



Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Panel's Recommendations

- Uncomplicated oropharyngeal candidiasis (OPC) infection can be effectively treated with topical therapy using clotrimazole troches or nystatin suspension (**AII**).
- Oral fluconazole is recommended for moderate or severe OPC disease (**AI***).
- For fluconazole-refractory OPC, itraconazole oral solution is recommended, although it is less well tolerated than fluconazole (**AI**).
- If OPC initially is treated topically, failure or relapse should be treated with oral fluconazole or itraconazole oral solution (**AI***).
- Systemic therapy is essential for esophageal disease (**AI***).
- Oral or intravenous fluconazole, amphotericin B, or an echinocandin (caspofungin, micafungin, anidulafungin), administered for 14 to 21 days, is highly effective for treatment of Candida esophagitis (**AI***).
- For fluconazole-refractory esophageal disease, oral therapy can include itraconazole solution or voriconazole (**AIII**).
- Central venous catheters should always be removed when feasible in HIV-infected children with candidemia (**AII**).
- In severely ill children with candidemia, an echinocandin is recommended. In less severely ill children who have not had previous azole therapy, fluconazole is an alternative therapy (**AI***).
- For patients infected with *Candida glabrata* or *Candida krusei*, an echinocandin is recommended (**AII***).
- For patients infected with *Candida parapsilosis*, fluconazole or amphotericin B is recommended (**AII***).
- Alternatively, an initial course of amphotericin B therapy can be administered for invasive candidiasis and then carefully followed by completion of a course of fluconazole therapy (**BIII**).
- Data are insufficient to support routine use of combination antifungal therapy in children with invasive candidiasis (**BIII**).
- The potential for drug interactions, particularly with antiretroviral drugs such as protease inhibitors, should be carefully evaluated before initiation of antifungal therapy (**AIII**).
- Amphotericin B lipid formulations have a role in children who are intolerant of conventional amphotericin B (deoxycholate) or are at high risk of nephrotoxicity because of preexisting renal disease or use of other nephrotoxic drugs (**BII**).
- Children with candidemia should be treated for at least 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 (**AII***).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials *in children*[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

The most common fungal infections in HIV-infected children are caused by *Candida* spp. Localized disease caused by *Candida* is characterized by limited tissue invasion to the skin or mucosa. Examples of localized candidiasis include oropharyngeal and esophageal disease, vulvovaginitis, and diaper dermatitis. Once the organism penetrates the mucosal surface and widespread hematogenous dissemination occurs, invasive candidiasis ensues. This can result in candidemia, meningitis, endocarditis, renal disease, endophthalmitis, and hepatosplenic disease.

Oral thrush and diaper dermatitis occur in 50% to 85% of HIV-infected children. Oropharyngeal candidiasis (OPC) continues to be one of the most frequent opportunistic infections in HIV-infected children during the

combination antiretroviral therapy (cART) era (28% of children), with an incidence rate of 0.93 per 100 child-years.¹ 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).² However, *Candida* esophagitis continues to be seen in children who are not responding to antiretroviral therapy.^{3,4} Children who develop esophageal candidiasis despite cART may be less likely to have typical symptoms (e.g., odynophagia, retrosternal pain) or have concomitant OPC⁵; during the pre-cART era, concomitant OPC occurred in 94% of children with *Candida* esophagitis.³ Risk factors for esophageal candidiasis include low CD4 T lymphocyte (CD4) cell count (<100 cells/mm³), high viral load, and neutropenia (<500 cells/mm³).¹⁻⁴

