REVIEW

Optimal management of oropharyngeal and esophageal candidiasis in patients living with HIV infection

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Abstract: Mucocutaneous candidiasis is frequently one of the first signs of human immunodeficiency virus (HIV) infection. Over 90% of patients with AIDS will develop oropharyngeal candidiasis (OPC) at some time during their illness. Although numerous antifungal agents are available, azoles, both topical (clotrimazole) and systemic (fluconazole, itraconazole, voriconazole, posaconazole) have replaced older topical antifungals (gentian violet and nystatin) in the management of oropharyngeal candidiasis in these patients. The systemic azoles, are generally safe and effective agents in HIV-infected patients with oropharyngeal candidiasis. A constant concern in these patients is relapse, which is dependent on the degree of immunosuppression commonly seen after topical therapy, rather than with systemic azole therapy. *Candida* esophagitis (CE) is also an important concern since it occurs in more than 10% of patients with AIDS and can lead to a decrease in oral intake and associated weight loss. Fluconazole has become the most widely used antifungal in the management of mucosal candidiasis. However, itraconazole and posaconazole have similar clinical response rates as fluconazole and are also effective alternative agents. In patients with fluconazole-refractory mucosal candidiasis, treatment options now include itraconazole solution, voriconazole, posaconazole, and the newer echinocandins (caspofungin, micafungin, and anidulafungin).

Keywords: oropharyngeal candidiasis, esophageal candidiasis, HAART, antifungal agents, HIV, AIDS

Introduction

Fungi are found ubiquitously in nature in association with plants and mammals. Accordingly, humans are continually exposed to multiple genera of fungi via various routes, but particularly by the ingestion of food, allowing for the colonization of the gastrointestinal tract. Depending on the interaction between the host's mucosal defense mechanisms, fungal virulence factors, and antifungal utilization, colonization may be transient or persistent and local disease may ensue.

Of the numerous pathogenic fungi, *Candida* is the dominant genus responsible for fungal diseases in humans.[1] *Candida albicans* is the species with the highest prevalence among human yeast isolates and is the main opportunistic yeast pathogen in most warm-blooded animals.[1]

Symptomatic mucosal candidiasis (MC) arises in subjects colonized with *Candida* who are predisposed by illness, debility, or a local reduction in host resistance to an overgrowth of their own indigenous flora. *Candida* species are frequently isolated from the oral cavity and are detected in 31%–60% of healthy individuals.[1,2] Colonization rates generally increase with the severity of illness and duration of hospitalization.[3]

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In a recent study, the frequency of oral yeast carriage in the competent host varied as a function of age.[2] The colonization rates increase from 24% in persons aged 5–7 years, to 59% in persons above the age of 60. In the hospitalized non-HIV infected individual, *C. albicans* accounted for 70%–80% of oral isolates and *C. glabrata* and *C. tropicalis* each represented approximately 5%–8%, while the other non-*albicans Candida* species were recovered only rarely.[4,5]

In the past decade, there has been a significant increase in the frequency of non-*albicans Candida* species isolated from HIV-infected individuals with MC.[6,7] In the 1980's, non-*albicans Candida* species accounted for 3.4% of oral isolates from HIV-infected patients, while in the 1990's, 16.8% of isolates recovered from HIV patients were non-*albicans Candida* species.[6,7] The more commonly recovered non-*albicans Candida* species, include *C. glabrata, C. parapsilosis*, *C. tropicalis*, and *C. dubliniensis*. In 5%–10% of circumstances multiple *Candida* species may be recovered from a single specimen. The more common combinations include *C. albicans* with *C. glabrata*, *C. krusei, C. dubliniensis*, or *C. tropicalis*.

Several local and systemic host and exogenous factors increase the prevalence of gastrointestinal (GI) tract *Candida* carriage and population levels.[8] The acuteness and extent of candidal infections increase with the number and severity of predisposing factors. The role of CD4+ T cells is to be the normal gastrointestinal mucosal defense mechanism against *Candida* species and this relation is highlighted by the frequent occurrence of oropharyngeal candidiasis (OPC) and esophageal candidiasis (EC) in patients with low CD4+ T cells and acquired immunodeficiency syndrome (AIDS).[8,9] In HIV infection, oral carriage of yeast and risk of mucosal invasion increase with a progressive reduction in CD4+ T cells.[8,10] The anti-*Candida* protective mechanism of CD4+ T cells at a mucosal level is still incompletely understood. Recently, investigators have shown that cytokines, especially gamma interferon, can inhibit the transformation of *Candida* blastoconidia to the more invasive hyphal phase.[8,11] In addition, several investigators have shown that a decrease in E-cadherin levels and a loss of CD4+ T cells in the mucosa are associated with episodes of acute OPC.[12] The most commonly reported cause of higher GI yeast carriage rates and symptomatic oral candidiasis is the use of antibiotics.[1,8] Elimination of bacterial competition is almost certainly the important mechanism by which antibiotics affect *Candida* numbers *in vivo*.

It is important to note that the introduction of highly active antiretroviral therapy (HAART), including protease inhibitors, has significantly reduced the prevalence of oropharyngeal and esophageal candidiasis in HIV-infected patients. In the first 12–24 months after the introduction of HAART, the prevalence of OPC decreased from 50%–80% down to ~10%.[13] In addition, a decrease of 25%–50% in the occurrence of EC was also documented. Unfortunately, there have been no further studies describing the epidemiology, incidence, or significance of either OPC or EC since 2004.

