, respectively) [49] showed potential value in suppression of *Candida* species. Chlorhexidine rinse has been assessed in patients with leukemia, and suppression of *Candida* colonization has been demonstrated [31]. In patients with symptomatic oral mucositis, alcohol content, the presence of phenol, and intense flavoring agents may limit use of commercial antiseptic products because of mucosal irritation.

Care should be taken when using more than one topical agent simultaneously. Two studies that examined the compatibility of nystatin with chlorhexidine digluconate in the treatment of patients with oropharyngeal candidiasis found that both drugs become ineffective when combined [50,51]. Several studies

have compared various topical and systemic agents (eg, nystatin and amphotericin B with fluconazole or ketoconazole) to determine what is best tolerated, most effective, and least expensive in different patients [19,52–55].

The azoles are fungistatic and interfere with synthesis of ergosterol in the fungal organism, which causes an increased permeability of the cell membrane [1]. Clotrimazole, an imidazole, was the first broad-spectrum antifungal agent of its class [1]. Clotrimazole troches are more palatable than nystatin oral suspension and may be used in patients who cannot tolerate the taste of nystatin [12,56]. Clotrimazole has been reported to be effective for prophylaxis and treatment of oropharyngeal candidiasis in cancer patients, in whom it may prevent the development of esophagitis [57], but it seems to be less effective than fluconazole in treating HIV-infected patients with oropharyngeal candidiasis [5,58]. Like nystatin oral troches, however, clotrimazole troches may be poorly tolerated by AIDS patients or patients with xerostomia caused by cancer therapy [12]. Miconazole also has been shown to be effective in patients with oropharyngeal and esophageal candidiasis [59].

When topical agents cannot effectively control oropharyngeal candidiasis, combining topical therapy with a systemic agent may eradicate the infection while allowing a lower dose and shorter course of the systemic agent [1].

#### Systemic therapy

Systemic therapy may be necessary in patients with oropharyngeal candidiasis that is refractory to

topical treatment, in patients who cannot tolerate topical agents, and in patients at high risk for systemic infection. It may be chosen for convenience of use and ease of patient compliance (Table 2).

#### Amphotericin B

Intravenous amphotericin B has been shown to be effective in patients with severe oropharyngeal candidiasis and in patients with infection refractory to other agents [2,6]. Low-dose, prophylactic use has been shown to be effective in neutropenic HCT recipients [60]. Amphotericin B also has been used prophylactically in solid organ transplant recipients [61]. Amphotericin B is used primarily in patients at risk for progressive and potentially fatal fungal infections because of the potential toxicity of the medication. Potential toxicities include general toxicities (eg, fever, shaking chills, malaise, weight loss), renal toxicity, gastrointestinal effects (eg, nausea, vomiting, diarrhea, cramping, altered liver function), neurologic symptoms (eg, headache, hearing loss, dizziness, visual changes, peripheral neuropathy), muscle/joint pain, dermatologic reactions (eg, rash, itching), hematologic effects (eg, anemia), and cardiovascular and pulmonary toxicity. Despite its toxicity, amphotericin B remains the “gold standard” of antifungal medications because of its broad spectrum of action, clinical efficacy, and limited evidence of fungal resistance.

#### Azoles

The azoles (eg, miconazole, clotrimazole, ketoconazole, fluconazole, and itraconazole) have been

Table 2  
Strategy for managing fungal infections in high-risk neutropenic patients

Risk factor	Oral	Parenteral
Oral colonization	Topical antiseptic/polyene Fluconazole 400 mg/d	200 mg/d if no po
Oral candidiasis	Topical and oral/parenteral Fluconazole 400 mg/d	200 mg/d if no po
Probable or proven aspergillosis	Itraconazole 400 mg/d	Ambisome 200 mg/d Itraconazole 200 mg/d if no po
Possible fungal infection (fever of unknown origin)	Itraconazole 400 mg/d	Ambisome 200 mg/d Itraconazole 200 mg/d if no po
Infection by <i>Candida</i>	Fluconazole 400 mg/d for maintenance	Fluconazole 400 mg/d for treatment
Infection by <i>Aspergillus</i>	Itraconazole 400 mg/d for maintenance	Ambisome 200 mg/d

Oral route for prophylaxis and maintenance, parenteral for treatment; dose range 200–400 mg/d for fluconazole, with higher doses in North America.

