

Candida Infections

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Panel's Recommendations
Oropharyngeal Candidiasis <ul style="list-style-type: none">• Topical therapy using clotrimazole troches or nystatin suspension for 7–14 days is recommended to treat uncomplicated oropharyngeal candidiasis (OPC) (AI*).• Oral fluconazole for 7–14 days is recommended for moderate to severe OPC disease (AI).<ul style="list-style-type: none">◦ For fluconazole-refractory OPC, itraconazole oral solution is recommended, although itraconazole is less well tolerated than fluconazole (AI*). Posaconazole is an alternative, particularly for fluconazole- and itraconazole-refractory OPC (AI*).• Chronic suppressive therapy for OPC is not routinely recommended (AII*), as treatment of recurrence is typically effective and potential risks include toxicities, resistance, drug–drug interactions, adherence challenges, and costs; the primary modality of preventing recurrences is immune reconstitution via antiretroviral therapy. If required on a case-by-case basis (e.g., due to frequent or severe recurrences despite antiretroviral therapy), fluconazole three times weekly is preferred (AI*).
Esophageal Candidiasis <ul style="list-style-type: none">• Systemic therapy is always required for esophageal disease (AI*).• Oral fluconazole for 14–21 days is recommended as first-line therapy, but intravenous fluconazole, an echinocandin (caspofungin, micafungin, anidulafungin), or amphotericin B^a can be used in those who cannot tolerate oral therapy (AI*).• For refractory esophageal disease, oral therapy should include itraconazole solution or voriconazole for 14–21 days (AI*).• If required, suppressive therapy with fluconazole three times weekly is recommended for recurrent infection, pending immune reconstitution on antiretroviral therapy (AII*).
Invasive Candidiasis <ul style="list-style-type: none">• 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 (AI*).• Alternatively, an initial course of amphotericin B^a therapy can be administered for invasive candidiasis (BI*) with careful transition to fluconazole therapy to complete the treatment course (BII*).• For central nervous system (CNS) candidiasis, initial treatment should use amphotericin B^b (AIII).• Children with candidemia should be treated for ≥14 days after documented clearance of <i>Candida</i> from the last positive blood culture, resolution of neutropenia, and resolution of clinical signs and symptoms of candidemia (AIII).• Central venous catheters should be removed when feasible in children with candidemia (AII*). For CNS candidiasis, infected CNS devices should be removed if possible (AIII).
Antiretroviral Therapy <ul style="list-style-type: none">• Antiretroviral therapy should be initiated in all infants and children with HIV, particularly those with candidiasis (AI for children aged <3 months, AI* for older children).

^a Amphotericin B lipid formulations are generally preferred in children based on non-inferior efficacy and lower toxicity compared to conventional amphotericin B (deoxycholate), particularly in children who are at high risk of nephrotoxicity because of preexisting renal disease or use of other nephrotoxic drugs (AI). Amphotericin B deoxycholate is acceptable if a lipid formulation is unavailable or infeasible (BI*).

^b For initial treatment in neonates, amphotericin B deoxycholate or liposomal amphotericin B (caution with suspected urinary tract involvement) is recommended (BIII). Beyond the neonatal/infant period, liposomal amphotericin B is recommended with or without flucytosine (AIII).

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 postpubertal adolescents

Epidemiology

The most common fungal infections in children with HIV are caused by *Candida* spp. Antifungal-resistant *Candida* is a public health threat that was exacerbated by the COVID-19 pandemic. The Centers for Disease Control and Prevention (CDC)'s 2022 special report on COVID-19's U.S. impact on antimicrobial resistance identified that previously decreasing U.S. trends in cases of antifungal-resistant *Candida* had reversed, with a 1-year 26% increase in hospital-onset antifungal-resistant *Candida* in 2020 (28,100 drug-resistant cases total, 12,900 hospital-onset cases), while antifungal-resistant *C. auris* continued to increase in cases, with a 1-year 60% increase to 754 U.S. cases.¹ In 2022, the World Health Organization (WHO) released its first fungal priority pathogens list as the first global effort to systematically prioritize fungal pathogens concerning their unmet research and development needs and their perceived public health importance. *C. auris* and *C. albicans* were included in the critical priority group, and *C. glabrata* (*Nakaseomyces glabrata*), *C. tropicalis*, and *C. parapsilosis* were included in the high priority group.² These developments have highlighted the importance of diagnosing, preventing, and treating pediatric candidiasis.