Based upon epidemiological studies, it is apparent that humans are exposed repeatedly to *Candida* in food and other sources. The natural history of this commensal "normal" colonization over weeks, months, and years is poorly understood. Nevertheless, one may reasonably conclude that *Candida* colonization is almost universal.

Oropharyngeal candidiasis

Oral candidiasis has been known since the era of Hippocrates, although Hippocrates used the term "aphthae" to describe this infection.[1] Several clinical forms of oral candidiasis exist; thrush is the most commonly and widely recognized and is also called acute pseudomembranous candidiasis (Figure 1). Oropharyngeal candidiasis remains the most frequent opportunistic fungal infection among HIV-positive patients and is frequently the initial manifestation of HIV infection. Currently, it is estimated that approximately 80%–90% of HIV-infected patients develop OPC at some time during the progression of their disease from HIV infection to AIDS.[1,13,14,15]

C. albicans is the species responsible for the majority of cases of OPC.[1,15] The ability of *C. albicans* to adhere to buccal epithelial cells is critical in establishing oral colonization. After colonization, the organisms may persist for months or years in low numbers in the absence of inflammation. These low numbers are the result of effective host defense mechanisms in the oral cavity. Genotyping of *Candida* strains obtained from HIV-infected patients with either OPC or EC indicate a genotype distribution frequency similar to that seen in non-HIV-infected subjects, suggesting that HIV-associated MC is not caused by a unique or particularly virulent strain of *Candida*, but likely results from defects in host defense mechanisms.[16]
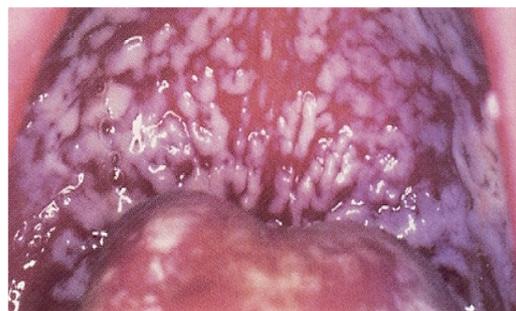
Figure 1 Pseudomembranous oropharyngeal candidiasis.

Symptoms of OPC can be extremely variable and range from asymptomatic oral lesions, to a sore, painful mouth, a burning tongue, and associated dysphagia. Clinical signs include diffuse erythema and white patches that appear as discrete lesions on the surfaces of the buccal mucosa, throat, tongue, and gums.[1,14] Severe OPC may ultimately impair quality of life and result in a reduction of fluid or food intake. The most serious complication of untreated OPC is extension of the infection into the esophagus resulting in decreased nutritional intake.

Candida esophagitis

Candida is the most common cause of infectious esophagitis and, after the oropharynx, the esophagus is the second most common site of gastrointestinal candidiasis. The prevalence of *Candida* esophagitis (CE) has increased mainly because of its association with HIV-infected individuals. Approximately 10%–15% of patients with AIDS will eventually suffer from this entity during their lifetime.[1,15,17–19]

The same organisms that are recovered from the esophageal surface are generally the same organisms identified in oral secretions. *C. albicans* remains the most common organism identified in CE. In contrast to oral candidiasis, little is known about host and yeast factors operative in the pathogenesis of esophageal candidiasis and experimental models have not been established. However, it is likely that the usual yeast virulence factors and defects in host defense mechanisms are responsible. Esophageal candidiasis in HIV-positive patients may be the first manifestation of AIDS. The high prevalence of esophagitis in connection to AIDS indicates the critical role of cell-mediated immunity in normally protecting the esophagus from *Candida* invasion. *Candida* esophagitis tends to occur later in the natural history of HIV infection and almost invariably at lower $CD4^+$ T cell counts (range 10–105, mean 79, median 30 cells).[1,17–19] It is not uncommon for patients with advanced AIDS, and near the end of life, suffering from severe esophageal candidiasis manifested by the inability to have any form of oral intake.

Candida esophagitis commonly causes dysphagia, odynophagia, and retrosternal pain. Although CE may arise as an extension of OPC, in approximately 10% of cases the esophagus maybe the only site involved affecting the distal two-thirds, rather than the proximal one-third, which is the area more commonly affected (Figure 2). An occasional feature of CE is the complete lack of clinical symptoms despite extensive objective esophageal involvement.[1,17–19]

A reliable diagnosis can only be made by direct visualization of the esophagus along with histological evidence of tissue invasion in biopsy material.[22,21] However,

Figure 2 Esophageal candidiasis.

clinical criteria may be accepted as a basis for initiating antifungal therapy in high risk patients. The differential diagnosis of EC must include gastroesophageal reflux disease (GERD), idiopathic HIV-ulcers, and viral esophagitis due to either cytomegalovirus or herpes simplex virus.[1,20,21]

Therapy

Numerous antifungal agents are available for the treatment of OPC and EC in the HIV-positive patient (Tables 1 and 2). In addition, guidelines for the management of mucosal candidiasis in HIV-infected patients have been published by the Centers for Disease Control, National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.[22] However, several factors should be considered when selecting antifungal agents for patients with HIV infection. In HIV-positive patients, antifungals are frequently less efficacious than in patients with other immunodeficiencies such as

