

Panel's Recommendations

I. What is the preferred antifungal treatment for oropharyngeal candidiasis (OPC) in children with HIV infection?

- Uncomplicated OPC infection can be effectively treated with topical therapy using clotrimazole troches or nystatin suspension for 7 to 14 days (**strong, moderate**).
- Oral fluconazole for 7 to 14 days is recommended for moderate or severe OPC disease (**strong, high**).
- For fluconazole-refractory OPC, itraconazole oral solution is recommended, although itraconazole is less well tolerated than fluconazole (**strong, moderate**).
- Chronic suppressive therapy is usually unnecessary; if it is required, fluconazole 3 times weekly is recommended (**strong, high**).

II. What is the preferred antifungal treatment for esophageal candidiasis in children with HIV infection?

- Systemic therapy is always required for esophageal disease (**strong, moderate**).
- Oral fluconazole is recommended for 14 to 21 days, but amphotericin B or an echinocandin (caspofungin, micafungin, anidulafungin) can be used in patients who cannot tolerate oral therapy (**strong, moderate**).
- For refractory esophageal disease, oral therapy can include itraconazole solution or voriconazole for 14 to 21 days (**strong, low**).
- Suppressive therapy with fluconazole 3 times weekly is recommended for recurrent infection (**strong, moderate**).

III. What is the preferred antifungal treatment for invasive candidiasis in children with HIV infection?

- In moderately severe to severely ill children with invasive candidiasis, an echinocandin is recommended. In less severely ill children who have not had previous azole therapy, fluconazole is recommended (**strong, moderate**).
- Alternatively, an initial course of amphotericin B therapy can be administered for invasive candidiasis with careful transition to fluconazole therapy to complete the treatment course (**strong, moderate**).
- Amphotericin B lipid formulations have a role in children who are intolerant of conventional amphotericin B (deoxycholate) or who are at high risk of nephrotoxicity because of preexisting renal disease or use of other nephrotoxic drugs (**weak, moderate**).
- Children with candidemia should be treated for ≥ 14 days after documented clearance of *Candida* from the last positive blood culture and resolution of neutropenia and of clinical signs and symptoms of candidemia (**strong, low**).
- Central venous catheters should be removed when feasible in children with candidemia (**strong, moderate**).

Rating System

Strength of Recommendation: Strong; Weak

Quality of Evidence: High; Moderate; Low; or Very Low

Epidemiology

The most common fungal infections in children with HIV infection are caused by *Candida* spp. Candidiasis is characterized as either localized or invasive. Localized disease caused by *Candida* is characterized by limited tissue invasion of the skin or mucosa. Examples of localized candidiasis include oropharyngeal and esophageal disease, vulvovaginitis, and diaper dermatitis. *Candida* can gain access to the bloodstream causing candidemia either by penetration from local mucosal or cutaneous infection or via medical devices such as central venous catheters. Once candidemia is present, widespread hematogenous dissemination to any organ is possible. Concerning manifestations of disseminated infection include, but are not limited to, meningitis, endocarditis, renal disease, endophthalmitis, and hepatosplenic disease. Candidemia with or without dissemination is collectively referred to as invasive candidiasis.

Localized Candidiasis

Oral thrush and diaper dermatitis occur in 50% to 85% of children with HIV infection. Oropharyngeal candidiasis (OPC) continues to be one of the most frequent opportunistic infections in children with HIV infection during the combination antiretroviral therapy (cART) era (28% of children), with an incidence rate of 0.93 per 100 child-years. The incidence of esophageal or tracheobronchial candidiasis has decreased from 1.2

per 100 child-years before the pre-cART era to 0.08 per 100 child-years during the cART era (2001–2004).¹ However, *Candida* esophagitis continues to be seen in children who are not responding to antiretroviral therapy (ART).^{2,3} Children who develop esophageal candidiasis despite ART may be less likely to have typical symptoms (e.g., odynophagia, retrosternal pain) or have concomitant OPC;⁴ during the pre-cART era, concomitant OPC occurred in 94% of children with *Candida* esophagitis.² Risk factors for esophageal candidiasis include low CD4 T lymphocyte (CD4) cell count (<100 cells/mm³), high viral load (>5,000 copies/mL), and neutropenia (absolute neutrophil count [ANC] <500 cells/mm³).^{1-3,5}

Invasive Candidiasis

Invasive candidiasis is less frequent than localized disease in children with HIV infection. However, *Candida* can disseminate from the esophagus, particularly during co-infection with herpes simplex virus (HSV) or cytomegalovirus (CMV).^{2,6} Candidemia occurs in up to 12% of children with HIV infection who have chronic indwelling central venous catheters placed for administration of total parenteral nutrition or intravenous (IV) antibiotics.^{3,7} While *Candida albicans* remains the most common cause of all candidiasis, approximately 50% of reported cases of *Candida* bloodstream infections in children are caused by non-*albicans* *Candida* spp. including: *Candida tropicalis*, *Candida kefyr* (*Candida pseudotropicalis*), *Candida parapsilosis*, *Candida glabrata*, *Candida krusei*, and *Candida dubliniensis*. In some settings, non-*albicans* species cause the majority of blood stream infections. The non-*albicans* *Candida* species are important to identify because several are resistant to antifungals. In general, *C. krusei* is considered resistant to fluconazole, and *C. glabrata* isolates have an increased rate of resistance to both fluconazole and voriconazole. Recently, an increasing number of *C. glabrata* isolates are also resistant to echinocandins. *C. lusitaniae* is inherently resistant to amphotericin B. Many children who develop candidemia have previously received systemically absorbed oral antifungal azole compounds (e.g., ketoconazole, fluconazole) for control of oral and esophageal candidiasis, which may predispose to resistant isolates.³ In one study of Cambodian children with HIV infection and on ART who had candidiasis, seven (75%) of nine isolated *C. glabrata* were resistant to fluconazole, and three (40%) of seven *C. parapsilosis* isolated were resistant to >3 azole agents.⁸ However, clinicians should be aware of local resistance trends as the epidemiology of species-specific resistance may vary widely by geographic location and hospital.