Disseminated candidiasis is infrequent in HIV-infected children, but *Candida* can disseminate from the esophagus particularly when coinfection with herpes simplex virus (HSV) or cytomegalovirus (CMV) is present.^{3,6} Candidemia occurs in up to 12% of HIV-infected children with chronically indwelling central venous catheters for total parental nutrition or intravenous (IV) antibiotics.^{4,7} *Candida albicans* is the most common cause of mucosal, esophageal, and invasive candidiasis, but approximately 50% of reported cases of *Candida* bloodstream infections in HIV-infected children are caused by non-*albicans* *Candida* spp., including *Candida tropicalis*, *Candida pseudotropicalis*, *Candida parapsilosis*, *Candida glabrata*, *Candida krusei*, and *Candida dubliniensis*. The non-*albicans* *Candida* species are important to recognize because several are resistant to fluconazole and other antifungals. In one study of Cambodian HIV-infected children on cART 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 more than three azole agents.⁸ Species-specific epidemiology also varies widely by geographic location and hospital. Many children who develop candidemia have received systemically absorbed oral antifungal azole compounds (e.g., ketoconazole, fluconazole) for control of oral and esophageal candidiasis, which may predispose to resistant isolates.⁴

Clinical Manifestations

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

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

New-onset fever in an HIV-infected child with advanced disease and a central venous catheter is the most common clinical manifestation of candidemia. Renal candidiasis presents with candiduria and ultrasonographically demonstrated renal parenchymal lesions, often without symptoms related to renal disease.⁴

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 cobblestoning appearance on barium swallow. Findings on endoscopy may range from few, small, white, raised 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 techniques⁴ 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* antigen mannan,^{14,15} (1,3)-beta-D-gulcan assay,^{16,17} and real-time polymerase chain reaction^{18,19} are promising diagnostic alternatives under development for early diagnosis of invasive candidiasis. Although several of these assays are helpful in diagnosing adult patients, none of them have been validated for use in children.

Prevention Recommendations

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals, and no measures are available to reduce exposure to these fungi except reducing exposure to unneeded antibiotic exposure that may predispose to *Candida* colonization.

Preventing First Episode of Disease

Routine primary prophylaxis of candidiasis in HIV-infected infants and children is not indicated, given the low prevalence of serious *Candida* infections (e.g., esophageal, tracheobronchial, disseminated) during the cART era and the availability of effective treatment. Concerns exist about the potential for resistant *Candida* strains, drug interactions between antifungal and antiretroviral (ARV) agents, and lack of randomized controlled trials in children.²⁰

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 (**BII**).²¹⁻²⁴ Debridement can be considered as adjunctive therapy in OPC. Resistance to clotrimazole can develop as a consequence of previous exposure to clotrimazole itself or to other azole drugs; resistance correlates with refractory mucosal candidiasis.²⁵

Systemic therapy with 1 of the oral azoles (e.g., fluconazole, itraconazole) for 7 to 14 days is recommended for moderate to severe OPC.²¹⁻²³ 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 if systemic therapy is used (**AI***).^{22,26}

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 (**AI**).²⁷ Gastric acid enhances absorption of itraconazole solution; itraconazole solution 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 absorption also varies, and therefore neither itraconazole capsules nor ketoconazole are recommended for treating OPC if fluconazole or itraconazole solutions are available (**BII***). Additional choices for fluconazole-refractory OPC include voriconazole or posaconazole or IV treatment with amphotericin B or an echinocandin (caspofungin, micafungin, anidulafungin) if required. Chronic suppressive therapy is usually unnecessary for HIV-infected patients (**AI***).

Esophageal Disease

Systemic therapy is essential for esophageal disease (**AI***) and should be initiated empirically in HIV-infected children 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 recommended highly effective for treatment of *Candida* esophagitis (**AI***).^{21,28} IV fluconazole, amphotericin B, or an echinocandin should be used for patients who cannot tolerate oral therapy. For fluconazole-refractory disease, itraconazole solution, voriconazole, amphotericin B, or an echinocandin are alternatives. Suppressing therapy with fluconazole three times weekly is recommended for recurrent infections.