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. Oropharyngeal candidiasis (OPC) continues to be one of the most frequent opportunistic infections in children with HIV in the United States during the antiretroviral therapy (ART) era (in the pre-ART era, 28% of children with HIV had a history of OPC), with an incidence rate of 0.93 per 100 child-years.³ In high

HIV-burden regions from 2004 through 2016, OPC remained the most common incident non-tuberculous WHO stage 3 (WHO-3) event in children, constituting 46% of such events in the pre-ART era (7.0 WHO-3 events per 100 child-years) and 31% of such events in the ART era (2.1 WHO-3 events per 100 child-years).⁴ In children with HIV in the United States, the incidence of esophageal or tracheobronchial candidiasis decreased from 1.2 per 100 child-years before the pre-ART era to 0.08 per 100 child-years during the ART era (2001–2004).³ Based on data from the CDC’s National HIV Surveillance System through 2018, among children with HIV and born between 1997 to 2016, the numbers and rates of all opportunistic infections (OIs) decreased over time, but pulmonary or esophageal candidiasis remained the second-most common OI among children (15.4% of OIs) in the more recent cohort (born 2007–2016).⁵ *Candida* esophagitis continues to be seen in children who are not responding to ART.^{6,7} Children who develop esophageal candidiasis despite ART may be less likely to have typical symptoms (e.g., odynophagia, retrosternal pain) or have concomitant OPC⁸; during the pre-ART era, concomitant OPC occurred in 94% of children with *Candida* esophagitis.⁶ 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).^{3,6,7,9}

Invasive Candidiasis

Invasive candidiasis is less frequent than localized disease in children with HIV. However, *Candida* can disseminate from the esophagus, particularly during coinfection with herpes simplex virus (HSV) or cytomegalovirus (CMV).^{6,10} Candidemia occurs in up to 12% of children with HIV who have chronic indwelling central venous catheters placed for administration of total parenteral nutrition or intravenous (IV) antibiotics.^{7,11} 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 most bloodstream infections.^{12,13} 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 resistance to both fluconazole and voriconazole. An increasing number of *C. glabrata* isolates are also resistant to echinocandins. *C. lusitaniae* frequently have or acquire resistance to amphotericin B.^{14–16} 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.⁷ In one study of Cambodian children with HIV 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.¹⁷ However, clinicians should be aware of local resistance trends as the epidemiology of species-specific resistance may vary widely by geographic location and hospital.

Although uncommon in children in the United States, *C. auris* is an important emerging fungal pathogen because it is often multidrug resistant, spreads easily in health care facilities, and can cause severe, invasive infections with high mortality.^{18–20} In cases reported to U.S. state and local health departments and the CDC from 2016 to 2021, *C. auris* clinical cases and screening cases have increased in frequency and geographical distribution.²¹ In 2020, azole resistance was high (86% of isolates) and amphotericin B resistance was common (26% of isolates), although susceptibility patterns varied by U.S. geographical region in association with local circulation of specific clades. Echinocandin resistance across all clades and geographical regions has been low (<5%), but echinocandin-resistant and pan-resistant isolates have been reported and increased in 2021.^{21–23}

Almost all reported U.S. *C. auris* cases have been in adults, but a cluster of pediatric *C. auris* was identified in two health care facilities where procedural areas were shared between children and adults. Although no direct transmission link was identified, the cases highlight the potential for *C. auris* spread from adults to children.^{24,25}

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 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.⁷

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 techniques⁷ or automated broth-based systems.²⁶ When candidemia is present, particularly among immunocompromised children or those with persistent candidemia, further investigation for dissemination should strongly be considered (**AII**). Additional diagnostics that should be considered in this clinical scenario include, but are not limited to, fundoscopic exam for intraocular infection, a lumbar puncture for central nervous system (CNS) disease; an echocardiogram for endocarditis; an abdominal ultrasound or computed tomography to evaluate the kidney, liver and spleen; and magnetic resonance imaging for osteomyelitis (if suspected by symptoms) or bone scans (if suspecting multifocal disease). In a multicenter cohort study of 662 pediatric candidemia episodes, use of adjunctive diagnostic studies varied across sites.²⁷ Longer durations of candidemia, immunocompromised status (not specific to HIV), and intensive care at candidemia onset were associated with use of adjunctive diagnostic studies. Positive findings were reported in 3% of ophthalmic exams, 6% of abdominal imaging, 3% of echocardiograms, 6% of neuroimaging, and 4% of lumbar punctures. Pediatric participants with

immunocompromise or persistent or relapsed candidemia more commonly had positive findings. Notably, ophthalmic exams had positive findings in only 1% of non-immunocompromised participants,²⁷ which was consistent with a systemic review of adults and pediatric patients with candidemia.²⁸ Similar risk factors for dissemination, including prolonged candidemia (especially with a central venous catheter), prematurity, and immunocompromised status, were identified in single-center studies previously.²⁹⁻³² The utility of universal ophthalmic examinations in settings of candidemia has been subject to discrepant opinions by professional societies across disciplines.^{28,33,34} Data are limited regarding the optimal indications and visual outcomes following ophthalmologic screening in children with candidemia. However, the available data suggest that ophthalmic screening may be most useful in children with prolonged candidemia, immunocompromised status (including prematurity), more severe illness or other evidence of dissemination, or those unable to verbalize symptoms or indicate signs of ocular disease. As most neonates, infants, and children fall into the last category, a universal ophthalmic screening approach remains a reasonable option. Management of these populations should involve collaboration among primary providers, infectious diseases physicians, and ophthalmologists.