Clinical Manifestations

Clinical manifestations of OPC vary and include pseudomembranous (thrush), erythematous (atrophic), hyperplastic (hypertrophic), and angular cheilitis presentations. Thrush appears as creamy white, curd-like patches with inflamed underlying mucosa that is exposed after removal of the exudate and can be found on the oropharyngeal mucosa, palate, and tonsils. Erythematous OPC is characterized by flat erythematous lesions on the mucosal surface. Hyperplastic candidiasis presents as raised white plaques on the lower surface of the tongue, palate and buccal mucosa, and cannot be removed. Angular cheilitis presents as red fissured lesions in the corners of the mouth.

Esophageal candidiasis often presents with odynophagia, dysphagia, or retrosternal pain, and children, unlike adults, often experience nausea and vomiting. Therefore, children with esophageal candidiasis may present with dehydration and weight loss. Classic symptoms and signs of OPC may be absent in children with esophageal candidiasis, particularly those receiving ART.

New-onset fever in a child with HIV infection who has advanced disease, a central venous catheter, or both is the most common clinical manifestation of candidemia. Unfortunately, there are limited clinical signs or symptoms to denote dissemination to a particular organ, and detection of end organ involvement is often dependent on radiographic imaging. For example, renal candidiasis can present with candiduria, but ultrasonographic demonstration of renal parenchymal lesions is often not associated with symptoms related to renal disease.³

Diagnosis

Oral candidiasis can be diagnosed with a potassium hydroxide preparation and culture with microscopic demonstration of budding yeast cells in wet mounts or biopsy specimens. Esophageal candidiasis has a classic cobblestone appearance on barium swallow. Findings on endoscopy may range from a few, small, raised, white plaques to elevated confluent plaques with hyperemia and extensive ulceration. Endoscopy is also helpful for ruling out other causes of refractory esophagitis, such as HSV, CMV, and *Mycobacterium avium* complex.

Candidemia is best diagnosed with blood cultures using lysis-centrifugation techniques,³ or automated broth-based systems.⁹ When candidemia is present, retinal examination for endophthalmitis, cardiac echocardiogram for endocarditis, abdominal computed tomography or ultrasound for hepatic or renal involvement, and bone scans for osteomyelitis (if suspected by symptoms) should be considered.

New diagnostic techniques such as the urine D-arabinitol/L-arabinitol ratio,^{10,11} serum D-arabinitol/creatinine ratio,^{12,13} *Candida* mannan antigen and anti-mannan antibody,^{14,15} (1,3)-beta-D-glucan assay,^{16,17} T2 biosystems for *Candida*¹⁸ and real-time polymerase chain reaction^{19,20} are promising diagnostic alternatives under development for early diagnosis of invasive candidiasis. Although several of these assays are helpful in diagnosing invasive candidiasis in adult patients, none of them have been validated or Food and Drug Administration (FDA)-approved for use in children.

As noted above, candidemia can result in dissemination of infection to any organ site. There are no pediatric data to guide decisions on when to perform additional diagnostic testing to evaluate for a deep-seated focus. However, among children with persistent candidemia, further investigation for dissemination should strongly be considered. Additional diagnostics to consider in this clinical scenario would include, but not be limited to, an echocardiogram, abdominal ultrasound to evaluate the kidney, liver and spleen, a lumbar puncture and an eye exam (**strong, low**).

Prevention Recommendations

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals; no measures are available to reduce exposure to these fungi except by reducing exposure to unneeded antibiotics that may predispose a patient to *Candida* colonization.

Preventing First Episode of Disease

Routine primary prophylaxis of candidiasis in infants and children with HIV infection is not indicated for multiple reasons. In the era of ART, the prevalence of serious *Candida* infections (e.g., esophageal or invasive candidiasis) is low. Additionally, there is a lack of randomized controlled trials of routine, primary prophylaxis of candidiasis in children with HIV infection, concern for potentiating resistant *Candida* strains, and the potential for drug-drug interactions between antifungal and antiretroviral (ARV) agents.²¹

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treating Disease

Oropharyngeal Candidiasis

Early, uncomplicated infection can be effectively treated with topical therapy using clotrimazole troches or oral nystatin suspension for 7 to 14 days (**strong, high**).²²⁻²⁵ Debridement can be considered as adjunctive

therapy in OPC. Resistance to clotrimazole can develop because of previous exposure to clotrimazole or to other azole drugs; resistance correlates with refractory mucosal candidiasis.²⁶

Systemic therapy with 1 of the oral azoles (e.g., fluconazole, itraconazole, posaconazole) for 7 to 14 days is recommended for moderate to severe OPC.²²⁻²⁴ Oral fluconazole is more effective than nystatin suspension for initial treatment of OPC in infants, easier to administer to children than the topical therapies, and the recommended treatment when systemic therapy is used (**strong, high**).^{23,27}

For fluconazole-refractory OPC, itraconazole oral solution should be used. Itraconazole solution has efficacy comparable to fluconazole and can be used to treat OPC, although it is less well tolerated than fluconazole (**weak, low**).²⁸ Gastric acid enhances absorption of itraconazole solution, thus it should be taken without food when possible. Itraconazole capsules and oral solution should not be used interchangeably because, at the same dose, drug exposure is greater with the oral solution than with capsules, and absorption of the capsule formulation varies. Ketoconazole tablet absorption also varies, and therefore neither itraconazole capsules nor ketoconazole tablets are recommended for treating OPC if fluconazole or itraconazole solutions are available (**strong, moderate**). Additional choices for fluconazole-refractory OPC include voriconazole or posaconazole, or IV treatment with amphotericin B or an echinocandin (caspofungin, micafungin, anidulafungin), if required.

Esophageal Disease

Systemic therapy is essential for esophageal disease (**strong, high**) and should be initiated empirically in children with HIV infection who have OPC and esophageal symptoms. In most patients, symptoms should resolve within days after the start of effective therapy. Oral fluconazole for 14 to 21 days is highly effective for treatment of *Candida* esophagitis and is considered first line therapy (**strong, high**).^{22,29} IV fluconazole, amphotericin B, or an echinocandin should be used for patients who cannot tolerate oral therapy. For fluconazole-refractory disease, itraconazole solution, posaconazole, voriconazole, amphotericin B, or an echinocandin are alternatives.