Invasive Disease

Central venous catheters should always be removed when feasible in HIV-infected children with candidemia (**AI**).^{4,29} Among children with persistent candidemia despite appropriate therapy, investigation for a deep tissue focus of infection, such as with echocardiogram, renal or abdominal ultrasound, should be conducted. The treatment of choice for invasive disease in HIV-infected children depends on severity of disease, previous azole exposure, and *Candida* isolate obtained (if known). An echinocandin is recommended for most severely ill children with candidiasis because of the fungicidal nature of these agents as well as the lack of adverse events (**AI***). Fluconazole is a reasonable alternative for patients who are less critically ill and who have no recent fluconazole 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 (**AII**). However, for patients already receiving fluconazole or voriconazole who are clinically improving despite *C. glabrata* infection, continuing use of the azole is reasonable. In addition, infection with *C. krusei* should be treated with an echinocandin because of the inherent resistance to fluconazole. Amphotericin B is an effective but less attractive alternative (**BII**). Amphotericin B lipid formulations have a role in children who are intolerant of conventional amphotericin B (deoxycholate), have disseminated candidal infection that is refractory to conventional amphotericin B, or are at high risk of nephrotoxicity because of preexisting renal disease or use of other nephrotoxic drugs (**BII**). For infection with *C. parapsilosis*, fluconazole or amphotericin B is recommended (**AII**) because of data showing a decreased response from this species to the echinocandins.³⁰ However, 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. Recommended duration of therapy for candidemia is 14 days after documented clearance from the blood and resolution of neutropenia and of clinical signs and symptoms of candidemia.

Conventional amphotericin B (sodium deoxycholate complex) pharmacokinetics (PK) in children are very similar to adults. In children who have azotemia or hyperkalemia or who are receiving high doses (≥ 1 mg/kg), a longer infusion time of 3 to 6 hours is recommended (**BIII**).³¹ In children with life-threatening disease, the target daily dose of amphotericin B should be administered from the beginning of therapy (**BIII**). Flucytosine has been used in combination with amphotericin B in some children with severe invasive candidiasis, particularly in those with central nervous system disease (**CIII**), but it has a narrow therapeutic index and should no longer be used for this purpose.

Fluconazole PK vary significantly with age, and fluconazole is rapidly cleared in children. Daily fluconazole dose needs to be 6 to 12 mg/kg daily for children, and treatment of invasive candidiasis requires higher doses of fluconazole than are used for mucocutaneous disease. Alternatively, an initial course of amphotericin B can be administered and then carefully followed by completion of a course of fluconazole therapy (**BIII**). Species identification is necessary when using fluconazole because of intrinsic drug resistance among certain *Candida* spp. (e.g., *C. krusei*, *C. glabrata*). 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.³²

Itraconazole oral solution provides levels lower than those seen in adults; therefore, dosing should be 2.5 mg/kg per dose twice daily. **(BII*)**.

Experience with voriconazole in children is growing, both in dosing and efficacy, including esophageal candidiasis or candidemia.^{3,21,33,34} Usually children are started on voriconazole IV and then switched to oral administration to complete therapy after stabilization. The optimal pediatric dose of voriconazole is higher than used in adults due to differing PK. Voriconazole has been shown to be tolerated to a similar degree regardless of dosage and age; a dosage approaching 8 mg/kg 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 compared to adults is lower, therefore there is a need for higher weight-adjusted oral dosages than dosages used for IV therapy.^{33,34} The recommended voriconazole dosage for children is 9 mg/kg every 12 hours IV loading on day 1, followed by 8 mg/kg IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg orally every 12 hours **(BII)**.³⁵ In addition, therapeutic voriconazole drug levels should be monitored because of significant interpatient variation in PK of voriconazole in children with invasive fungal infection.³⁶ For example, voriconazole clearance depends on allelic polymorphisms of CYP2C19, resulting in poor and extensive metabolizers of voriconazole.^{37,38} For example, it is estimated that 15% to 20% of Asian compared with 3% to 5% of Caucasian and African populations are poor metabolizers, further underscoring the importance of monitoring voriconazole levels to ensure proper dosing.³⁷