Diagnostic techniques such as the *Candida* mannan antigen and anti-mannan antibody,^{35,36} (1,3)-beta-D-glucan assay,^{37,38} T2 biosystems for *Candida*,³⁹ real-time polymerase chain reaction,^{40,41} and next-generation sequencing for microbial cell-free DNA⁴²⁻⁴⁴ are diagnostic alternatives for invasive candidiasis. As newer diagnostic modalities become more accessible, a pediatric infectious diseases specialist should be involved in decisions about the use of certain novel diagnostics (e.g., microbial cell-free DNA), which may have high costs,⁴⁵ unclear roles in diagnostic algorithms, and undetermined applicability to specific pediatric populations with varying immunocompromising disease states. Although several of these assays are helpful in diagnosing invasive candidiasis in adults, only a few have been studied in children, and performance characteristics in adults have not necessarily translated into pediatric populations. A multicenter prospective observational cohort study of 500 children without HIV aged >120 days to <18 years at 22 centers in three countries evaluated the performance characteristics of the T2Candida, Fungitell (1→3)-β-D-glucan, Platelia *Candida* Antigen Plus, and Platelia *Candida* Antibody Plus assays for detection of candidemia. This study used a reference standard of proven or probable invasive candidiasis as defined by the 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria for invasive fungal disease made on or between Day 0 through Day 14 of study.⁴⁶ Of these biomarkers, T2Candida had the highest sensitivity (79.2%) and specificity (97.1%) and was the only biomarker with sufficient performance characteristics to be considered as an individual tool for diagnosis of candidemia in at-risk children and adolescents. However, combining T2Candida with the Platelia *Candida* Antigen assay could provide additional optimization according to the specific goals of the clinical situation.

Prevention Recommendations

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals; thus, complete prevention of exposure may not be feasible. However, some measures may decrease *Candida* colonization or overgrowth, such as avoiding unnecessary antibiotics (especially broad-spectrum antimicrobial agents) or minimizing use of systemic corticosteroids, if able. Maintaining good oral health, hygienic care for central venous or peritoneal dialysis catheters, and management of predisposing comorbid conditions, such as diabetes mellitus, should also be beneficial.⁴⁷

Preventing First Episode of Disease

Routine primary prophylaxis of candidiasis in infants and children with HIV 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, concern for potentiating resistant *Candida* strains, and the potential for drug–drug interactions between antifungal and antiretroviral (ARV) agents.⁴⁸ If a child with HIV has a comorbid condition (e.g., prolonged, severe neutropenia), then primary prophylaxis should be guided by recommendations for management of children with the comorbid condition.

Discontinuing Primary Prophylaxis

Not applicable.

Treatment Recommendations

Treating Disease

Oropharyngeal Candidiasis

For early, uncomplicated infection, topical therapy using clotrimazole troches or oral nystatin suspension for 7 to 14 days is recommended (**AI***).⁴⁹⁻⁵⁷ 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.⁵⁸

Systemic therapy with one of the oral azoles (e.g., fluconazole, itraconazole, posaconazole) for 7 to 14 days is recommended for moderate to severe OPC.^{34,49-51} 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 (**AI**).^{50,53}

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***).^{59,60} 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. Therefore, itraconazole capsules are **not recommended** for treating OPC if fluconazole or itraconazole solutions are available (**AII**), although itraconazole tablets may retain a role when administration of itraconazole solution is impractical (e.g., volume, intolerance considerations). Posaconazole is a second-generation orally bioavailable triazole. Randomized clinical trial data of adults with HIV allocated to either posaconazole or fluconazole for primary treatment of OPC demonstrated that posaconazole was as effective as fluconazole in producing a successful clinical outcome (91.7% vs. 92.5%, 95% confidence interval [CI], –6.6 to 5.0), but posaconazole was more effective in clinical success after treatment was stopped, with greater mycological success at Day 42 (40.6% vs. 26.4%) and fewer recipients with clinical relapse (31.5% vs. 38.2%).⁶¹ Posaconazole has also been effective in adolescents and adults with HIV who have fluconazole- and itraconazole-refractory OPC or esophageal candidiasis.^{62,63} Although experience in children is still limited, newer posaconazole formulations provide more consistent absorption and drug exposures or the option of IV therapy.^{63,64} Thus,

posaconazole is recommended as an alternative for OPC in children, particularly for fluconazole- and itraconazole-refractory OPC (**AI***). Additional choices for fluconazole-refractory OPC include voriconazole, an echinocandin (caspofungin, micafungin, anidulafungin), or amphotericin B, if required.

