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Oropharyngeal Candidiasis in the Era of Antiretroviral Therapy

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Abstract

Oropharyngeal candidiasis (OPC) remains a common problem in the HIV-infected population despite the availability of antiretroviral therapy (ART). Although *Candida albicans* is the most frequently implicated pathogen, other *Candida* spp. may also cause infection. The emergence of antifungal resistance within these causative yeasts, especially in patients with recurrent oropharyngeal infection or with long-term use of antifungal therapies, requires a working knowledge of alternative antifungal agents. Identification of the infecting organism and antifungal susceptibility testing enhances the ability of clinicians to prescribe appropriate antifungal therapy. Characterization of the responsible mechanisms has improved our understanding of the development of antifungal resistance and could enhance the management of these infections. Immune reconstitution has been shown to reduce rates of oropharyngeal candidiasis but few studies have evaluated the current impact of ART on the epidemiology of oropharyngeal candidiasis and antifungal resistance in these patients. Preliminary results from an ongoing clinical study showed that in patients with advanced AIDS oral yeast colonization was extensive, occurring in 81.1% of the 122 patients studied and symptomatic infection occurred in a third. In addition, resistant yeasts were still common occurring in 25.3% of patients colonized with yeasts or with symptomatic infection. Thus, oropharyngeal candidiasis remains a significant infection in advanced AIDS even with ART. Current knowledge of the epidemiology, pathogenesis, clinical presentation, treatment, and mechanisms of antifungal resistance observed in oropharyngeal candidiasis are important in managing patients with this infection and are the focus of this review.

Keywords

thrush; OPC; oral candidiasis; *Candida*; resistance

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INTRODUCTION

Oropharyngeal candidiasis (OPC), or thrush, is a common and localized infection typically caused by the yeast *Candida albicans*, a normal component of the human gastrointestinal microflora. While the incidence of OPC has declined for HIV-infected persons with access to antiretroviral therapy (ART)^{1–3}, it remains a significant problem for those in resource-limited settings or those with a poor immunologic response despite the initiation of ART⁴. Oropharyngeal candidiasis may also be an early indicator of HIV infection and may predict progressive immunodeficiency⁵.

This manifestation of underlying immunosuppression was seen in up to 90% of at risk individuals infected with HIV prior to the availability of ART⁶. OPC is typically managed with oral fluconazole and further attempts to improve patient's ability to mount an effective immunologic response⁷. However, mycological resistance, which is most commonly found in the setting of advanced HIV with extensive prior triazole use continues to occur^{8, 9}. Fluconazole failure, while less frequent than prior to the widespread availability of ART, remains difficult to manage in patients with advanced immunodeficiency^{10, 11}.

EPIDEMIOLOGY

Prior to the availability of active antiretroviral therapy, oropharyngeal candidiasis was a very common finding in patients with HIV/AIDS. With the development of effective antiretroviral drugs, rates of oral candidiasis were reported to decrease^{1–3}. Declining rates of oropharyngeal candidiasis and carriage of *C. albicans* were associated with trends toward reduced rates of carriage of fluconazole-resistant *C. albicans* in human immunodeficiency virus-infected patients¹². The epidemiology of oral candidiasis in patients receiving antiretroviral therapy and the significance of antifungal resistance in this population is not well-described. In preliminary results reported at the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy we described oral yeast colonization and infection from an ongoing clinical trial in patients with advanced HIV infection. In that report, we evaluated the presence of symptomatic oral candidiasis or asymptomatic yeast colonization. We found 99/122 (81.1%) of patients were colonized by oral yeasts and thirty-three of these patients (33.3%) had symptomatic infection. Fluconazole resistant yeasts were frequently isolated even in the setting of ART, with detection in 25/99 (25.3%) patients¹³.

Candida albicans is responsible for the majority of OPC episodes. However other species such as *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, and *C. dublinensis* have also often been implicated, particularly in patients with advanced HIV/AIDS before the availability of active antiretroviral therapy, but also in other populations including patients undergoing bone marrow transplantation and in patients receiving therapy for head and neck cancer^{11, 14–16}.

These pathogens warrant discussion due to their potential to harbor antifungal resistance mechanisms. Results of our recent clinical data show that while *C. albicans* remains the most common etiological agent in patients with advanced AIDS (54% of isolates) *C. dublinensis* (17%) and *C. glabrata* (16%) are the second and third most frequently isolated species (Table 1). Both of these latter two organisms may exhibit decreased susceptibility or frank resistance to fluconazole so that recognition of these important causes of OPC may aid the clinician in cases recalcitrant to fluconazole therapy.