Modified from Wingard JR. Approach to invasive fungal infection after blood or marrow transplantation. *Transplant Proc* 2000;32:1543–4.

widely used to treat patients with superficial and systemic fungal infections. Ketoconazole was the first imidazole found to have systemic activity, and although it is effective in the treatment of oropharyngeal candidiasis in patients with cancer and HIV, several studies have shown that ketoconazole is less effective than fluconazole [5,14,30,62,63]. Ketoconazole requires gastric acidity for absorption, which may reduce its effectiveness in patients with AIDS or other gastrointestinal disorders and persons with limited food intake [1]. The most frequent adverse effects described for ketoconazole include nausea, vomiting, abdominal pain, and itching [1,62]. The adverse event of greatest concern is hepatotoxicity, which may result in hepatitis and, rarely, hepatic failure [1,40,43,45,62]. Ketoconazole is less costly than the newer azoles. A study by Donnelly et al [54] found ketoconazole to be no more effective than amphotericin B in preventing yeast infection in neutropenic patients, and use was not recommended [64].

The triazoles, fluconazole and itraconazole, are in common use. Both medications have been shown to be effective in the treatment of oropharyngeal candidiasis in patients with cancer and HIV infection, and they are widely used in these patients [15,30,55,57,63,65]. Itraconazole and fluconazole have fewer side effects than the azoles, and are available in oral formulations. Fluconazole offers no protection against *Aspergillus* species and has been associated with fungal resistance [27], although this may be overcome in many cases by increasing the dose. Fluconazole is useful in patients who require prolonged antifungal therapy, because it is well tolerated and is taken only once a day [25]. Fluconazole prophylaxis against candidiasis in HCT patients and patients with leukemia has been conducted, and it is used in some centers [18,66]. Although studies show reduction in *Candida* colonization, not all studies have shown an effect on systemic infection [18]. Unfortunately, *C. krusei* is resistant to fluconazole, and increased infection by *C. krusei* in patients with leukemia indicates the need for caution in the use of fluconazole in these patients [18]. Further studies are needed to establish optimal doses in patients with HIV infection and different types of oropharyngeal candidiasis [25]; studies are also needed regarding the usefulness of fluconazole in and HCT patients and patients with leukemia [18,66].

#### Resistance to antifungal agents

Resistance of *Candida* to polyenes is virtually unknown despite years of common clinical use [67]. Reports of resistance to the azoles, however, particularly among AIDS patients, are increasing [26,65,68–

76]. Therapeutic failure caused by fluconazole-resistant strains in AIDS patients is increasingly reported [26,68,69,73–76], although one study found fluconazole effective when other agents were not [77]. Risk of resistance seems to develop in patients with advanced HIV disease or after repeated or long-term fluconazole therapy [26,68,69,73]. Resistant species, specifically *C. krusei*, have been increasingly identified in HCT patients and patients with leukemia because of effective killing of *C. albicans* and selection for *C. krusei* [18] and have been described with ketoconazole [68]. A study by Fan-Havard et al [78] did not find large-scale resistance in the *Candida* populations isolated from patients who receive long-term azole therapy. There are reports of fluconazole selecting more resistant strains of *Candida* species and of cross-resistance between the azoles [30,47,62,72,79]. The optimal management of fungal infections in children with HIV remains to be determined [80].

The azoles, particularly ketoconazole, can interact with many other agents, including antacids, omeprazole, histamine-2 antagonists, rifampin, phenytoin, oral anticoagulants, insulin, cyclosporine, and corticosteroids [5,43,62]. Such interactions may result in either increased or decreased blood levels of these agents, thus altering their potential efficacy or toxicity.