Invasive Candidiasis

The treatment of choice for invasive disease in children with HIV infection depends on severity of disease, previous azole exposure, and *Candida* isolate obtained (if known). An echinocandin is recommended for severely ill children with candidiasis because of the fungicidal nature of these agents, as well as the lack of adverse events (**strong, high**). Fluconazole is a reasonable alternative for patients who are less critically ill and who have no recent azole exposure. Voriconazole can be used in situations in which mold coverage is also warranted. For infections with *C. glabrata*, an echinocandin is recommended because of the increasing resistance seen against fluconazole for this species (**strong, moderate**). Despite this recommendation, clinicians should be aware of the increasing frequency of *C. glabrata* echinocandin resistance. For patients already receiving fluconazole or voriconazole who are clinically improving despite *C. glabrata* infection, continuing use of the azole is reasonable. Infection with *C. krusei* should be treated with an echinocandin because of the inherent resistance to fluconazole. For infection with *C. parapsilosis*, fluconazole or amphotericin B is recommended (**strong, moderate**). Previous data suggested a decreased response of *C. parapsilosis* isolates to echinocandins.³⁰ However, recent adult comparative effectiveness data reveal that initial therapy with an echinocandin for *C. parapsilosis* did not result in worse outcomes.³¹ Thus, if a patient is receiving empiric therapy with an echinocandin and showing clinical improvement when culture of *C. parapsilosis* returns, continuing with this therapy is reasonable.

For many of these clinical scenarios, amphotericin B is an effective but less attractive alternative given concerns for therapy-related toxicity (**weak, moderate**). Amphotericin B lipid formulations may be preferable to conventional amphotericin B deoxycholate given their improved side effect profile (see Monitoring and Adverse Events section below), especially in children at high risk of nephrotoxicity due to preexisting renal disease or use of other nephrotoxic drugs (**weak, moderate**). Regardless of the antifungal agent chosen, the recommended duration of therapy for candidemia is 14 days after documented clearance

from the blood along with resolution of neutropenia (if initially present) and resolution of clinical signs and symptoms of candidemia. In children with evidence of deep-seated foci (e.g., endocarditis or osteomyelitis), duration of therapy will be longer and ultimately should be guided by an infectious diseases specialist.

If a child is initiated on an intravenous antifungal agent, such as an echinocandin or an amphotericin B formulation, step-down therapy to an oral agent such as fluconazole when the patient is clinically improved to complete the course can be considered (**strong, moderate**). Species identification is preferred when stepping down to fluconazole because of intrinsic or acquired drug resistance among certain *Candida* spp. (e.g., *C. krusei*, *C. glabrata*).

Finally, in children with HIV infection who have a central venous catheter in place at the time of candidemia onset, the central line should always be removed when feasible (**strong, moderate**).^{3,32} While there has never been a randomized controlled trial performed that proves the benefit of removal of a central venous catheter, there are well-designed observational studies that have reasonably accounted for confounding by indication for line removal (i.e., central lines were removed in the relatively well patients and retained in the critically ill patient) and still show a benefit for line removal. Additionally, Andes et al. performed a patient level systemic review of adult patients with candidemia and found that central line removal provided a protective effect against mortality. Therefore, it is reasonable to conclude that a central venous catheter should be removed when feasible.

Pharmacokinetics and Dosing of Antifungal Agents

Azoles

Fluconazole pharmacokinetics (PK) vary significantly with patient age, and fluconazole is rapidly cleared in children.

Daily fluconazole dosing for invasive candidiasis requires higher doses of fluconazole (12 mg/kg/day) than are used for mucocutaneous disease (6 mg/kg/day), with many experts suggesting a loading dose of fluconazole 25 mg/kg for children.

Because of more rapid clearance in children, fluconazole administered to children at 12 mg/kg/day provides exposure similar to standard 400-mg daily dosing in adults. Dosing of fluconazole for invasive candidiasis in children and adolescents should generally not exceed 600 mg/day.³³

The bioavailability of itraconazole oral solution is lower in children than in adults; therefore, dosing in children should be 2.5 to 5 mg/kg per dose twice daily (**strong, moderate**). This dosing contrasts with the once daily dosing of itraconazole used in adult patients. Administering itraconazole oral solution on an empty stomach improves absorption (in contrast to the capsule formulation, which is best administered under fed conditions), and monitoring itraconazole serum concentrations, like most azole antifungals, is key in management (generally itraconazole trough levels should be >0.5 to 1 µg/mL; trough levels >3 µg/mL may be associated with increased toxicity). In adult patients, itraconazole is recommended to be loaded at 200 mg twice daily for 2 days, followed by itraconazole 200 mg daily starting on the third day.

There is now considerable experience with voriconazole in children, including for treatment of esophageal candidiasis and candidemia.^{2,22,34,35} Usually children are started on voriconazole IV and then switched to oral administration to complete therapy after they are clinically stable. The optimal dose of voriconazole used in children is higher than that used in adults because of differing PK. Voriconazole has been shown to be tolerated to a similar degree regardless of dosage and age; a maintenance daily dosage of 8 mg/kg IV in children aged 2 to 11 years was needed to attain voriconazole plasma levels achieved in adults with a 4 mg/kg IV dosage. Also, the oral bioavailability of voriconazole in children is lower than in adults (approximately 50%), therefore, in children, weight-adjusted dosages are higher for oral therapy than for IV therapy.^{34,35} The recommended voriconazole dosage for children is 9 mg/kg every 12 hours IV loading on day 1, followed by voriconazole 8 mg/kg IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg orally every 12 hours (**strong, moderate**).³⁶ In addition, therapeutic trough voriconazole drug levels