Additionally, previous antifungal treatment regimens have had a significant impact on the development of resistance¹⁷. The use of repeated or suppressive courses of low-dose fluconazole (50–100 mg/day) has contributed to the development of fluconazole resistant *C. albicans* as well as other intrinsically resistant yeasts such as *C. krusei* and *C. glabrata*¹⁷. In fact, other reports have identified *C. glabrata* as the second most common cause of OPC, with

C. krusei third, although *C. krusei* was the fifth most common isolate in our study¹⁸. To combat the emergence of these resistant pathogens a new drug class, the echinocandins, has recently been introduced. Cross-resistance between these new, intravenous agents and other antifungals has not been observed due their unique mechanism of action within the fungal cell wall. However *C. parapsilosis* and *C. guilliermondii* are often resistant to this class, and other *Candida* spp. have developed resistance when exposed to echinocandin therapy^{19, 20}. Unfortunately, the echinocandin class of antifungal agents is available only in an intravenous preparation so that their use in non-complicated oropharyngeal candidiasis is very limited. Thus, resistance of yeast to antifungals remains a significant clinical problem.

PATHOGENESIS

Candida spp. are part of the normal skin, genitourinary, and gastrointestinal microflora. In fact, *C. albicans* has been isolated in up to 65% of healthy individuals without signs of clinical disease. However under immunocompromising conditions the incidence of carriage may increase and rapid conversion to symptomatic infection may occur⁵. Protection against the conversion of yeast from colonizer to opportunistic/invasive pathogen is provided by both systemic and local immunity²¹. Th-1 type immunity provided by CD4+ T-lymphocytes is a critical component of protection and secondary defense is provided by CD8+ T-lymphocytes and oral epithelial cells through a variety of mechanisms.

The absolute CD4+ T-lymphocyte count has traditionally been cited as the greatest risk factor for the development of OPC and current guidelines suggest increased risk once CD4+ T-lymphocyte counts fall below 200 cells/ μ L (<15%). Yet OPC remains more common in HIV-infected patients than those with a similar degree of immunosuppression (bone marrow transplant, or patients receiving chemotherapy). This observation suggests that HIV itself may play a role in host susceptibility. Recent studies support this finding and suggest that the HIV viral load may be as important or more important than the CD4+ cell count. The absence of CD4+ T-lymphocytes in a murine model of oral candidiasis did not enhance host development of OPC^{22, 23} although transgenic mice expressing human immunodeficiency virus type 1 within immune cells were at an increased risk to develop OPC²⁴. Additionally, some authors have found the HIV viral load the most predictive factor in the development of OPC²⁵ and the development of OPC is thought to increase once the HIV-viral loads surpasses 10,000 copies/mL²⁵. This data is further corroborated by the observation that an improvement in CD4 T-lymphocyte cell counts following the initiation of antiretroviral therapy does not fully account for the reduction in the observed incidence of OPC²⁶.

Candida spp. have a multitude of virulence factors responsible for the ability to cause invasive infection. Their abilities to adhere to both endothelial and epithelial cells, develop hyphae/pseudohyphae, secrete proteinases and other lytic enzymes, and the capacity for phenotypic switching to gain access to the inside of a cell have all been found to play a role in pathogenesis²⁷.

CLINICAL PRESENTATION/PHYSICAL FINDINGS

OPC may be the patient's initial complaint prompting the clinician to consider testing for HIV or it may be incidentally discovered. The pseudomembranous form most commonly occurs when CD4+ cell counts drop below 200 cells/ μ L (Figure 1). This form appears as painless, creamy white, plaque-like lesions on the tongue, palate, buccal mucosa, or oropharynx and is frequently asymptomatic. Pseudomembranous lesions can typically be "wiped" away from the underlying mucosa²⁸.

Chronic atrophic candidiasis is more common in older adults and is typically located under dentures and consists primarily of erythema without plaque formation. This form may be more

frequently recognized as the HIV-infected population continues to age due to improved survival. Angular cheilitis (painful fissuring at the corners of the mouth) has also been attributed to *Candida* overgrowth and is frequently overlooked by even the astute clinician (Figure 2). Although OPC is frequently asymptomatic, dysguesia or a “cotton” taste are the most frequent complaints. Pain during eating or swallowing are often harbingers of more extensive disease such as *Candida* esophagitis.