Table 1 Antifungals for oropharyngeal candidiasis*

Antifungal agent	Form	Strength	Usage	Cost
Topical				
Nystatin	Pastille	200 000 units	1–2 pastilles, 4 times daily	+
	Suspension		5 mL swish-and-Swallow, 4 times daily	+
				+
Clotrimazole	Oral troche	10 mg troche	Dissolve 1 troche, 5 times daily	+
Amphotericin B	Suspension	1 mg/mL	1 mL swish-and-swallow, 4 times daily	+
	Lozenge	100 mg	Four times daily	+
	Tablet	10 mg	Four times daily	+
Miconazole (Lauriad®)	Lauriad	10 mg	Apply to gum once daily	TBD
Systemic				
Ketoconazole	Tablet	200 mg	1–2 tablets, once to twice daily	+
Fluconazole	Tablet	100 mg	1 tablet daily	++
	Solution	10 mg/mL	10 mL, once daily	++
Itraconazole	Capsule	100 mg	2 capsules, once daily	++
	Solution	10 mg/mL	10–20 mL, once daily	++
Posaconazole	Suspension	100 mg/2.5 mL	2 tsp daily	+++

Notes: *Oral therapy preferred when tolerated. Cost index: (+) inexpensive; (++) modest expense; (+++) expensive; TBD = to be determined.

cancer. Similarly, the time to clinical response also tends to be delayed in this population.[17,22,23] Moreover, the relapse rate is higher in patients with HIV than in any other patient population.[1,17,22,23] For unknown reasons, a subgroup of HIV-positive patients experience recurrent episodes of OPC and thus receive numerous courses of antifungals during their lifetime. As their HIV infection progresses they tend to experience shorter disease-free intervals between episodes of mucosal candidiasis and thus have greater antifungal exposure, which may ultimately lead to the development of clinical and *in vitro* antifungal resistance and its associated morbidity and mortality.

It is important to note that, as with some opportunistic pathogens in this patient population, antifungal treatment merely reduces the signs and symptoms of infection and thus produces a transient clinical response by lowering the quantity of organisms in the affected area. It is extremely difficult to fully eradicate *Candida* from the mucosal surfaces of patients who are immunocompromised, especially those who are HIV-positive.[8,18,23] The combination of frequent clinical relapses and increased antifungal utilization are frequently associated with antifungal resistance.[24] This is reflected, clinically, by the ineffectiveness of antifungals to which a patient has not previously been exposed. Thus, we are becoming increasingly aware that choosing the appropriate agent, even in the early stages of disease, is extremely important because of the future repercussions of these selections in advanced stages of infection.

Table 2 Antifungals for esophageal candidiasis

Antifungal agent	Form	Strength	Usage
Azoles			
Ketoconazole	Tablets	200 mg	1–2 tablets, once to twice daily
Fluconazole	Tablet	100 mg	1 tablet daily
	SolutionIV piggyback	10 mg/mL	10 mL, once daily 100 mg, once daily
Itraconazole	Capsule	100 mg	2 capsules, once daily
	Solution	10 mg/mL	20 mL, once daily
Posaconazole	Suspension	100 mg/2.5 mL	4 tsp, twice daily
Voriconazole	Tablet/IV piggyback	200 mg	Once daily
Caspofungin	Intravenous	50 mg	Once daily
Micafungin	Intravenous	150 mg	Once daily
Anidulafungin	Intravenous	50 mg	Once daily
Amphotericin B	Intravenous	0.3–0.7 mg/kg	Once daily

Classes of agents used in the treatment of MC in HIV includes the polyenes (eg, amphotericin B, nystatin), pyrimidine synthesis inhibitors (flucytosine), azoles (miconazole, clotrimazole, ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole), and, more recently, the echinocandins (caspofungin, micafungin, anidulafungin).[17,22,24] Common dosage regimens of these agents are listed in Tables 1 and 2.

The key trials evaluating antifungals in the treatment of OPC and EC are summarized in Table 3. Most controlled studies to date have evaluated the azole antifungal agents and in general, clinical response rates appear to be similar. Clinical response varies widely, as does the rate of relapse. Studies of antifungal treatment in MC can be problematic to evaluate, particularly in the HIV-positive population. Limitations often include a small number of patients, open label design, and a short follow-up time. Additional studies are particularly needed among patients with low CD4+ T lymphocyte counts, as this population tends to have lower clinical and mycological response rates. A recent meta-analysis suggested that larger studies using more consistent outcome measures and reporting would be helpful in applying future research to current clinical practice.[25] Additionally, these authors also suggested that future investigations should include less expensive antifungal interventions and, at the same time, evaluate symptom-free periods, quality of life, survival, and the development of clinical and *in vitro* resistance.

Therapy of oropharyngeal candidiasis

Prior to the development of the polyenes and the azoles, topical therapy consisted of gentian violet applications that were reasonably effective in localized MC, but were extremely messy because of the purple color.[24,26]

While topical therapies have historically been effective in less severe disease and are relatively inexpensive compared to some of the systemic therapies, their use has diminished

Table 3 Clinical trials of antifungal agents for the treatment of OPC and EC in HIV-positive patients