#### New therapies

Unlike with the azoles, resistance to polyenes, including amphotericin B, rarely develops during therapy [41]. The drug's principal limitation is its toxicity when used systemically [41,82]. The use of amphotericin B oral suspension as a topical antifungal agent was first studied nearly 40 years ago and has been available commercially in Europe for the treatment of patients with oropharyngeal candidiasis [5,47,48]. In vitro studies have shown that amphotericin B is more active than nystatin against *C. albicans* [83,84]. Virtually no amphotericin B oral suspension is absorbed systemically, and the toxicity concerns associated with intravenous amphotericin B use are eliminated [47,85–88]. Unfortunately, the formulation is poorly tolerated and the rinse has been withdrawn from the US market [47,62,63,65]. An amphotericin B lozenge/chlorhexidine combination has been used in Scandinavia to treat patients with denture stomatitis [81]. Amphotericin B lozenges are effective in patients susceptible to *Candida* infection, because long-lasting concentrations of the drug in the saliva can be achieved [81,82].

New formulations of systemic amphotericin B have been developed with the goal of reducing toxicity. Systemic amphotericin B has been studied in

lipid complex, colloidal dispersion, and liposomal forms. Although there are limited data on the therapeutic advantage of new formulations, toxicity seems to be reduced [8].

New triazoles in late stage development (voriconazole, posaconazole, ravuconazole) have increased the spectrum of antifungal activity, including against *Aspergillus* and additional *Candida* species, and safety seems excellent. New classes of antifungal agents, including echinocandin agents that affect the fungal cell membrane (versus cell wall), are in development [7]. These agents, with different mechanisms of action, offer the future potential to manage cases with new drug combinations.

#### *Combination therapy antifungal agents*

Combined therapies have been evaluated to seek synergy of different agents for use in potentially fatal fungal infections, including *Cryptococcus*, *C. albicans*, and *Aspergillus*, in immunocompromised and neutropenic patients [89]. In vitro study of possible synergy of fluconazole and granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage-colony stimulating factor (GM-CSF), human serum treated neutrophils, showed that the combination caused increased killing by the antifungal agents [89]. Monoclonal antibodies also were shown to facilitate fungal cell death in combination with antifungals, as have combinations with proinflammatory cytokines, interleukin-1, interferon, and tumor necrosis factor-alpha [89]. Use of polyene and azole antifungal agents has interfered with fungal killing in vitro; however, animal studies and clinical trials suggest that dosing schedules of the drugs may be key, and conflicting results may be related to the dosing schedule and the animal model used. Although combining azoles and polyenes may lead to enhanced effect, there are no clear guidelines for their combined use [89].

## Discussion

Oropharyngeal candidiasis is increasingly common because of changes in medical care, HIV infection, and advances in medicine that allow patients with cancer and other debilitating diseases to live longer, although in an immunocompromised state. Use of xerostomia-inducing medications, broad-spectrum antibiotics, and topical and systemic steroids has led to increased oropharyngeal colonization and subsequent infection. Patients with xerostomia, persons who smoke tobacco, and denture

wearers are also at increased risk for candidiasis. The clinical presentation of this infection may vary and may be asymptomatic or cause severe, persistent symptoms. Common oral findings may include white plaques that can be wiped off, erythema, and, less commonly, leukoplakia.

Treatment of uncomplicated oropharyngeal candidiasis in the non-immunocompromised patient is usually straightforward. Selecting the form of a topical medication requires consideration of the oral condition, the length of contact time with the medication, and the taste, texture, and cost of the product. In patients with severe oropharyngeal candidiasis, particularly individuals with a compromised immune system, or in patients with refractory oropharyngeal candidiasis, treatment is often more difficult. Relapses are common, and unless the underlying conditions that predispose to infection are managed effectively, long-term or frequent intermittent therapy is often required.

Topical agents are generally effective in uncomplicated cases but may be inadequate in some cases, including complicated infections in patients with AIDS or neutropenic cancer patients. The most effective regimen for fungal prophylaxis in patients with protracted neutropenia has yet to be determined. Systemic agents, such as amphotericin B, ketoconazole, fluconazole, and itraconazole, have been used extensively in these patients. A major concern with these agents, particularly with fluconazole, is the increase in fungal resistance and in selection of non-albicans species, particularly in patients who require long-term or recurrent therapy. Strategies must be developed for preventing and managing the increasing prevalence of more resistant strains of *C. albicans* and selecting resistant species. Intravenous amphotericin B is the gold standard for patients with systemic mycoses and, occasionally, persons with refractory oropharyngeal candidiasis; however, its routine use for oropharyngeal candidiasis is limited by its toxicity.

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