Data from studies using echinocandins including caspofungin, micafungin, and anidulafungin are now sufficient to recommend these agents as alternatives to fluconazole for esophageal candidiasis and as first-line therapy for disseminated candidiasis **(AII)**.³⁹⁻⁵³ Caspofungin was effective in treating candidemia, renal candidiasis, and endocardial infection in 10 infants, including 1 term and 9 premature infant(s) who were unresponsive to or intolerant of deoxycholate amphotericin B.⁴⁰ A PK study of caspofungin in immunocompromised HIV-uninfected children aged 2 to 17 years demonstrated that 50 mg/m² body surface area/day (70 mg/day maximum) provides comparable exposure to that obtained in adults receiving a standard 50-mg daily regimen.⁴¹ A retrospective report in which caspofungin was administered to 20 children aged ≤16 years who had invasive fungal infections (seven had invasive candidiasis) but not HIV infection, found the drug to be efficacious and well tolerated.⁴² In a prospective open-label study of children aged 6 months to 17 years, primary or salvage treatment with caspofungin was well tolerated and successful in 81% of *Candida* infections, including 30 of 37 patients with invasive candidiasis, and 1 of 1 patient with esophageal candidiasis.⁴³ The first pediatric double-blind, randomized controlled trial of empiric antifungal therapy comparing liposomal amphotericin B with caspofungin in children aged 2 to 12 years with cancer, neutropenia, and persistent fever, found comparable efficacy between the 2 treatment arms.⁴⁴

Micafungin has been studied in children treated with 2 to 4 mg/kg daily, but neonates require doses as high as 10 to 12 mg/kg daily **(AII)**.⁴⁵⁻⁴⁹ Micafungin demonstrates dose-proportional PK and an inverse relationship between age and clearance, suggesting a need for increased dosage in young children.⁵⁰ Clearance of the drug in neonates was more than double that in older children and adults.⁵¹ Dosages of 10 to 15 mg/kg/day have been studied in premature neonates, resulting in area-under-the-curve values consistent with an adult dosage of 100 to 150 mg/day. In a clinical trial comparing micafungin versus liposomal amphotericin B(L-AmB) using an intent-to-treat analysis of children and adults with candidiasis/candidemia and with or without cancer, 42 children with or without neutropenia (13 with malignancies/29 without malignancies) received 2 mg/kg/day of micafungin and 3 mg/kg/day of L-AmB. Micafungin was as effective as L-AmB in treating candidiasis/candidemia and well tolerated in these patients.⁴⁹

One PK study of anidulafungin in 25 HIV-uninfected neutropenic children aged 2 to 17 years, including 12 aged 2 to 11 years and 13 aged 12 to 17 years, showed drug concentrations at 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.⁵² In a case report of a term 11-day infant with peritoneal candidiasis and failure of L-AmB therapy, an IV dose of 1.5 mg/kg/day of anidulafungin was successful in treating the infection.⁵³

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.²¹ Data are insufficient to support routine use of combination therapy in children with invasive candidiasis (**BIII**).⁵⁴

Monitoring and Adverse Events, Including IRIS

No adverse effects have been reported with use of oral nystatin for treatment of oral candidiasis, but 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 co-administered drug or development of unexpected toxicity from the co-administered 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 (**AIII**).

The most frequent adverse effects of the azole drugs are gastrointestinal, including nausea and vomiting (10%–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 drugs are associated with asymptomatic increases in transaminases (1%–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.⁵⁵ Cardiac arrhythmias and renal abnormalities including nephritis and acute tubular necrosis also have been reported with voriconazole use.

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 occurs usually within 1 to 3 hours after the infusion is started, typical duration is <1 hour, and the febrile reactions 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 have 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. 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, and decreased hemoglobin and elevated alanine aminotransferase in 1).⁴¹ In this study, children weighing <50 kg received 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, 5 (13%) patients experienced one or more drug-related clinical adverse events, including 1 patient each with fever, diarrhea, phlebitis, proteinuria, and transient extremity rash. Two patients reported one or more drug-related laboratory adverse events, 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.⁴¹ 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.⁴³

In a double-blind randomized trial comparing micafungin with liposomal amphotericin B (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 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%] versus 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 creatine 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.⁴⁶