Esophageal Disease

Systemic therapy is essential for esophageal disease (**AI***) and should be initiated empirically in children with HIV who have OPC and esophageal symptoms. In most children and adolescents, 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 (**AI***).^{34,65} For individuals who cannot tolerate oral therapy, IV fluconazole, an echinocandin, or amphotericin B should be used (**AI***).

For fluconazole-refractory disease, oral therapy can include itraconazole solution or voriconazole for 14 to 21 days (**AI***).^{65,66} Approximately 50% to 60% of individuals with fluconazole-refractory OPC and 80% of individuals with fluconazole-refractory esophageal candidiasis will respond to itraconazole solution.^{67,68} Voriconazole has supporting randomized control trial data in immunocompromised adults (most with HIV) demonstrating that voriconazole is at least as effective as fluconazole in treatment of biopsy-proven esophageal candidiasis (98.3% vs. 95.1%; 95% CI, −1.0 to 7.5), but adverse events (AEs) associated with voriconazole were more frequent and interindividual variability in pharmacokinetics is high.⁶⁶ In a study of voriconazole in children aged 2 years to <18 years, 7 of 10 children with confirmed esophageal candidiasis had successful global response, although two successes subsequently experienced recurrence.⁶⁹

Recommended alternatives for fluconazole-refractory esophageal candidiasis include an echinocandin (**BI***), amphotericin B (**BI***), posaconazole (**CII***), or isavuconazole (**CII***). Randomized clinical trials in adults with HIV have demonstrated good treatment response when using an echinocandin for esophageal candidiasis, but relapse is more frequent, particularly for OPC. Caspofungin demonstrated comparable efficacy to fluconazole for treatment of esophageal candidiasis (81.5% vs. 85.1%, difference −3.6 [95% CI, −14.7 to 7.5]).⁷⁰⁻⁷³ However, caspofungin efficacy against OPC was numerically lower but not statistically significant (71.4% vs. 83.3%, difference −11.9 [95% CI, −26.8 to 3.0]), while OPC relapse was more frequent with caspofungin at 14 days post-treatment (42.5% vs. 13.2%, difference 29.3% [95% CI, 11.5–47.1] and 28 days post-treatment (59.0% vs. 35.3%, difference 23.7% [95% CI, 3.4–43.9]).⁷⁴ Micafungin demonstrated non-inferior efficacy by overall therapeutic cure (both clinical and endoscopic cure) compared to fluconazole for treatment of esophageal candidiasis (85.8% vs. 85.3%, difference 0.5% [95% CI, −5.6 to 6.6]).⁷⁵⁻⁷⁷ Although micafungin efficacy at end of treatment was comparable to fluconazole for OPC treatment (83.5% vs. 82.1%), symptomatic relapse at 2 weeks post-treatment was more common in micafungin-treated participants than fluconazole-treated participants (32.3%, 18.1%, difference 14.2% [95% CI, 5.6–22.8]).^{75,76} Anidulafungin demonstrated similar endoscopic success (cure or improvement) when compared to fluconazole (97.4% vs. 98.7%, difference −1.3% [95% CI, −3.8 to 1.2]) as well as clinical success (cure or improvement in clinical symptoms) (99.1% vs. 99.6%) at the end of therapy.⁷⁸⁻⁸⁰ However, endoscopically confirmed relapses 2 weeks after end of therapy were more common in the anidulafungin group (53.3% vs. 19.3%, difference 34.0%, [95% CI, 25.8–42.3]). Pediatric bridging studies evaluating echinocandin pharmacokinetics (PK) and safety have determined appropriate dosing of echinocandins and support their good safety profile at these doses. Amphotericin B has historically been used in treatment of esophageal candidiasis with efficacy as a comparator in adult randomized controlled trials (RCTs) of esophageal candidiasis;

however, toxicities are frequent.^{71,73,81} Posaconazole has limited efficacy data for treatment of esophageal candidiasis,⁶² but newer formulations provide IV and oral options with more stable PK and generally good safety profiles.⁶⁴ Isavuconazole (in the form of isavuconazonium sulfate) has promising Phase 2 efficacy and safety data for treatment of uncomplicated esophageal candidiasis in adults with bridging pharmacokinetic data of IV and oral options in children.^{82,83}