(generally thought to be >1 to 2 µg/mL) should be monitored because of significant interpatient variability in voriconazole PK in children with invasive fungal infection.³⁷ For example, voriconazole clearance depends on allelic polymorphisms of CYP2C19, resulting in poor and extensive metabolizers of voriconazole.^{38,39} It is estimated that 15% to 20% of Asian and 3% to 5% of white and African populations are poor metabolizers of voriconazole, further underscoring the importance of monitoring voriconazole levels to ensure proper dosing.³⁸

There is limited experience with the use of **posaconazole** in children and currently has an oral suspension and extended-release tablet formulation approved for patients 13 years and older, and an IV formulation approved for patients aged ≥18 years. Effective absorption of the oral suspension strongly requires taking the medication with food, ideally a high-fat meal; taking posaconazole on an empty stomach will result in approximately one-fourth of the absorption as in the fed state. The tablet formulation has better absorption given its delayed release in the small intestine, but absorption will still be slightly increased with food. If the patient is unable to take food, the tablet is recommended. There is potential for overdosing if this tablet formulation is dosed inappropriately.⁴⁰ The exact pediatric dosing for posaconazole has not been completely determined and the dose recommended by some experts for treating invasive disease is posaconazole 18 mg/kg/day divided three times daily. The pediatric IV or extended release tablet dosing is completely unknown and under study, but adolescents can likely follow the adult dosing schemes. In adult patients, IV posaconazole is loaded at 300 mg twice daily on the first day, then posaconazole 300 mg once daily starting on the second day. Similarly, in adult patients the extended-release tablet is dosed as posaconazole 300 mg twice daily on the first day, then 300 mg once daily starting on the second day. In adult patients, the maximum amount of posaconazole oral suspension given is 800 mg per day (given its excretion), and that dosage has been given as posaconazole 400 mg twice daily or 200 mg four times a day in severely ill patients because of findings of a marginal increase in exposure with more frequent dosing.

Isavuconazole is a new triazole that was FDA-approved in March 2015 for treatment of invasive aspergillosis and invasive mucormycosis with both oral (capsules only) and IV formulations. Dosing in adult patients is loading with isavuconazole 200 mg (equivalent to isavuconazonium sulfate 372 mg) every 8 hours for 2 days (6 doses), followed by isavuconazole 200 mg once daily for maintenance dosing. No specific pediatric dosing data currently exist for isavuconazole.

Echinocandins

Data from studies using echinocandins (casprofungin, micafungin, and anidulafungin) are now sufficient to recommend these agents as alternatives to fluconazole for esophageal candidiasis, and as first-line therapy for invasive candidiasis (**strong, high**).⁴¹⁻⁵⁵ However, echinocandins are not recommended for treatment of central nervous system *Candida* infections due to concerns that these agents penetrate cerebrospinal fluid poorly.

A PK study of casprofungin in immunocompromised children with HIV infection aged 2 to 17 years demonstrated that 50 mg/m² body surface area/day (70 mg/day maximum) provides exposure comparable to that obtained in adults receiving a standard 50-mg daily regimen.⁴³ Significantly higher doses of casprofungin have been studied in adult patients without any clear added benefit in efficacy, but if the 50 mg/m² dose is tolerated and does not provide adequate clinical response, the daily dose can be increased to 70 mg/m². Dosing for casprofungin in neonates is 25 mg/m²/day.

The recommended dose of micafungin for children aged 2 years to 17 years is 2 to 4 mg/kg daily, but neonates require doses of micafungin 10 mg/kg daily (**strong, moderate**).⁴⁷⁻⁵¹ Micafungin demonstrates dose-proportional PK, and an inverse relationship between age and clearance, suggesting a need for increased dosage in young children.⁵² Clearance of the drug in neonates was more than double that in older children and adults.⁵³ Dosages of micafungin 10 mg/kg/day are recommended in premature neonates, resulting in area-under-the-curve values consistent with an adult dosage of micafungin 100 to 150 mg/day.

One PK study of anidulafungin in 25 neutropenic children without HIV infection aged 2 years to 17 years (including 12 children aged 2 years to 11 years and 13 children aged 12 years to 17 years) showed drug

concentrations with 0.75 mg/kg per dose and 1.5 mg/kg per dose were similar to drug concentrations in adults with 50 mg per dose and 100 mg per dose, respectively.⁵⁴ In a case report of a term 11-day infant with peritoneal candidiasis and failure of (liposomal amphotericin B [L-AmB]) therapy, an IV dose of 1.5 mg/kg/day of anidulafungin was successful in treating the infection.⁵⁵

Polyenes

Conventional amphotericin B (sodium deoxycholate complex) PK in children and adults are very similar. In children who have azotemia or hyperkalemia, or who are receiving high doses of amphotericin B (i.e., ≥ 1 mg/kg), a longer infusion time of 3 to 6 hours is recommended (**weak, moderate**).⁵⁶ Three lipid preparations of amphotericin B approved in the mid-1990s decrease toxicity with no apparent decrease in clinical efficacy. Decisions on which lipid amphotericin B preparation to use should, therefore, largely focus on side effects and costs. Two clinically useful lipid formulations exist: one in which ribbon-like lipid complexes of amphotericin B are created (amphotericin B lipid complex [ABLC]), Abelcet, and one in which amphotericin B is incorporated into true liposomes (L-AmB), AmBisome. The standard dosage of these preparations is 5 mg/kg/day, in contrast to the 1 mg/kg/day of amphotericin B-D. In most studies, the side effects of L-AmB were somewhat less than those of ABLC, but both have significantly fewer side effects than AmB-D. The advantage of the lipid preparations is the ability to safely deliver a greater overall dose of the parent AmB drug. Despite *in vitro* concentration-dependent killing, a clinical trial comparing L-AmB at doses of 3 mg/kg/day and 10 mg/kg/day found no efficacy benefit for the higher dose and only greater toxicity.⁵⁷ Therefore, use of any AmB preparations at very high dosages (i.e., >5 mg/kg/day) is generally not recommended, as it will likely only incur greater toxicity with no real therapeutic advantage. There are reports of using higher dosing in very difficult infections where amphotericin B is the first-line therapy (e.g., mucormycosis), and while experts remain divided on this practice, it is clear that ≥ 5 mg/kg/day of a lipid amphotericin B formulation should be used. Amphotericin B has a long terminal half-life and, coupled with the concentration-dependent killing, the agent is best used as single daily doses. These PK explain the use in some studies of once weekly amphotericin B for antifungal prophylaxis. If the overall amphotericin B exposure needs to be decreased due to toxicity, it is best to increase the dosing interval (e.g., 3 times weekly) but retain the full mg/kg dose for optimal PK.