DIAGNOSIS

The diagnosis of OPC is generally a clinical one. Oropharyngeal swab cultures may demonstrate *Candida* species, but since colonization of the oral mucosa by *Candida* is common, this is not necessarily diagnostic. Confirmation of a diagnosis of oral candidiasis can be accomplished via a 10% potassium hydroxide (KOH) slide preparation of a mucosal scraping from a suggestive oral lesion. Others have found periodic acid-Schiff (PAS) staining yields higher sensitivity in the detection and identification of fungal organisms, and in some cases, may reveal the presence of fungi that were not detected in a KOH preparation. Microscopic examination characteristically reveals pseudohyphae and budding yeast forms. However the diagnosis of OPC is often made presumptively and a trial of antifungal therapy initiated. If oral lesions fail to improve despite compliance with antifungal therapy, attempts to ensure that a definitive diagnosis has been made, and the possibility of a resistant organism should be explored. This commonly requires culture and susceptibility testing. However improved culture screening and PCR methods that may expedite accurate diagnosis are currently in development.

A presumptive diagnosis of *Candida* esophagitis can be made in the OPC patient with dysphagia. Barium swallow is often suggestive, but endoscopy is required for definitive diagnosis. Prior to these expensive and more invasive measures a trial of fluconazole is prudent²⁹. Most patients with esophageal candidiasis respond to antifungal therapy within 3–7 days³⁰. Empirical oral antifungal therapy with fluconazole has been found highly efficacious, safe, and cost-effective for HIV-infected patients with new-onset esophageal symptoms³¹. Earlier endoscopy without a trial of empiric antifungal therapy may be pursued in those without concurrent OPC or with atypical symptoms. If the patient fails to improve with appropriate systemic antifungal therapy, then endoscopy is indicated to exclude other causes of esophagitis including herpes simplex virus (HSV) or cytomegalovirus (CMV), both common causes of esophagitis in immunocompromised populations.

MANAGEMENT AND TREATMENT

A number of antifungal agents are available for the treatment of OPC (Table 2). However fluconazole remains first-line therapy and is typically administered as 100mg or 200mg per day and continued for 7–14 days after the resolution of symptoms³². Recent data suggests a one-time dose of fluconazole 750mg for the treatment of OPC is as effective and has an equivalent relapse rate to that of standard therapy³³. This strategy may provide lower costs and allow for directly observed therapy thus ensuring patient compliance.

Topical clotrimazole troches or nystatin suspension are recommended under existing guidelines although the frequency of administration and palatability of these options reduces their attractiveness compared to once daily oral fluconazole. Relapse is also more common when topical therapy is prescribed³⁴. Itraconazole, voriconazole, and posaconazole have also been found effective in the treatment of OPC, however few situations exist where they would be preferred over fluconazole as a first-line agent³⁵.

A minority of patients with OPC have refractory disease, and fail treatment with fluconazole. This scenario is most common in those with advanced HIV infection who are heavily

fluconazole exposed. Current guidelines suggest itraconazole solution following fluconazole failure, and prior reports have observed a 64–80% success rate with this strategy^{32, 34, 36}. Oral amphotericin solution has shown to be effective in some of these cases but must be compounded by a pharmacy, since it is not available commercially in the US³⁷. A compounding pharmacy can be located by calling 1-800-927-4227, or the use of the International Academy of Compounding Pharmacists website (<http://www.iacprx.org>). Posaconazole has been found effective in 74% of patients who failed previous antifungal therapy and voriconazole is likely equally effective^{38, 39}. Echinocandins may be useful in this setting due to their unique mechanism of action and thus lack of overlapping resistance with the triazoles^{40–42}. This new class of agents inhibit the synthesis of β -1,3 glucan, a component of the fungal cell wall. This inhibition impairs cell wall integrity and leads to osmotic lysis. Although these agents are only available intravenously - somewhat limiting their use in the outpatient setting.

Infrequently these agents are ineffective and intravenous amphotericin B is required⁴³. Immunomodulatory attempts have been made using granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon-gamma (IFN- γ) however use of the agents should be restricted to specialists within the field and attempted only when other options have been exhausted^{44, 45}.

Esophageal candidiasis warrants systemic therapy and topical agents should not be used. A 14–21 day course of fluconazole or oral itraconazole is usually effective. Intravenous caspofungin, micafungin, and anidulafungin are also approved for use in the treatment of esophageal candidiasis^{41, 42}, however these agents have a greater relapse rate than fluconazole and are more expensive and are not available in an oral formulation. They are thus typically reserved for refractory cases as discussed above.

Although flucytosine has activity against most *Candida* spp., resistance readily occurs during monotherapy and it should not be used as a single agent in the management of OPC.