Invasive Candidiasis

The treatment of choice for invasive disease in children with HIV depends on severity of disease, previous azole exposure, and *Candida* isolate obtained (if known). RCTs in adults without HIV have demonstrated that an echinocandin used to treat candidemia and/or invasive candidiasis had similar efficacy compared to amphotericin B by favorable outcomes at the end of IV therapy (caspofungin 74.3%, amphotericin B 67.8%, difference 7.5% [95% CI, -5.4 to 20.3]; overall study mortality, caspofungin 33.0%, amphotericin B 30.4%); similar efficacy compared across echinocandins (micafungin 70.7%, caspofungin 63.3%, difference 7.4% [95% CI, -2.0 to 16.3])⁸⁴⁻⁸⁸; overall study mortality micafungin 29.0%, caspofungin 26.4%); and superior efficacy compared to fluconazole (anidulafungin 75.6%, fluconazole 60.2%, difference 15.4 [95% CI, 3.9-27.0]; overall study mortality, anidulafungin 22.8%, fluconazole 31.4%). In a pediatric multicenter, prospective open-label study of caspofungin, 30 of 37 participants with invasive candidiasis and one of one participant with esophageal candidiasis had a successful clinical and microbiological response at the end of therapy.⁸⁹ In a pediatric multicenter, prospective observational cohort study of treatment for invasive candidiasis in 541 children without HIV, initial directed therapy with an echinocandin (compared with an azole or amphotericin B) was associated with reduced treatment failure at 14 days (unadjusted, echinocandin 9.8%, azole/amphotericin B 13.1%; adjusted risk difference -7.1% [95% CI, -13.1 to -2.4]) but not at 30 days (adjusted risk difference -0.4% [95% CI, -7.5 to 6.7]).¹³

An echinocandin is recommended for moderately severe to severely ill children with candidiasis because of the fungicidal nature of these agents, as well as the lack of AEs. Fluconazole is a reasonable alternative for people who are less critically ill and who have no recent azole exposure (**AI***). Voriconazole can be used in situations in which mold coverage is also warranted (**BI***).⁹⁰ Although isavuconazole has activity against *Candida*, a Phase 3, randomized, double-blind, multinational clinical trial for the primary treatment of adults with candidemia or invasive candidiasis failed to demonstrate isavuconazole non-inferiority versus caspofungin (overall response at end IV therapy 60.3% vs. 71.1%, adjusted difference -10.8 [95% CI, -19.9 to 1.8]). Secondary endpoints of all-cause mortality and safety were similar across arms, and median times to bloodstream clearance was comparable.⁹¹

For infections with *C. glabrata*, an echinocandin is recommended because of the increasing resistance seen against fluconazole for this species (**AII**).⁹² Despite this recommendation, clinicians should be aware of the increasing frequency of *C. glabrata* echinocandin resistance. For those 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 intrinsic resistance to fluconazole. For infection with *C. parapsilosis*, fluconazole or amphotericin B is recommended (**BII***). Previous data suggested a decreased response of *C. parapsilosis* isolates to echinocandins.^{84,86,87,93} However, subsequent adult comparative effectiveness data reveal that initial therapy with an echinocandin for *C. parapsilosis* did not result in worse outcomes.⁹⁴ Thus, if a person is receiving empirical therapy with an echinocandin and showing clinical improvement when culture of *C. parapsilosis* returns, continuing with this therapy is reasonable. For infections with *C. auris*, an echinocandin is recommended (**AII***), but clinicians

should check available data on their local susceptibility patterns. Azole resistance is high and amphotericin B resistance is common, but susceptibilities are variable by clade and geographical distribution.²¹ *C. auris* resistance to echinocandins is increasing, and pan-resistant *C. auris* has been reported.²¹⁻²³

For many of these clinical scenarios, amphotericin B is an effective but less attractive alternative given concerns for therapy-related toxicity (**BI***).^{84,85,95} Amphotericin B lipid formulations are 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 (**AI**).⁹⁶⁻⁹⁸ However, amphotericin B deoxycholate is acceptable if a lipid formulation is unavailable or infeasible (**BI***).

Regardless of the antifungal agent chosen, the recommended duration of therapy for candidemia should be treated for ≥ 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 (**AIII**). 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 a pediatric infectious diseases specialist.