Combination antifungal therapy

Data in adults are limited on use of combination antifungal therapy for invasive candidal infections; combination amphotericin B and fluconazole resulted in more rapid clearance of *Candida* from the bloodstream but no difference in mortality.²² Flucytosine has been used in combination with amphotericin B in some children with severe invasive candidiasis, particularly in those with central nervous system disease, but it has a narrow therapeutic index. Overall there are insufficient data to support routine use of combination therapy in children with invasive candidiasis (**weak, low**).⁵⁸

Monitoring and Adverse Events, Including IRIS

No adverse effects have been reported with use of oral nystatin for treatment of oral candidiasis, but the drug's bitter taste may contribute to poor adherence.

The azole drugs have relatively low rates of toxicity, but because of their ability to inhibit the cytochrome P450 (CYP450)-dependent hepatic enzymes (ketoconazole has the strongest inhibitory effect) and their metabolism by these enzymes, they can interact substantially with other drugs undergoing hepatic metabolism. These interactions can result in decreased plasma concentration of the azole because of increased metabolism induced by the coadministered drug, or development of unexpected toxicity from the coadministered drug because of increased plasma concentrations secondary to azole-induced alterations in hepatic metabolism. The potential for drug interactions, particularly with ARV drugs such as protease inhibitors, should be carefully evaluated before initiation of therapy (**strong, low**).

The most frequent adverse effects of the azole drugs are gastrointestinal, including nausea and vomiting

(10% to 40% of patients). Skin rash and pruritus can occur with all azoles; rare cases of Stevens-Johnson syndrome and alopecia have been reported with fluconazole therapy. All azole drugs are associated with asymptomatic increases in transaminases (1% to 13% of patients). Hematologic abnormalities have been reported with itraconazole, including thrombocytopenia and leukopenia. Of the azoles, ketoconazole is associated with the highest frequency of side effects. Its use has been associated with endocrinologic abnormalities related to steroid metabolism, including adrenal insufficiency and gynecomastia, hemolytic anemia, and transaminitis. Dose-related, reversible visual changes, such as photophobia and blurry vision, have been reported in approximately 30% of patients receiving voriconazole.⁵⁹ Cardiac arrhythmias and renal abnormalities, including nephritis and acute tubular necrosis, also have been reported with voriconazole use. Hallucinations have also been attributed to voriconazole exposure.⁶⁰ More recently, voriconazole administration has been associated with fluorosis. Voriconazole is a tri-fluorinated agent with up to 16% fluoride and after prolonged exposure can result in excess fluoride accumulation in the recipient. Patients will often present with non-specific bone pain and have periosteal reaction seen on radiographs.⁶¹ Another common reason for discontinuation of voriconazole is phototoxic skin reaction associated with chronic use; these phototoxic skin reactions have been reported to develop into carcinoma.^{62,63}

Amphotericin B deoxycholate undergoes renal excretion as inactive drug. Adverse effects of amphotericin B are primarily nephrotoxicity, defined by substantial azotemia from glomerular damage, and can be accompanied by hypokalemia from tubular damage. Nephrotoxicity is exacerbated by use of concomitant nephrotoxic drugs. Permanent nephrotoxicity is related to cumulative dose. Nephrotoxicity can be ameliorated by hydration before amphotericin B infusion. Infusion-related fevers, chills, nausea, and vomiting occur less frequently in children than in adults. Onset of the febrile reactions occurs usually within 1 to 3 hours after the infusion is started; the reactions typically last for <1 hour and tend to decrease in frequency over time. Pre-treatment with acetaminophen or diphenhydramine may alleviate febrile reactions. Idiosyncratic reactions, such as hypotension, arrhythmias, and allergic reactions, including anaphylaxis, occur less frequently. Hepatic toxicity, thrombophlebitis, anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures) also can occur.

Lipid formulations of amphotericin B cause less acute and chronic toxicity than amphotericin B deoxycholate. In approximately 20% of children, lipid formulations of amphotericin B can cause acute, infusion-related reactions, including chest pain; dyspnea; hypoxia; severe pain in the abdomen, flank, or leg; or flushing and urticaria. Compared with infusion reactions with conventional amphotericin B, most (85%) of the reactions to the lipid formulations occur within the first 5 minutes after infusion and rapidly resolve with temporary interruption of the amphotericin B infusion and administration of IV diphenhydramine. Premedication with diphenhydramine can reduce the incidence of these reactions.

The echinocandins have an excellent safety profile, presumably because the antifungal target (β -1,3-glucan) is lacking in humans. In a retrospective evaluation of 25 immunocompromised children who received caspofungin, the drug was well tolerated, although 3 patients had adverse events potentially related to the drug (hypokalemia in all 3 children, elevated bilirubin in 2 children, and decreased hemoglobin and elevated alanine aminotransferase in 1 child).⁴³ In this study, children weighing <50 kg received caspofungin 0.8 to 1.6 mg/kg body weight daily, and those weighing >50 kg received the adult dosage. In the PK study of 39 children who received caspofungin at 50 mg/m² body surface area/day, five (13%) patients experienced one or more drug-related clinical adverse events, including 1 patient each with fever, diarrhea, phlebitis, proteinuria, and transient extremity rash. One or more drug-related laboratory adverse events were reported in 2 patients, including one patient each with hypokalemia and increased serum aspartate transaminase. None of the drug-related adverse events in this study were considered serious or led to discontinuation of caspofungin.⁴³ In a prospective multicenter trial for primary or salvage treatment of *Candida* and *Aspergillus* infections in 48 children aged 6 months to 17 years, a caspofungin dose of 50 mg/m² per day (maximum: 70 mg/day; after 70 mg/m² on day 1) was generally well tolerated, with drug-related clinical and laboratory adverse events occurring in 26.5% and 34.7% of patients, respectively, similar to rates seen in adults. Drug-related clinical adverse events were typically mild and did not lead to therapy discontinuation. An increased

level of hepatic transaminase, often occurring in the context of other medical conditions or concomitant therapies that may have contributed to elevations in hepatic enzymes, represented the most common drug-related laboratory adverse event. None of the drug-related laboratory adverse events led to therapy interruption or discontinuation.⁴⁵