A multicenter, ascending-dosage study of anidulafungin in 25 HIV-uninfected neutropenic children aged 2 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 slowing the infusion rate.⁵²

Immune reconstitution inflammatory response syndrome associated with *Candida* infection has not been described in HIV-infected children. However, evidence suggests that candidiasis (other than *Candida* esophagitis) occurs with increased frequency in adults during the first 2 months after initiation of cART.⁵⁶

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 (**AI***).^{27,57}

Approximately 50% to 60% of patients with fluconazole-refractory OPC and 80% of patients with fluconazole-refractory esophageal candidiasis will respond to itraconazole solution (**AII***).^{58,59} Posaconazole is a second-generation orally bioavailable triazole that has been effective in HIV-infected adults with azole-refractory OPC or esophageal candidiasis.⁶⁰ However, experience in children is limited, and an appropriate pediatric dosage has not been defined; thus data in children are insufficient to recommend its use in HIV-infected children (**CIII**).^{61,62}

Amphotericin B (oral suspension at 1 mL 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 (**CIII**).⁵⁹ Low-dose IV amphotericin B (0.3–0.5 mg/kg/day) has been effective in children with refractory OPC or esophageal candidiasis (**BII**).^{21,59,63,64}

Experience is limited with use of echinocandins in treatment of azole-refractory OPC or esophageal candidiasis in children (HIV-infected or -uninfected); however, given their excellent safety profile, the echinocandins⁶¹ could be considered for treatment of azole-refractory esophageal candidiasis (**BIII**).

Invasive Disease

Although lipid formulations appear to be at least as effective as conventional amphotericin B for treating serious fungal infections,^{65,66} 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. Experience with these preparations in children is limited.⁶⁷⁻⁶⁹

For invasive candidiasis, amphotericin B lipid complex is administered as 5 mg/kg body weight IV once daily over 2 hours.^{67,68,70} Liposomal amphotericin B is administered IV as 3 to 5 mg/kg body weight once daily over 1 to 2 hours. The role of the echinocandins in invasive candidiasis has not been well studied in HIV-infected children. However, 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 in treatment of invasive candidiasis but reserved as alternative, second-line therapy to currently available treatment modalities (**CIII**).

Preventing Recurrence

Secondary prophylaxis of recurrent OPC usually is not recommended because treatment of recurrence is typically effective, potential exists for development of resistance and drug interactions, and additional rounds of prophylaxis are costly (**BIII**). Immune reconstitution with cART in immunocompromised children should be a priority (**AIII**). However, if recurrences are severe, data from studies of HIV-infected adults with advanced disease on cART suggest that suppressive therapy with systemic azoles, either with oral fluconazole (**BII***) or voriconazole or itraconazole solution (**BII**), can be considered.^{27,71-73} Potential azole resistance should be considered when long-term prophylaxis with azoles is used.

Experience with HIV-infected adults suggests that, in children with fluconazole-refractory OPC or esophageal candidiasis who responded to voriconazole or posaconazole therapy or to echinocandins, continuing the effective drug as secondary prophylaxis can be considered because of the high relapse rate until cART produces immune reconstitution (**BIII**).

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 with HIV-infected adults 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 (**CIII**).⁷⁴

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

Indication	Preventive Regimen		
	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> <ul style="list-style-type: none"> Fluconazole, 3–6 mg/kg body weight daily (maximum 200 mg), 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 (max 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-U flavored pastilles by mouth 4–5 times daily <p><i>Treatment Duration:</i></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><i>Treatment Duration:</i></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> <ul style="list-style-type: none"> Anidulafungin <ul style="list-style-type: none"> Aged 2–17 years, loading dose of 3 mg/kg body weight/daily and then maintenance at 1.5 mg/kg body weight/dose daily IV Caspofungin <ul style="list-style-type: none"> Infants aged <3 months, 25 mg/m² body surface area/dose daily IV Aged 3 months–17 years, 70 mg/m²/day IV loading dose followed by 50 mg/m²/day IV (maximum 70 mg). Note: dosing based on surface area is recommended for children for caspofungin. 	<p>Itraconazole 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 HIV-infected children 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 HIV-uninfected immunocompromised children.</p> <p><u>Voriconazole Dosing in Pediatric Patients:</u></p> <ul style="list-style-type: none"> 9 mg/kg body weight/dose every 12 hours IV loading for day 1, followed by 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 6 mg/