For CNS candidiasis, initial treatment should use amphotericin B (**AIII**).^{33,34} Recommended initial treatment in neonates is amphotericin B deoxycholate 1 mg/kg IV daily or liposomal amphotericin B 5 mg/kg IV daily (**BIII**). Addition of flucytosine 25 mg/kg four times daily may be considered as salvage therapy for neonates who have not responded clinically to initial amphotericin B deoxycholate, but toxicities are common. CNS disease in the neonate typically manifests as a meningoencephalitis. Although all amphotericin B formulations penetrate the CNS and have fungicidal activity in the CNS, amphotericin B deoxycholate and liposomal amphotericin B had the highest drug exposures and greatest antifungal efficacy in a rabbit model of hematogenous *C. albicans* meningoencephalitis.^{34,99} A comparative effectiveness study found higher mortality in infants treated with lipid formulations of amphotericin B than with amphotericin B deoxycholate or fluconazole.^{34,100} However, the study had heterogeneity among the lipid formulations used and institutional care practices, and some institutions have subsequently reported successful outcomes with liposomal amphotericin B in neonates. Lipid formulations may not adequately penetrate the kidneys and thus should only be used with caution in neonates when urinary tract involvement is suspected or confirmed. In a prospective observational study evaluating treatment outcomes of CNS candidiasis in neonates, median time to clear the cerebrospinal fluid (CSF) was longer for infants who received flucytosine plus amphotericin B deoxycholate compared with amphotericin B deoxycholate alone.^{34,101} Further, flucytosine is poorly tolerated in neonates, and gastrointestinal toxicity may hinder oral feeding. Micafungin 10 to 15 mg/kg/dose IV daily may be considered in neonates with CNS candidiasis as alternative therapy in special circumstances, such as salvage therapy or situations in which toxicity or drug resistance (e.g., *C. glabrata*) preclude the use of the preferred agents. Beyond the neonatal/infant period, liposomal amphotericin B 5 mg/kg IV daily is recommended with or without flucytosine (**AIII**), although doses up to 10 mg/kg IV daily have been used in non-candidal CNS mycoses with associated higher toxicities. After the patient has responded to initial treatment, fluconazole 12 mg/kg daily may be considered for isolates susceptible to fluconazole. (See [the Pharmacokinetics and Dosing of Antifungal Agents section](#) below for characteristics of various antifungal agents.)¹⁰²⁻¹⁰⁴ Therapy should be continued for at least one month until all signs, symptoms, and CSF and radiological abnormalities have resolved.^{34,105} Infected CNS devices, including ventriculostomy drains and shunts, should be removed if possible (**AIII**). For ocular candidiasis (e.g., endophthalmitis), systemic fluconazole or voriconazole provide most optimal intraocular drug concentrations, while systemic liposomal amphotericin B may be an

alternative, especially when resistant to other antifungal agents. The roles of intravitreal antifungal therapy or vitrectomy should be evaluated jointly on a case-by-case basis by infectious diseases physicians and ophthalmologists.^{28,33,34} If a child with uncomplicated invasive candidiasis 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 can be considered when the patient has shown clinical improvement, isolates susceptible to the oral agent, and negative repeat blood cultures following initiation of antifungal therapy **(BII*)**.^{103,104,106,107} 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*). Decisions to step down to an oral agent should also be guided by considerations of the site of infection and antifungal pharmacokinetics, such as bioavailability and penetration into the target tissues.

Finally, in children who have a central venous catheter in place at the time of candidemia onset, the central line should always be removed when feasible **(AII*)**.^{7,108} 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.⁹⁴ Additionally, an individual patient-level quantitative review of seven randomized trials of adults with candidemia and found that central line removal provided a protective effect against mortality (odds ratio [OR] 0.50; 95% CI, 0.35–0.72).⁹³ *Candida* infections tend to generate biofilm formation in indwelling catheters or implanted devices, such as prosthetic heart valves.¹⁰⁹ Biofilms are generally resistant to intravenous antifungals. Neglecting to remove catheters increases the chances of treatment failure and/or disease recurrence. Therefore, it is reasonable to conclude that a central venous catheter should be removed when feasible.

Pharmacokinetics and Dosing of Antifungal Agents

Azoles

Fluconazole PK vary significantly with age, and fluconazole is rapidly cleared in children. Daily fluconazole dosing for invasive candidiasis requires higher doses of fluconazole than are used for mucocutaneous disease, with many experts suggesting a loading dose of fluconazole 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 (see [Drug Dosing Table](#)).¹¹⁰ Therapeutic drug monitoring (TDM) should be considered routinely for prevention and management of invasive candidiasis when using itraconazole, voriconazole, posaconazole (esp. for oral suspension, consider for other formulations), or flucytosine.^{33,111} TDM should also be considered (by drug and clinical scenario) in populations at risk of extremely low or high drug exposures (e.g., premature neonates, critically ill patients with altered volume of distribution or extracorporeal circuits, altered protein binding [e.g., severe hypoalbuminemia], gastrointestinal absorption problems, drug–drug interactions, or extremes of weight [e.g., morbid obesity or severe acute malnutrition]) or in patients experiencing treatment failure.^{33,111} (Note that recommended TDM targets and timing are typically based on adult data and may be derived from non-candidal fungal infections.)