Authors	Regimens evaluated (n = number of subjects)	Clinical response	Relapse rate
Oropharyngeal candidiasis (OPC)			
DeWit et al[37]	Fluconazole 50 mg/day (n = 17)	100%	46% at 30 days
	Ketoconazole 200 mg/day (n = 16)	75%	11%
Smith et al[106]	Ketoconazole 200 mg BID (n = 40)	93%	>80% at 90 days
	Itraconazole 200 mg/day (n = 46)	93%	>80%
Barchiesi et al[107]	Fluconazole 200 mg/day (n =38)	42%	62%
	Ketoconazole 400 mg/day (n = 39)	34%	22%
Pons et al[30]	Fluconazole 100 mg/day (n = 152)	98%	34% at 42 days
	Clotrimazole 10 5/day (n = 136)	48%	40%
de Repentigny et al[108]	Ketoconazole 200 mg/day (n = 52)	60%	80% at 60 days
	Itraconazole 200 mg/day (n = 46)	71%	80% at 60 days
Vazquez et al[58]	Fluconazole 100 mg/day (n = 94)	51%	37% at 30 days
	Posaconazole 50 mg/day (n = 98)	74%	41%
	Posaconazole 100 mg/day (n = 102)	80%	38%
	Posaconazole 200 mg/day (n = 91)	74%	35%
	Posaconazole 400 mg/day (n = 100)	83%	36%
Vazquez et al[32]	Miconazole lauriad 10 mg/day (n = 283)	68%	27%
	Clotrimazole 10 mg 5/day (n = 281)	74%	28%
Esophageal candidiasis (EC)			
Laine et al[66]	Ketoconazole 200 mg/day (n = 71)	65%	N/A
	Fluconazole 100 mg/day (n = 72)	85%	
de Repentigny et al[108]	Ketoconazole 200 mg/day (n = 19)	100%	58% at 60 days
	Itraconazole 200 mg/day (n = 12)	65%	82% at 60 days
Ally et al[72]	Fluconazole 200 mg/day (n = 141)	90%	N/A
	Voriconazole 200 mg BID (n = 115)	95%	
Villaneueva et al[77]	Fluconazole 200 mg/day (n = 94)	89%	17% at 28 days
	Caspofungin 50 mg/day (n = 81)	90%	28% at 28 days
de Wet et al[78]	Fluconazole 200 mg/day (n = 60)	80%	N/A
	Micafungin 50 mg/day (n = 64)	84%	
	Micafungin 100 mg/day (n = 62)	92%	
	Micafungin 150 mg/day (n = 59)	92%	
Krause et al[79]	Fluconazole 400 mg/day (n = 255)	99%	11% at 14 days
	Anidulafungin 200 mg then 100 mg/day (n = 249)	99%	36%

due to poor tolerability and poor adherence. Topical therapy of OPC can be accomplished with a multitude of antifungal agents including nystatin, amphotericin B, clotrimazole, and, more recently, miconazole (Table 1).[17,22,24,26–31] Nystatin is available in several formulations, including pastilles and suspension. Limitations of topical agents such as nystatin include a bitter taste, GI-adverse effects, and frequent dosing, all of which may contribute to reduced adherence.[24,27] Importantly, nystatin has not demonstrated significant efficacy in severely immunocompromised patients, such as those with advanced HIV infection.[27,28] For instance, in HIV-positive patients, nystatin exhibited lower rates of both clinical cure (52% vs 87%) and mycological cure (6% vs 60%) when compared to oral fluconazole. Additionally, the 28- day relapse rate was found to be greater with nystatin (44% vs 18%) when compared to fluconazole.[27]

Amphotericin B is also an option for topical therapy and is available in suspension, lozenge, and tablet form.[1,22] Neither nystatin, nor amphotericin B is absorbed from the gastrointestinal tract so administration must be frequent (four times daily) to provide adequate drug exposure to the infected mucosal tissues.[1,22] Prospective, comparative studies evaluating amphotericin B oral solution against other antifungals are limited. Topical azole antifungal agents, such as clotrimazole 10 mg troches, administered five times daily, provide another option for OPC patients. Topical clotrimazole has been used successfully in treating mild-to-moderate OPC during the early stages of HIV disease.[28–30]

The newest topical antifungal is the mucoadhesive buccal tablet (MMBT) containing 50 mg of miconazole (Loramyc®).[31] This novel formulation of miconazole has been approved in Europe since 2008 for the treatment of OPC in immucocompromised hosts. The formulation is unique, because 50 mg of miconazole is contained in each mucoadhesive tablet and is applied to the mucosa of the upper gum over the canine fossa, once daily, for 7–14 days. The MMBT adheres to the gum surface because of the milk protein concentrate composition of the tablet. This interaction leads to a rapid and prolonged adhesion to the mucosa due to an adsorption mechanism, followed by a protein-protein interaction. In pharmacokinetic studies, 50 mg of MMBT provides a maximum salivary concentration of 15 μg/mL, up to seven hours after the application of the tablet.[31] Three separate clinical studies have evaluated the use of MMBTs for the treatment of OPC in the HIV-positive population and in patients with head and neck cancers.[32–34] In a phase III, double-blind, double-dummy, multicenter trial evaluating 578 patients with HIV and OPC, MMBT treatment was compared to clotrimazole troches (10 mg, five times daily,

for a period of 14 days).[32] The results at the primary endpoint of test of cure (TOC) in both the intent-to-treat (ITT) population and in the per-protocol population (PP) demonstrated that the once daily administration of a MMBT was as effective as the five times daily clotrimazole treatment. Clinical cure rates at TOC in both the ITT (61% vs 65%) and PP (68% vs 74%) populations demonstrated no inferiority to clotrimazole. In addition, secondary endpoints such as safety and tolerability were similar between both treatment groups.