Prophylaxis

Neither primary nor secondary prophylaxis are recommended for most patients exhibiting oral or esophageal candidiasis. This recommendation is based on the effectiveness of available therapy, the low attributable mortality, and the potential for resistant *Candida* spp. to develop over time with continued antifungal pressure. Although if recurrences are frequent or severe, daily fluconazole can be used and continued until immune reconstitution has occurred (CD4 >200 cells/ μ L)⁷. Long-term suppressive therapy with fluconazole has been compared to episodic fluconazole use for the development of symptomatic disease. We showed that in patients with frequent relapses effective suppression of recurrent oropharyngeal candidiasis reduced symptomatic relapses¹⁷. In that study, mycological resistance was common but not increased in patients receiving either frequent courses of fluconazole for recurrent OPC or with continuous suppressive therapy. In another large trial of the AIDS Clinical Trial Group/ Mycoses Study Group (ACTG/MSG), continuous suppressive therapy reduced relapse rates more effectively than intermittent therapy, but was associated with increased mycological resistance although the frequency of refractory disease was the same in each group⁴⁶.

Antifungal mechanisms of action and drug resistance

Resistance to antifungal agents is a continuing problem in the most commonly isolated *Candida* spp. (Table 3). Because susceptibility patterns are usually predictable based on *Candida* species, culture results that identify the organism to the species level can be very useful to help guide empirical choices of therapy. Although some species harbor intrinsic resistance to varying antifungals (i.e. *C. krusei* resistance to fluconazole, *C. lusitanae* resistance to amphotericin) the development of resistance while receiving appropriate therapy

has been well described in several *Candida* spp. and resistance testing should be considered in refractory or recalcitrant cases. Thus, in patients with refractory infection formal susceptibility testing can be useful. Methods for determining susceptibility to antifungal agents have been established by the Clinical Laboratory Standards Institute (CLSI)⁴⁷. Additional screening methods using disc diffusion have been established for fluconazole and voriconazole^{48, 49}. We previously developed a Chromogenic agar-based screen to rapidly identify heterogenous resistance in oral flora by adding fluconazole to the CHROMagar *Candida* (BioMerieux, Marcy l'Etoile, France) (Figure 3)⁵⁰. Addition of fluconazole to this media suppresses growth of susceptible yeasts (most typically *Candida albicans*) and allows detection of small numbers of resistant organisms along with their presumptive identification based on phenotypic colony appearance. Although this method is useful in identifying minority populations of resistant *Candida* spp. it is not currently commercially available. If resistant *Candida* spp are responsible for clinically apparent disease it is likely unnecessary to use such media as the offending organism will be present in large quantity.

The frequent administration of long-term low-dose fluconazole in the HIV-infected population has resulted in triazole resistant *C. albicans* isolates⁵¹. The mechanisms associated with antifungal resistance in *Candida* have been extensively investigated over the last several years and several excellent comprehensive reviews have been published^{51, 52}. The azoles target lanosterol 14 α -demethylase, the product of the *ERG11* gene. Point mutations within this gene are known to confer varying degrees of triazole resistance⁵³. Drug efflux from cells is another potential mechanism of resistance and overexpression of efflux pumps (*CDR1*, *CDR2*, or *MDR1*) has been correlated with triazole resistance⁵³. Additionally, overexpression of lanosterol 14 -demethylase, the target enzyme, may also occur. More recently mutations in transcription factors as well as other mechanisms have also been described (Table 4)^{54–58}.

Although rare, recent reports have also illustrated the potential for echinocandin resistance to emerge during therapy^{19, 59}. Some of these reports describing reduced echinocandin susceptibility in *Candida* isolates have identified mutations within genes encoding subunits of the glucan synthase complex, the target of echinocandins. All mutations described to date reside within highly conserved regions of *FKS1* or its homolog, *FKS2*. These genes are known to encode a large integral membrane protein subunit of the glucan synthase complex and thus point mutations confer a reduction in echinocandin in vitro and in vivo efficacy^{19, 60–63}.

In conclusion oropharyngeal candidiasis remains a significant problem in those with HIV. Fluconazole remains the standard of care in the treatment of this condition. However resistance to the triazoles and other antifungal agents has been described. These recent reports have illustrated the potential for resistant species to emerge despite therapy and have mandated clinicians possess a working knowledge of alternative antifungal agents.

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FIGURE 1.
Pseudomembranous form of OPC.

FIGURE 2.
Erythematous candidiasis and angular cheilitis secondary to oropharyngeal candidiasis.

FIGURE 3.

The agar dilution screening technique allows rapid discernment of isolates with decreased fluconazole susceptibility. Shown are two Chromagar *Candida* plates which allow rapid species determination based on colony color. More important to this screening method is the inclusion of Fluconazole (8 or 16 mcg/ml). The plate on the left has no fluconazole, and the one on the right contains 8 mcg/ml flu. Without fluconazole, the susceptible *C. albicans* overwhelms the growth of the other more resistant organisms. With fluconazole (on right), susceptible organisms are suppressed to pinpoint colonies and resistant yeasts are easily seen. Reproduced with permission ⁴⁸.