Itraconazole oral solution bioavailability is lower in children than in adults (see [Drug Dosing Table](#)).^{60,112} Administering itraconazole oral solution on an empty stomach improves absorption (in contrast to the capsule formulation, which is best administered under fed and acidic conditions), and

monitoring itraconazole serum concentrations, like most azole antifungals, is key in management (generally itraconazole trough levels [timing: approximately 5–7 days with loading dose, 10–14 days without loading dose] should be ≥ 0.5 $\mu\text{g/mL}$ [prophylaxis] or ≥ 1 $\mu\text{g/mL}$ [treatment]; trough levels > 3 $\mu\text{g/mL}$ to 4 $\mu\text{g/mL}$ may be associated with increased toxicity).¹¹¹ Super-bioavailability itraconazole (SUBA-itraconazole) is approved by the U.S. Food and Drug Administration (FDA) in adults only; therefore, no pediatric dosing is available.^{113–117}

Voriconazole has considerable experience in children, including for treatment of esophageal candidiasis and candidemia.^{6,49,118,119} 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. 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 (see [Drug Dosing Table](#)).^{118–120} In addition, therapeutic trough (timing: 2–5 days [approximately 2 days with loading dose, approximately 5 days without loading dose]) voriconazole drug levels (generally thought to be ≥ 0.5 $\mu\text{g/mL}$ [prophylaxis] or ≥ 1 $\mu\text{g/mL}$ to 2 $\mu\text{g/mL}$ [treatment]; toxicity ceiling 4 to 5.5 $\mu\text{g/mL}$) should be monitored because of significant interindividual variability in voriconazole PK in children with invasive fungal infection.^{111,121} For example, voriconazole clearance depends on allelic polymorphisms of cytochrome P450 (CYP) CYP2C19, resulting in poor and extensive metabolizers of voriconazole.^{122,123} It is estimated that 20% of Asian and 3% to 5% of White populations are poor metabolizers of voriconazole, further underscoring the importance of monitoring voriconazole levels to ensure proper dosing.¹²²

Posaconazole is available in four formulations for use in children.⁶⁴ **Note that the various formulations are not substitutable and have differences in dosing.** The original posaconazole *oral suspension* is FDA approved in people aged ≥ 13 years.¹²⁴ Effective absorption of the posaconazole oral suspension strongly requires taking the medication with food, ideally a high-fat meal (or liquid nutritional supplement or acidic carbonated beverage in people who cannot eat a full meal); taking posaconazole oral suspension on an empty stomach will result in approximately one-fourth of the absorption as in the fed state. The exact pediatric dosing for posaconazole oral suspension 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. In adults, 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 people who are severely ill because of findings of a marginal increase in exposure with more frequent dosing (see [Drug Dosing Table](#)). Posaconazole *delayed-release tablets* are approved in children ≥ 2 years who weigh > 40 kg. The posaconazole delayed-release tablet formulation has better absorption given its delayed release in the small intestine, but absorption will still be slightly increased with food. If the person is unable to take food, the tablet is recommended; but tablets are to be swallowed whole, not divided, crushed, or chewed—although a case series of 10 encounters using crushed delayed-release tablets in nine children achieved target posaconazole concentrations in 90% of encounters.¹²⁵ There is potential for overdosing if this tablet formulation is dosed inappropriately.^{126,127} The posaconazole *PowderMix for delayed-release oral suspension* is approved in children aged ≥ 2 years who weigh ≤ 40 kg; note that the recommended dosage cannot be achieved with this formulation in children > 40 kg.¹²⁴ Posaconazole PowderMix for delayed-release oral suspension should be administered with food and using the copackaged notched tip syringe. The posaconazole *injection* is approved in children aged ≥ 2 years. Posaconazole *injection* must be administered through an in-line filter by slow intravenous infusion, not as a bolus injection (see [FDA package insert](#) for details).⁶⁴ For all formulations, posaconazole target trough (timing: 5 days with a loading dose, 7 days without a loading dose) levels

for prophylaxis are ≥ 0.5 $\mu\text{g/mL}$ to 0.7 $\mu\text{g/mL}$ with treatment targets ≥ 1 $\mu\text{g/mL}$ to 1.5 $\mu\text{g/mL}$; the trough toxicity ceiling is >3 $\mu\text{g/mL}$ to 3.75 $\mu\text{g/mL}$.¹¹¹