The use of topical antimycotic agents has been replaced with systemic azole antifungals such as ketoconazole, fluconazole, itraconazole, and more recently posaconazole (Table 1).[17,24] Part of the reason for this is that, although clinical cure rates may be similar, microbiologic cure and long term efficacy are not. In one example, a study comparing systemic oral fluconazole with clotrimazole troches in HIV-positive adults found clinical efficacy to be similar (98% vs 94%). However, microbiological cure rates were greater in patients treated with fluconazole (65% vs 48%) and clinical response sustained through a 2-week follow up was also greater (82% vs 50%).[30]

The currently available systemic azoles include ketoconazole, fluconazole, itraconazole, and posaconazole. Ketoconazole was the first available oral systemic imidazole antifungal agent with high rates of efficacy in OPC.[35,36] However, in comparative trials, ketoconazole was found to be less efficacious then fluconazole in both clinical and mycological cure rates.[37] In addition, the use of ketoconazole is further limited by potentially severe adverse reactions including hepatotoxicity, poor oral bioavailability, and a host of drug–drug interactions.[36] Ketoconazole is a very potent inhibitor of cytochrome P450 3A4 and is relatively contraindicated with some HIV-protease inhibitors.[38] Because the drug's absorption is dependent upon an acidic pH, there are also concerns that systemic absorption may be inadequate in patients receiving acid-suppressive therapy or with AIDS-related hypochlorhydria.[39] In view of the lower clinical efficacy rates and the associated adverse event profile (ie, hepatotoxicity), ketoconazole is not widely used anymore. In contrast to ketoconazole, other azoles such as fluconazole, itraconazole, voriconazole, and posaconazole have demonstrated improved efficacy, as well as excellent safety profiles, and have thus become the drugs of choice for OPC, especially in HIV-positive patients (Table 3).[1,22,24,30]

Fluconazole is the most commonly used antifungal in the treatment of MC in HIV-infected patients. It is available in oral suspension, tablet, and parenteral formulations. Fluconazole is more readily absorbed than other oral azoles without being affected by either food or gastric acidity. The clinical

efficacy of fluconazole has been established in many well controlled clinical trials, such that it has become the standard comparator in clinical trials of novel agents.[24,30,37,40–42] Most studies of fluconazole have used an initial loading dose of 200 mg followed by 100 mg daily, but clinical success has been achieved with doses as low as 50 mg/day.[40] Clinical response is usually apparent within 10 days with 50 mg/day, and 5 to 7 days for doses of 100–200 mg/day.[17,40] Of the available azoles, fluconazole is associated with the fewest drug–drug interactions because it has less affinity for the CYP3A4 enzyme.[38,43] The pharmacological interactions with fluconazole include concomitantly administered phenytoin, rifampin, rifabutin, cyclosporin A, and possibly some of the protease inhibitors.[38,39,43–45] Fluconazole is generally well tolerated, however, as with any other azole being used long term, periodic surveillance of liver enzymes to monitor for hepatotoxicity is useful.[24,43]

Itraconazole is supplied in a cyclodextrin oral solution or capsule; the parenteral formulation is no longer manufactured in the United States.[1,24,46] Like ketoconazole, itraconazole exhibits a strong potential for drug–drug interactions through the CPY3A4 enzyme system.[38,46,47] The itraconazole oral solution has greater bioavailability than the capsule and absorption is further enhanced by postprandial administration.[40,46–48] One prospective, randomized trial in HIV-positive and AIDS patients with OPC, found itraconazole oral solution to have similar efficacy and safety as fluconazole (clinical response 97% vs 87%).[49] However, approximately 50% of the patients in both groups experienced relapses at the 1-month follow-up evaluation.

Posaconazole is the newest triazole on the market and is approved for the treatment of acute OPC and antifungal-refractory MC.[50–52] It is an oral extended-spectrum triazole with potent *in vitro* activity against pathogenic yeast and moulds, including fluconazole- and itraconazole-resistant *Candida* strains.[50] As with other azoles, posaconazole inhibits lanosterol 14-α-demehylase. It appears that mutations near the heme cofactor of CYP51 reduce the binding affinity of compact azoles, such as fluconazole and itraconazole, and may lead to azole crossresistance.[50] However, 3-dimensional binding models suggest that the long side chain of posaconazole may result in tighter binding affinity.[53,54] Thus, posaconazole may be less susceptible than some azoles to the development of secondary azole resistance. Posaconazole is absorbed in an oral suspension.[50] It is important to note that posaconazole absorption is enhanced by coadministration with food, especially high fatty meals, or with a nutritional supplement such as Boost® Plus (Nestlé, Fremont, MI).[55,56]

When food intake is limited, dividing the daily dose from BID (twice daily) to QID (four times daily) also increases the plasma concentration. Unlike itraconazole and voriconazole, posaconazole is not primarily metabolized by fungal cytochrome P450 enzymes.[57] During several drug interaction trials evaluating the effects of posaconazole on the CYP450 enzymes, posaconazole did demonstrate an inhibitory effect on CYP3A4, but did not influence the other isoenzymes. In a large multicenter, randomized clinical trial, a 100 mg daily dose of posaconazole was compared to a 100 mg daily dose of fluconazole in HIV-positive patients with OPC.[58] Clinical success was reported in 92% of the posaconazole recipients compared with a success rate of 92% for those patients that received fluconazole. The only difference was in the long-term follow-up, where clinical relapses occurred more frequently in the fluconazole group compared to the posaconazole group (38.2% vs 31.5%). In general, the adverse events reported in both groups were comparable.