In a double-blind randomized trial comparing micafungin with L-amB in 48 children aged <16 years with clinical signs of systemic *Candida* infection or culture confirmation of *Candida* infection, a micafungin daily dose of 2 mg/kg of body weight for patients who weighed 40 kg, and 100 mg for patients who weighed >40 kg, was well tolerated. Adverse events were similar for both treatment arms and reflected those experienced by patients with comorbid conditions. These adverse events included sepsis, fever, vomiting, diarrhea, anemia, thrombocytopenia, and hypokalemia. Patients in the micafungin group experienced significantly fewer adverse events leading to treatment discontinuation than those in the amphotericin B group (2/25 [3.8%] vs. 9/54 [16.7%], respectively), suggesting a safety advantage for micafungin in this population. Two patients receiving micafungin experienced serious adverse events, including a worsening of renal failure, a preexisting condition, and a moderate increase in serum creatinine resulting in discontinuation of therapy. Patients rarely experienced clinically meaningful changes in creatinine, aspartate transaminase, alanine transaminase, or bilirubin during treatment. Children aged ≥ 2 years in the micafungin treatment arm experienced a smaller mean peak decrease in the estimated glomerular filtration rate than those in the L-amB arm.⁴⁸

A multicenter, ascending-dosage study of anidulafungin in 25 children with neutropenia, without HIV infection and aged 2 years to 17 years, showed anidulafungin to be well tolerated and observed no drug-related serious adverse events. Fever was observed in one patient with a National Cancer Institute toxicity grade of 3, and facial erythema was observed in another patient, which resolved after the infusion rate was decreased.⁵⁴

Immune reconstitution inflammatory syndrome (IRIS) associated with *Candida* infection has not been described in children with HIV infection. However, evidence suggests that candidiasis (other than *Candida* esophagitis) occurs with increased frequency in adults during the first 2 months after initiation of ART.⁶⁴

Managing Treatment Failure

Oropharyngeal and Esophageal Candidiasis

If OPC initially is treated topically, failure or relapse should be treated with oral fluconazole or itraconazole oral solution (**strong, high**).^{28,65}

Approximately 50% to 60% of patients with fluconazole-refractory OPC and 80% of patients with fluconazole-refractory esophageal candidiasis will respond to itraconazole solution (**weak, moderate**).^{66,67} Posaconazole is a second-generation orally bioavailable triazole that has been effective in adults with HIV infection who have azole-refractory OPC or esophageal candidiasis.⁶⁸ However, experience in children is limited, and an appropriate dosage for children aged <13 years has not been defined; thus data in children are insufficient to recommend its use in children with HIV infection (**weak, low**).^{69,70}

An Amphotericin B dose of 1 mL given orally four times daily of a 100-mg/mL suspension sometimes has been effective in patients with OPC who do not respond to itraconazole solution; however, this product is not available in the United States (**weak, low**).⁶⁷ Low-dose IV amphotericin B (0.3–0.5 mg/kg/day) has been effective in children with refractory OPC or esophageal candidiasis (**strong, moderate**).^{22,67,71,72}

Data on the use of echinocandins to treat azole-refractory OPC or esophageal candidiasis in children with and without HIV infection are limited; however, given their excellent safety profile, the echinocandins⁶⁹ could be considered for treatment of azole-refractory esophageal candidiasis (**weak, moderate**).

Invasive Disease

As noted above, the treatment of choice for invasive disease in children with HIV infection depends on severity of disease, previous azole exposure, and *Candida* isolate and antifungal susceptibility (if known).

An echinocandin is recommended for severely ill children and fluconazole is recommended as a first line alternative for children who are not critically ill and have no recent azole exposure. The role of the echinocandins in invasive candidiasis has not been well studied in children with HIV infection, however there is extensive clinical experience with echinocandins in children. Invasive candidiasis associated with neutropenia in patients undergoing bone marrow transplantation has been treated successfully with this class of antifungals. These agents should be considered as first-line treatment of invasive candidiasis in neutropenic or critically-ill children (**strong, moderate**).

Various amphotericin B formulations exist for management of refractory disease. Although lipid amphotericin B formulations appear to be at least as effective as conventional amphotericin B for treating serious fungal infections,^{73,74} the drugs are considerably more expensive than conventional amphotericin B. However, the lipid formulations have less acute and chronic toxicity. Two lipid formulations are used: amphotericin B lipid complex and liposomal amphotericin B lipid complex.⁷⁵⁻⁷⁷

For invasive candidiasis, amphotericin B lipid complex is administered as 5 mg/kg body weight IV once daily over 2 hours.^{75,76,78} Liposomal amphotericin B is administered IV as 3 to 5 mg/kg body weight once daily over 1 to 2 hours.

Preventing Recurrence

Similar to recommendations regarding primary prophylaxis, secondary prophylaxis of recurrent OPC is also not routinely recommended because treatment of recurrence is typically effective, there are concerns for drug-drug interactions, the potential exists for development of resistance, and prophylaxis can prove costly (**strong, moderate**). Immune reconstitution with ART in immunocompromised children should be a priority (**strong, weak**). However, when recurrences are frequent and severe, secondary prophylaxis may be considered on a case-by-case scenario. Data from studies of adults with HIV infection on ART suggest that suppressive therapy with systemic azoles, either with oral fluconazole (**weak, moderate**) or voriconazole or itraconazole solution (**weak, moderate**), can be effective.^{28,79-81}

Experience with adults with HIV infection suggests that, in patients with initial fluconazole-refractory OPC or esophageal candidiasis that subsequently responded to voriconazole, posaconazole or echinocandins, continuation of the effective drug as secondary prophylaxis until ART produces immune reconstitution can be effective (**weak, low**).