TABLE 1

Candida spp. isolated from 122 consecutive HIV-infected patients upon enrollment to our longitudinal OPC study (includes patients with thrush and those colonized).

<i>Candida</i> spp.	No. of isolates (%)
<i>C. albicans</i>	110 (54)
<i>C. dublinensis</i>	35 (17)
<i>C. glabrata</i>	32 (16)
<i>C. tropicalis</i>	12 (6)
<i>C. krusei</i>	7 (3)
<i>C. parapsilosis</i>	5 (2)
<i>C. lusitaniae</i>	2 (1)
<i>C. guilliermondii</i>	1 (0.5)
<i>S. cerevisiae</i>	1 (0.5)

Table 2**Treatment of oropharyngeal candidiasis (OPC)**

First-line agents ^{1,2}	
Fluconazole (PO or IV)	100–200 mg daily
Clotrimazole troches	10mg five times daily
Nystatin suspension or pastilles	400,000 units four times daily
Second-line agents if above contraindicated	
Itraconazole solution (PO)	200mg daily
Voriconazole (PO or IV)	200mg twice daily
Posaconazole (PO)	400mg daily in divided doses
Agents used in refractory OPC	
Caspofungin (IV)	70mg loading dose followed by 50mg daily
Micafungin (IV)	100–150mg daily
Anidulafungin (IV)	100mg loading dose followed by 50mg daily
Amphotericin B oral suspension	500mg every 6 hours
Amphotericin B deoxycholate (IV)- ³	0.3mg/kg daily

¹ Fluconazole is recommended for moderate-to-severe disease, and topical therapy with clotrimazole or nystatin is recommended for mild disease.

² Oral fluconazole is preferred in esophageal candidiasis. For patients unable to tolerate an oral agent, IV fluconazole, an echinocandin, or an amphotericin B preparation is appropriate and this condition should be treated for 14–21 days.

³ Lipid formulations of amphotericin B are viable alternatives with the advantage of less nephrotoxicity than amphotericin B deoxycholate

TABLE 3

Antifungal spectrum of activity against *Candida* spp.

<i>Candida</i> spp.	AMB	FLU	ITR	POS	VOR	ANI	MICA	CAS	5FC
<i>C. albicans</i>	+	+	+	+	+	+	+	+	+
<i>C. glabrata</i>	+	+/-	+/-	+	+	+	+	+	+
<i>C. krusei</i>	+	-	+/-	+	+	+	+	+	+/-
<i>C. tropicalis</i>	+	+	+	+	+	+	+	+	+
<i>C. parapsilosis</i>	+	+	+	+	+	+/-	+/-	+/-	+
<i>C. guilliermondii</i>	+	+	+	+	+	-	-	-	+
<i>C. lusitanae</i>	-	+	+	+	+	+	+	+	+

AMB, amphotericin; FLU, fluconazole; ITR, itraconazole; POS, posaconazole; VOR, voriconazole; ANI, anidulafungin; MFG, micafungin; CAS, caspofungin; 5FC, flucytosine. (+) implies antifungal activity against isolates, (-) implies no or limited activity against isolate, (+/-) implies variable activity against isolates. Modified from 57.

Table 4
Summary of selected mechanisms responsible for antifungal resistance in *Candida* spp.

Gene	Gene product	Mechanism of Resistance	Antifungal class
<i>ERG11</i>	Lanosterol 14 α -demethylase enzyme involved in synthesis of ergosterol.	Point mutations or upregulation of gene result in decreased affinity or overexpression	Triazoles
<i>CDR1/CDR2</i>	Membrane pump belonging To ABC superfamily	Overexpression results in multidrug efflux	Triazoles
<i>MDR1</i>	Membrane pump belonging To ABC superfamily	Overexpression results in multidrug efflux	Triazoles
<i>FKS1/FKS2</i>	Glucan synthase	Point mutations found to alter binding affinity of Echinocandins	Echinocandins
<i>TAC1</i>	Tac1p protein	Transcription factor responsible for upregulation of <i>CDR1/CDR2</i> if point mutations occur.	Triazoles
<i>PDR1</i>	Pdr1p protein	Transcription factor responsible for upregulation of <i>CDR1</i> if point mutations occur.	Triazoles
<i>MRR1</i>	Mrr1p protein	Transcription factor responsible for upregulation of <i>MDR1</i> if point mutations occur.	Triazoles