Several concerns have been raised about the widespread use of the more potent oral azoles, which may offer only minor advantages for patients. These concerns include drug interactions, side effects, increased expense, and risk of developing antifungal resistance. An increased frequency of *C. glabrata* isolation has been described by several investigators of HIV-positive patients receiving prolonged courses of fluconazole.[59–62] In addition, although azole resistance in *C. albicans* is rare, several reports describe both clinical failure and *in vitro* resistance in both non-HIV patients and in HIV-infected patients on long-term azoles.[24,63]

Therapy of esophageal candidiasis

Systemic antifungal therapy using oral or parenteral fluconazole has been the mainstay in the management of EC for over a two decades (Tables 2 and 3).[1,17] Topical antifungals such as nystatin, clotrimazole, and miconazole are of minimal value in EC.[22,64] The initial step in the management of EC should always be to attempt to minimize all possible predisposing factors, such as corticosteroids, chemotherapeutic agents, and antimicrobials.[1,17,22]

Oral fluconazole has an excellent safety profile when compared to ketoconazole, demonstrates excellent gastric absorption, and can also be given intravenously when necessary. Similar to the observations in OPC research, studies comparing fluconazole with either clotrimazole or ketoconazole for CE demonstrate cure rates that are superior to those with other imidazoles. Moreover, fluconazole demonstrated a more rapid onset of action and quicker resolution of symptoms.[65–67] Itraconazole has also been shown to be effective in

the treatment of EC.[68–70] Patients treated with itraconazole oral solution (100–200 mg/day) had clinical response rates comparable to those of patients treated with fluconazole tablets (100–200 mg/day) of 94% and 91%, respectively, without significant adverse effects in either group.[68] The mycological cure rates were also similar at 92% and 78%, respectively.

Voriconazole, another broad spectrum systemic triazole is also approved for the treatment of EC at a dose of 200 mg BID for 14–21 days. *In vitro*, it has been shown to be 10- to 500-fold more potent than fluconazole against a wide array of yeast and moulds, including many isolates that have demonstrated *in vitro* itraconazole- and/or fluconazole-resistance.[71] In a double-blind, randomized, multicenter study, voriconazole 200 mg BID was compared to fluconazole 200 mg daily in EC.[72] The overall success rates were comparable at 98.2% for voriconazole vs 95% for fluconazole. Furthermore, the overall safety and adverse event profile of both agents was comparable. As with most azoles, voriconazole has an effect on the CYP450 enzymes, so caution regarding drug-drug interactions is warranted.[36,71] A common side effect with voriconazole includes photopsia (visual abnormalities) that may occur in 20%–30% of patients. These abnormalities eventually resolve after 3–4 days of continued usage. Other side effects may include elevations in transaminases (~10%) and skin rashes (~10%), with rare cases of photodermatitis in patients who are exposed to direct sunlight.[71]

Prior to the availability of azole antifungal agents, amphotericin B deoxycholate was used extensively. However, it is now rarely used in any patient and is generally reserved for antifungal-refractory cases of *Candida* esophagitis that do not respond to azoles or echinocandins.[73] If necessary, low dose amphotericin B (0.15–0.3 mg/kg/day or 10–20 mg/day for 10–14 days) is sufficient for moderate to severe disease.[1,17,73] However, because of the improved adverse event profiles of the lipid formulations of amphotericin B, they have also become popular. Oral flucytosine (100–150 mg/kg/day in divided doses), although effective, is rarely used because of the tendency for resistance to develop during therapy and the well described frequency of bone marrow suppression and transaminase elevation.[1,74] Furthermore, in one comparative clinical trial, clinical efficacy and mycological cure rates were lower for flucytosine when compared to fluconazole.[74]

The echinocandin class of antifungals, which includes caspofungin, micafungin, and anidulafungin are a novel class of antifungal agents with a completely different mechanism of action.[75] All three agents have demonstrated excellent *in vitro* activity against a broad array of *Candida*

species, including those that are resistant to fluconazole, itraconazole, or voriconazole.[75] There have been a total of five clinical trials evaluating the efficacy of the three echinocandins in treating EC in HIV-positive patients. In all studies, the echinocandins are compared to either fluconazole or amphotericin B. In a clinical trial comparing caspofungin to amphotericin B in both OPC and EC in a population that was predominantly HIV-positive, clinical success rates for caspofungin ranged from 74% to 91%, which was numerically greater than the success rate for amphotericin B (63%).[76] In a related study, 177 patients with EC were stratified to receive either fluconazole 200 mg/day or caspofungin 50 mg/day. Caspofungin was found to have similar response and relapse rates as fluconazole.[77] In another clinical trial, the treatment of EC among HIV-positive patients was also found to be similar for micafungin 150 mg/day when compared to fluconazole 200 mg/day.[78] In a separate multicenter clinical study in HIV-positive patients (n = 601, 75% with AIDS) evaluating anidulafungin versus fluconazole in patients with EC found this echinocandin to have similar clinical response rates when compared to fluconazole, in terms of both efficacy and safety.[79] So, while the echinocandins are not considered first line therapy for EC, they are effective antifungals for the treatment of MC in HIV-positive patients. Their use however, is limited because of the lack of an oral formulation.