Discontinuing Secondary Prophylaxis

In situations when secondary prophylaxis is instituted, no data exist on which to base a recommendation regarding discontinuation. On the basis of experience in adults with HIV infection with other opportunistic infections, discontinuation of secondary prophylaxis can be considered when a patient's CD4 count or percentage has risen to CDC Immunologic Category 2 or 1 (**weak, low**).⁸²

Recommendations

Treatment

I. What is the preferred antifungal treatment for oropharyngeal candidiasis (OPC) in children with HIV infection?

- Uncomplicated OPC infection can be effectively treated with topical therapy using clotrimazole troches or nystatin suspension for 7 to 14 days (**strong, moderate**).
- Oral fluconazole for 7 to 14 days is recommended for moderate or severe OPC disease (**strong, high**).
- For fluconazole-refractory OPC, itraconazole oral solution is recommended, although itraconazole is less well tolerated than fluconazole (**strong, moderate**).
- Chronic suppressive therapy is usually unnecessary; if it is required, fluconazole 3 times weekly is recommended (**strong, high**).

II. What is the preferred antifungal treatment for esophageal candidiasis in children with HIV infection?

- Systemic therapy is always required for esophageal disease (**strong, moderate**).
- Oral fluconazole is recommended for 14 to 21 days, but amphotericin B or an echinocandin (caspofungin, micafungin, anidulafungin) can be used in patients who cannot tolerate oral therapy (**strong, moderate**).
- For refractory esophageal disease, oral therapy can include itraconazole solution or voriconazole for 14 to 21 days (**strong, low**).
- Suppressive therapy with fluconazole 3 times weekly is recommended for recurrent infection (**strong, moderate**).

III. What is the preferred antifungal treatment for invasive candidiasis in children with HIV infection?

- In moderately severe to severely ill children with invasive candidiasis, an echinocandin is recommended. In less severely ill children who have not had previous azole therapy, fluconazole is recommended (**strong, moderate**).
- Alternatively, an initial course of amphotericin B therapy can be administered for invasive candidiasis with careful transition to fluconazole therapy to complete the treatment course (**strong, moderate**).
- Amphotericin B lipid formulations have a role in children who are intolerant of conventional amphotericin B (deoxycholate) or who are at high risk of nephrotoxicity because of preexisting renal disease or use of other nephrotoxic drugs (**weak, moderate**).
- Children with candidemia should be treated for ≥ 14 days after documented clearance of *Candida* from the last positive blood culture and resolution of neutropenia and of clinical signs and symptoms of candidemia (**strong, low**).
- Central venous catheters should be removed when feasible in children with candidemia (**strong, moderate**).

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Dosing Recommendations for Prevention and Treatment of Candidiasis (page 1 of 3)

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	Not routinely recommended	N/A	N/A
Secondary Prophylaxis	<p>Not routinely recommended but can be considered for frequent severe recurrences.</p> <p><u>Fluconazole:</u></p> <ul style="list-style-type: none"> Fluconazole 3–6 mg/kg body weight daily (maximum 200 mg) by mouth, or itraconazole oral solution, 2.5 mg/kg body weight/dose twice daily 	N/A	<p><u>Secondary Prophylaxis Indicated:</u></p> <ul style="list-style-type: none"> Frequent or severe recurrences <p><u>Criteria for Discontinuing Secondary Prophylaxis:</u></p> <ul style="list-style-type: none"> When CD4 count or percentage has risen to CDC immunologic Category 2 or 1 <p><u>Criteria for Restarting Secondary Prophylaxis:</u></p> <ul style="list-style-type: none"> Frequent severe recurrences
Treatment	<p><u>Oropharyngeal:</u></p> <ul style="list-style-type: none"> Fluconazole 6–12 mg/kg body weight (maximum 400 mg/dose) by mouth once daily Clotrimazole troches, 10-mg troche by mouth 4–5 times daily Nystatin suspension 4–6 mL by mouth 4 times daily, or 1–2, 200,000-unit flavored pastilles by mouth 4–5 times daily <p><u>Treatment Duration:</u></p> <ul style="list-style-type: none"> 7 to 14 days <p><u>Esophageal Disease:</u></p> <ul style="list-style-type: none"> Fluconazole 6–12 mg/kg body weight by mouth once daily (maximum dose: 600 mg) Itraconazole oral solution, 2.5 mg/kg body weight/dose by mouth twice daily <p><u>Treatment Duration:</u></p> <ul style="list-style-type: none"> Minimum of 3 weeks and for at least 2 weeks following the resolution of symptoms 	<p><u>Oropharyngeal (Fluconazole-Refractory):</u></p> <ul style="list-style-type: none"> Itraconazole oral solution 2.5 mg/kg body weight/dose by mouth twice daily (maximum 200–400 mg/day) <p><u>Esophageal Disease:</u></p> <ul style="list-style-type: none"> Amphotericin B (deoxycholate) 0.3–0.7 g/kg body weight IV once daily <p><u>Echinocandins</u></p> <p><u>Anidulafungin:</u></p> <ul style="list-style-type: none"> <i>Aged 2–17 Years:</i> Loading dose of 3 mg/kg body weight/daily and then maintenance at 1.5 mg/kg body weight/dose daily IV <i>Aged ≥18 Years:</i> 200-mg loading dose, then 100 mg/dose daily IV <p><u>Caspofungin:</u></p> <ul style="list-style-type: none"> <i>Infants Aged <3 Months:</i> 25 mg/m² BSA/dose daily IV <i>Aged 3 Months–17 Years:</i> 70 mg/m²/day IV loading dose followed by 50 mg/m²/day IV (maximum 70 mg). Note: Dosing of caspofungin for children should be based on body surface area. <i>Aged ≥18 Years:</i> 70-mg loading dose IV, then 50 mg/dose daily IV 	<p>Itritraconazole oral solution should not be used interchangeably with itraconazole capsules. Itraconazole capsules are generally ineffective for treatment of esophageal disease.</p> <p>Central venous catheters should be removed, when feasible, in children with HIV with fungemia.</p> <p>In uncomplicated catheter-associated <i>C. albicans</i> candidemia, an initial course of amphotericin B followed by fluconazole to complete treatment can be used (use invasive disease dosing).</p> <p>Voriconazole has been used to treat esophageal candidiasis in a small number of immunocompromised children without HIV.</p> <p><u>Voriconazole Dosing in Pediatric Patients:</u></p> <ul style="list-style-type: none"> Voriconazole 9 mg/kg body weight/dose every 12 hours IV loading for day 1, followed by voriconazole 8 mg/kg body weight/dose IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg body weight/dose orally every 12 hours. Children aged ≥12 years and weighing at least 40 kg can use adult dosing (load voriconazole 6 mg/kg body weight/dose every 12 hours IV on day 1, followed by 4 mg/kg body weight/dose every 12 hours IV. Conversion to oral therapy at 200 mg every 12 hours by mouth).