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

Indication	Preventive regimen		
	First Choice	Alternative	Comments/Special Issues
Treatment, continued	<p><u>Invasive Disease:</u> <i>Critically Ill</i> <u>Echinocandin Recommended:</u></p> <ul style="list-style-type: none"> • Anidulafungin <ul style="list-style-type: none"> • Aged 2–17 years, Load with 3 mg/kg body weight/daily dose and then maintenance at 1.5 mg/kg body weight once daily • Aged ≥18 years, 200 mg loading dose, then 100 mg once daily • Caspofungin <ul style="list-style-type: none"> • Infants aged <3 months, 25 mg/m² body surface area/dose once daily IV • Aged 3 months–17 years, 70 mg/m² body surface area/day loading dose followed by 50 mg/m² once daily (maximum, 70 mg) (note: dosing based on surface area is recommended for children for caspofungin); • Aged ≥18 years, 70-mg loading dose, then 50 mg once daily; 	<ul style="list-style-type: none"> • Aged ≥18 years, 70-mg loading dose IV, then 50 mg/dose daily IV • Micafungin <p>Note: In the United States, optimal dosing for children is not yet established, and there is no pediatric indication yet. Studies indicate linear PK; age and clearance are inversely related—see recommended doses below.</p> <ul style="list-style-type: none"> • Neonates, up to 10–12 mg/kg bodyweight/dose daily IV may be required to achieve therapeutic concentrations. • Infants, <15 kg body weight, 5–7 mg/kg body weight/dose daily IV • Children ≤40 kg body weight and aged 2–8 years, 3–4 mg/kg body weight/dose daily IV • Children ≤40 kg body weight and aged 9–17 years, 2–3 mg/kg body weight/dose daily IV • Children >40 kg body weight, 100 mg/dose daily IV • IV fluconazole <ul style="list-style-type: none"> • Children, 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>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.)</p> <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>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</p> <p><u>Treatment Duration:</u></p> <ul style="list-style-type: none"> • Patients with esophageal candidiasis should be treated for a minimum of 3 weeks and for at least 2 weeks following resolution of symptoms. <ul style="list-style-type: none"> • Aged ≥18 years, 400 mg/dose once daily (6 mg/kg body weight once daily). <p><u>Treatment Duration:</u></p> <ul style="list-style-type: none"> • Patients with esophageal candidiasis should be treated for a minimum of 3 weeks and for at least 2 weeks following resolution of symptoms.

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

Indication	Preventive regimen		
	First Choice	Alternative	Comments/Special Issues
Treatment, continued	<ul style="list-style-type: none"> • Micafungin <p>Note: In the United States, optimal dosing for children is not yet established, and there is no pediatric indication yet. Studies indicate linear PK; age and clearance are inversely related—see recommended doses below.</p> <ul style="list-style-type: none"> • Neonates, up to 10–12 mg/kg bodyweight/dose daily IV may be required to achieve therapeutic concentrations. • Infants <15 kg body weight, 5–7 mg/kg/day • Children ≤40 kg body weight and aged 2–8 years, 3–4 mg/kg body weight/dose daily IV • Children ≤40 kg body weight and aged 9–17 years, 2–3 mg/kg body weight/dose daily • Children >40 kg body weight, 100 mg/dose daily IV <p><i>Not Critically Ill</i></p> <p><u>Fluconazole Recommended:</u></p> <ul style="list-style-type: none"> • 12 mg/kg body weight/dose daily IV (max 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><u>Treatment Duration:</u></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: CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; IV = intravenous; PK = pharmacokinetic