Clinical relapse is not uncommon, especially in patients with persistent underlying immunodeficiency (eg, untreated and advanced HIV infection). Relapse appears to depend on the duration of antifungal therapy and degree of immunosuppression and may occur sooner following clotrimazole and ketoconazole therapy than after itraconazole, fluconazole, or posaconazole therapy.[30,71,80,81] After several recurrences of symptomatic OPC in patients with AIDS, clinicians may consider maintenance (secondary) prophylaxis.[80]

Several dosages of fluconazole as the primary prophylaxis have been evaluated. Although most studies documented a reduction in the frequency of MC in treated patients with AIDS, the regimens did not provide complete protection and occasional breakthrough infections occurred.[82,84] Powderly et al compared fluconazole 200 mg/day and clotrimazole troches 10 mg five-times/day prophylactically in HIV-positive patients.[83] Overall, fluconazole reduced the frequency of MC, superficial fungal infections, and cryptococcal disease when compared to clotrimazole.[83] The benefit was greatest in patients with less than 50 CD4^{+} T cells/mm^{3}. Unfortunately, in this study, the incidence of *in vitro* resistance and the effect fluconazole had on fungal flora was not evaluated. In addition, although the incidence of fungal infections was

reduced, the survival rate was similar in both groups. In this setting, one must weigh the benefits against the cost of daily drug administration, not only in the financial sense, but also the influence of the agent on the patient's mycoflora.

Schuman et al evaluated fluconazole 200 mg/week vs placebo in HIV-infected women with CD4+ T cell counts < 300 cells/mm.[85] The study concluded that weekly fluconazole was effective in preventing symptomatic OPC and vaginal candidiasis while the rates of clinical and *in vitro* resistance were low. Additionally, women receiving fluconazole had a reduction in the colonization rates of *C. albicans,* but had an increased isolation of non-*albicans Candida* species. In a recent multicenter, randomized clinical trial evaluating the role of prophylaxis in HIV-positive patients, Goldman et al showed that the number of episodes of OPC and other invasive fungal infections was statistically lower in HIV-positive patients with CD4+ T counts < 150 cells/mm³, when receiving continuous (three times a week fluconazole) when compared to those patients only receiving episodic treatment with fluconazole for OPC recurrences.[84] The study also demonstrated that the incidence of clinically significant resistance was no higher in the group receiving continuous therapy than in the group using episodic administration of fluconazole, provided the patients were on highly active antiretroviral therapy.

In general, when making the clinical decision to initiate secondary prophylaxis the physician should consider several key points: the impact of excessive recurrences on the patients well being and quality of life, the need for prophylaxis of other fungal infections, financial costs, adverse event profiles, and drug-drug interactions.

Management of antifungal-refractory mucosal candidiasis

The clinical impact of antifungal resistance in patients with AIDS has been demonstrated in patients who failed conventional antifungal therapy for MC.[24,86] After the development of fluconazole-resistant OPC, patients were noted to have a median survival of approximately 184 days. Moreover, after the onset of clinical resistance to parenteral amphotericin B, patients were found to have an astonishing 83-day median survival rate.[24,86] Although MC per se is not fatal, clinical failure is probably a comorbid factor associated with the rapid demise of these patients. Clinical failure may also be a marker of severe immunosuppression and a dysfunctional immune system.

Antifungal resistance can be divided into two categories, clinical and *in vitro*. Clinical resistance signifies failure of the antifungal to eradicate the infection in the absence of *in vitro* resistance. Such resistance may occur for a variety

of reasons. *In vitro* resistance can also be subdivided into either primary (innate or intrinsic) or secondary (acquired) resistance.[24,86]

The usefulness of bacterial *in vitro* susceptibility testing is well established in the management of patients with infectious diseases. However, despite the fact that a subcommittee for *in vitro* antifungal susceptibility testing published approved guidelines, the utility of these results in managing fungal infections is still somewhat controversial.[87,88] Several studies have revealed a correlation between the *in vitro* susceptibility minimum inhibitory concentration [MIC] results of *C. albicans* and the clinical response to antifungal treatment in HIV-infected patients.[60,87,88] Investigators have published therapeutic antifungal successes and failures in patients with OPC and *Candida* isolates for which MICs were both low and high. In fact, one group has reported several HIV-infected patients with documented *in vitro* fluconazole-resistant MC who were still able to respond to fluconazole therapy.

Initially, it was believed that the trigger for the emergence of resistance was primarily due to the use of low dose fluconazole for acute treatment as well as for prophylaxis.[86,89,90] More recently, investigators have demonstrated that MC due to resistant isolates is seen in patients with low CD4+ cell counts (<50 cells/mm³).[91] Conversely, another study indicated that a low CD4+ cell count did not predict azole-resistant MC in patients with AIDS.[61]

Investigators have be able to identify several key risk factors associated with the development of fluconazole-resistant MC in patients with AIDS, compared to those patients without evidence of fluconazole-resistant MC. These risk factors include: greater number of episodes of OPC (6.1 vs 1.8), lower median CD4+ cell count (11 vs 71 cells/mm³), longer median duration of antifungal therapy (419 vs 118 days), and longer duration of systemic azoles (272 vs 14 days).[91] When the authors used two controls matched by CD4+ cell count, resistant cases continued to have a greater median exposure time to azoles (272 vs 88 days; $P = 0.005$) as the significant risk factor.[61,91]

It is still not clear whether the total dose of antifungals, the duration of therapy, the type of antifungal, and/or the pattern of drug administration (continuous vs episodic) are the most important determinants in the development of antifungal-refractory fungal disease.[24,84,90,91] More than likely, the etiology is multifactorial involving a combination of advanced immunosuppression, high fungal burdens, and prolonged exposure time to antifungals.