Dosing Recommendations for Prevention and Treatment of Candidiasis (page 2 of 3)

Indication	First Choice	Alternative	Comments/Special Issues
<p>Treatment, continued</p>	<p>Invasive Disease</p> <p><u>Critically ill</u></p> <p><i>Echinocandin Recommended</i></p> <p><u>Anidulafungin:</u></p> <ul style="list-style-type: none"> • <i>Aged 2–17 Years:</i> Load with 3 mg/kg body weight/daily dose IV and then maintenance dose at 1.5 mg/kg body weight once daily • <i>Aged ≥18 Years:</i> 200-mg loading dose, then 100 mg once daily <p><u>Caspofungin:</u></p> <ul style="list-style-type: none"> • <i>Infants Aged <3 Months:</i> 25 mg/m² BSA/dose once daily IV • <i>Aged 3 months–17 years,</i> 70 mg/m² BSA/day loading dose followed by 50 mg/m² once daily (maximum 70 mg). Note: Dosing of caspofungin in children should be based on body surface area. • <i>Aged ≥18 Years:</i> 70-mg loading dose, then 50 mg once daily <p><u>Micafungin:</u></p> <ul style="list-style-type: none"> • Note: In the United States, optimal dosing for infants younger than 4 months is not yet established. Studies indicate linear PK; age and clearance are inversely related (see recommended doses below). 	<p><u>Micafungin:</u></p> <ul style="list-style-type: none"> • Note: In the United States, optimal dosing for infants younger than 4 months is not yet established. Studies indicate linear PK; age and clearance are inversely related (see recommended doses below). • <i>Neonates:</i> Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations. • <i>Infants <15 kg body weight,</i> 5–7 mg/kg body weight/dose daily IV • <i>Children ≤40 kg body weight and aged 2–8 years,</i> 3–4 mg/kg body weight/dose daily IV • <i>Children ≤40 kg body weight and aged 9–17 years,</i> 2–3 mg/kg body weight/dose daily IV • <i>Children >40 kg body weight,</i> 100 mg/dose daily IV <p><u>IV Fluconazole:</u></p> <ul style="list-style-type: none"> • <i>Children:</i> 6–12 mg/kg body weight/dose daily for infants and children of all ages (maximum dose: 600 mg daily). <p><u>Invasive Disease:</u></p> <ul style="list-style-type: none"> • Fluconazole 12 mg/kg body weight IV once daily (maximum 600 mg/day) for minimum 2 weeks after last positive blood culture (if uncomplicated candidemia) • Lipid formulations of amphotericin B, 5 mg/kg body weight IV once daily • Amphotericin B deoxycholate, 1 mg/kg body weight IV once daily 	<p><u>Anidulafungin in Children Aged 2–17 Years:</u></p> <ul style="list-style-type: none"> • Loading dose of 3 mg/kg body weight/once daily followed by 1.5 mg/kg body weight/once daily (100 mg/day maximum). <p><u>Fluconazole Dosing Considerations:</u></p> <ul style="list-style-type: none"> • If a neonate's creatinine level is >1.2 mg/dL for >3 consecutive doses, the dosing interval for fluconazole 12 mg/kg body weight may be prolonged to one dose every 48 hours until the serum creatinine level is <1.2 mg/dL. • <i>Aged ≥18 Years:</i> 400 mg/dose once daily (6 mg/kg body weight once daily).

Dosing Recommendations for Prevention and Treatment of Candidiasis (page 3 of 3)

Indication	First Choice	Alternative	Comments/Special Issues
<p>Treatment, continued</p>	<ul style="list-style-type: none"> • <i>Neonates</i>: Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations. • <i>Infants</i> <15 kg body weight: 5–7 mg/kg/day • <i>Children</i> ≤40 kg body weight and aged 2–8 years: 3–4 mg/kg body weight/dose daily IV • <i>Children</i> ≤40 kg body weight and aged 9–17 years: 2–3 mg/kg body weight/dose daily • <i>Children</i> >40 kg body weight: 100 mg/dose daily IV <p><i>Treatment Duration:</i></p> <ul style="list-style-type: none"> • Based on presence of deep-tissue foci and clinical response; in patients with candidemia, treat until 2 weeks after last positive blood culture. <p><u>Not critically ill</u></p> <p><i>Fluconazole Recommended:</i></p> <ul style="list-style-type: none"> • 12 mg/kg body weight/dose daily IV (maximum dose: 600 mg) for infants and children of all ages • Avoid fluconazole for <i>C. krusei</i> and <i>C. glabrata</i>, avoid echinocandin for <i>C. parapsilosis</i>. <p><i>Treatment Duration:</i></p> <ul style="list-style-type: none"> • Based on presence of deep-tissue foci and clinical response; in patients with candidemia, treat until 2 weeks after last positive blood culture. 		

Key to Abbreviations: BSA = body surface area; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; IV = intravenous; PK = pharmacokinetic