The management of fluconazole-resistant MC is frequently unsatisfactory and the clinical response is short-lived

with periodic and rapid recurrences. In some patients, the refractory candidiasis may respond to increases in the dose of fluconazole (Table 4). For example, if patients fail fluconazole 200 mg/day, a dosage increase to 400–800 mg/day will frequently produce a clinical response for a period of time. However, the response is generally transient and the disease recurs rapidly once patients have reached this stage. As noted, clinical and *in vitro* azole resistance is not uncommon in patients who fail to respond to fluconazole. Occasionally, in some patients with fluconazole-refractory MC, fluconazole suspension may be beneficial.[91] Several reports describe improvement in these patients, possibly associated with increased salivary levels of fluconazole, which results when the suspension is taken with a swish-and-swallow technique.[91]

Several clinical trials evaluating itraconazole oral solution have demonstrated promising results in patients with AIDS who failed fluconazole 200 mg/day.[92–95] A clinical cure or improvement occurred in 55%–70% of these patients. As expected, mycological cure rates were low (<30%) and relapses following treatment cessation were rapid, usually within 14 days.

The two newly expanded spectrum triazoles, voriconazole and posaconazole, have been used successfully in patients with refractory MC.[96,97] Posaconazole is licensed in the United States for the treatment of refractory OPC/EC. In the largest clinical trial evaluating antifungal agents for refractory OPC/EC,

posaconazole 400 mg suspension was given either QD (once daily) or BID and was evaluated in subjects with documented clinical resistance to either fluconazole or itraconazole.[96] Of the 176 subjects enrolled, 132 (75%) achieved a clinical response after 28 days of therapy with very few adverse events. Only eight patients discontinued the study drug because of a side effect. As expected, during the 4-week follow up period the overall clinical relapse rate was 74%.

It is important to note that with any fungal infection in patients with advanced HIV infection it is essential to continue suppressive antifungal therapy in an attempt to increase disease-free intervals and avoid morbidity and occasional mortality. These patients generally suffer from advanced-HIV disease and ultimately very low CD4+ T cells (<50) and high viral burdens along with uncontrolled HIV infection.[81]

It is important not to underestimate the significance of the underlying dysfunctional immune system in patients with AIDS and refractory fungal infections. Although randomized clinical trials have not been done, the initiation of HAART will frequently assist in the resolution of these recalcitrant infections. In fact, treatment with HAART alone without antifungals have eradicated antifungal-refractory OPC in patients with advanced HIV infection.[98,99]

The classic management of infections in the compromised host has depended upon antimicrobial agents, without taking into account host defects. Several cytokines developed and produced by recombinant technology show promise in assisting the host response to fungal infection.[100,101] There have been several reports describing the use of human recombinant granulocyte-macrophage colony stimulating factor (rhuGM-CSF) in patients with OPC or EC refractory to fluconazole and amphotericin B.[100,101] Although no large studies have been published, case reports describe good response rates with rhuGM-CSF in patients with advanced HIV infection and refractory mucosal candidiasis.[101,102] Further studies evaluating these cytokines are certainly warranted.

Alternative therapeutic modalities using organic substances are also being administered empirically to combat refractory MC. One of these formulations is *Melaleuca alternafolia*, or Australian tea tree oil that has been formulated into an oral solution. A small, single center pilot study evaluating the melaleuca oral solution in 14 patients with AIDS and fluconazole-refractory OPC has been completed.[103] The results appear to indicate relatively good efficacy in these difficult-to-treat patients, demonstrating a good clinical response in 10 of 12 patients after four weeks of antifungal therapy. However, larger comparative studies are necessary to evaluate the role of this agent in refractory candidiasis.

Table 4 Alternative therapies for the management of antifungal-refractory mucosal candidiasis in patients with AIDS

Antifungals
- Posaconazole suspension 400 mg twice daily
  - FDA approved for antifungal-refractory mucosal candidiasis
- High dose fluconazole (800–1600 mg/day)
- Itraconazole oral solution 200–300 mg twice daily
- Voriconazole tablets/solution 200–300 mg twice daily
- Amphotericin B deoxycholate 0.3–0.7 mg/kg/day
- Lipid formulations of amphotericin B 1–3 mg/kg/day
- Anidulafungin 100 mg IV daily
- Caspofungin 50 mg IV daily
- Micafungin 150 mg IV daily

Antifungal combinations
- Fluconazole + flucytosine 100 mg/kg day, divided QID
- rhuGM-CSF + fluconazole
- Amphotericin B + echinocandins
- Fluconazole + terbinafine
- Fluconazole + echinocandins

Investigational antifungal agents
- Melaleuca oral solution (Breathaway®)

Note: Many of the alternative therapies are not FDA approved and not supported by adequate clinical trials.
Abbreviations: FDA, US Food and Drug Administration; rhuGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; QID, four times daily.

In conclusion, significant advances in antifungal therapy have been made in the last decade. The impressive clinical trial results and the low grade side effect profile of the azole compounds continue to make them attractive choices in the management of fungal infections in any immunocompromised patient, especially HIV-positive patients. However, difficulties in managing these infections should remind us that we can not rely solely on antifungals. We must continue to find ways to improve the body's dysfunctional immune system. In addition, we must continue to develop more effective antifungal agents with different mechanisms of action and different modes of administration.

Disclosure

The author reports no conflict of interest in this work.

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