Isavuconazole is a new triazole that was FDA approved in 2015 for treatment of invasive aspergillosis and invasive mucormycosis with both oral (capsules only) and IV formulations. Isavuconazole has activity against *Candida*.⁹¹ Isavuconazole is available for administration in its prodrug form isavuconazole sulfate. In adults, isavuconazonium sulfate has a mean plasma half-life of 130 hours after IV administration; the oral capsule has an absolute bioavailability of 98%.¹²⁸ As of December 2023, isavuconazonium sulfate (prodrug of isavuconazole) *injection* is FDA approved in children ≥ 1 year old, and isavuconazonium sulfate *capsules* are approved in children ≥ 6 years old who weigh ≥ 16 kg (see [Drug Dosing Table](#)). The FDA approval is based on a Phase 1 pediatric safety, tolerability, and PK study⁸³ and a Phase 2 open-label, noncomparative, multicenter study for treatment of invasive aspergillosis or invasive mucormycosis in 31 children aged 1 to 17 years who experienced 6.5 % (95% CI, 0.79–21.42) all-cause mortality through 42 days.¹²⁹

Echinocandins

Data from studies using echinocandins (caspofungin, micafungin, and anidulafungin) are sufficient to recommend these agents as alternatives to fluconazole for esophageal candidiasis (**BI***) and as first-line therapy for invasive candidiasis (**AI***).^{13,88,89,95,130-141}

Echinocandins are generally not recommended for treatment of CNS *Candida* infections due to concerns that these agents penetrate CSF poorly. However, some research has evaluated the potential of echinocandins for neonatal hematogenous *Candida* meningoencephalitis. A nonneutropenic rabbit model of neonatal hematogenous *Candida* meningoencephalitis found untreated *Candida albicans* infection burdens in CSF cultures beneath the limit of quantification, despite the presence of established infection in various other CNS subcompartments (e.g., cerebrum, cerebellum, spinal cord, and meninges), and micafungin penetrated most CNS compartments (highest concentrations in meninges and choroid, not reliably detected in CSF) when dosed sufficiently.¹⁴² Micafungin doses ≥ 10 mg/kg/dose once daily (with safety data supporting up to 15 mg/kg/day) may be necessary for the treatment of candidemia with meningoencephalitis.^{137,138,142,143} Population pharmacokinetics and modeling of micafungin in 47 infants with proven or presumptive disseminated candidiasis indicated that a dose of 10 mg/kg/dose daily resulted in 83% of infants with micafungin areas under the concentration-time curve (AUC) that are associated with near-maximal decline in fungal burden within the CNS.¹³⁸ An RCT evaluating micafungin 10 mg/kg/dose daily versus amphotericin B in infants <4 months with suspected or proven *Candida* meningoencephalitis was terminated early (due to slow recruitment) with only 30 participants enrolled (20 allocated to micafungin, 10 amphotericin B), which was 13% of the targeted enrollment. Prior to study termination, fungal-free survival at 1 week after end of therapy was 60% for micafungin versus 70% for amphotericin B with all-cause mortality 15% (micafungin) versus 10% (amphotericin B).¹⁴⁴

A PK study of caspofungin in immunocompromised children with HIV 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.¹³² Significantly higher doses of caspofungin have been studied in adults 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 caspofungin in neonates is 25 mg/m²/day. A multicenter RCT of infants <3 months old with invasive candidiasis with allocation to caspofungin 2 mg/kg/dose IV daily (equivalent to median dose of 25 mg/m²/day) versus amphotericin B deoxycholate

1 mg/kg/dose IV daily was terminated early for low enrollment.^{145,146} In the full-analysis-set population, fungal-free survival in at 2 weeks after treatment was similar across arms (71.0% versus 68.8%; difference, stratified by weight, -0.9% [95% CI, -24.3% to 27.7%]), with a smaller proportion of AEs in the caspofungin arm.

The recommended dose of micafungin for children aged 2 years to 17 years is 2 to 4 mg/kg/dose daily, but neonates require doses of micafungin 10 to 15 mg/kg/dose daily and infants <15 kg may benefit from 5 to 7 mg/kg/dose daily (see [Drug Dosing Table](#) below for recommended dosing according to age/weight bands).^{88,95,135-137,147,148} Micafungin demonstrates dose-proportional PK, and an inverse relationship between age and clearance, suggesting a need for increased dosage in young children.¹³⁸ Clearance of the drug in neonates was more than double that in older children and adults.¹³⁹ Dosages of micafungin at least 10 mg/kg/day are recommended in premature neonates. Doses of 10 mg/kg/day results in AUC values consistent with an adult dosage of micafungin 100 to 150 mg/day; safety data from clinical studies at doses of 10 to 15 mg/kg daily for infants <4 months old did not reveal new safety signals.^{105,136-138}

In 2020, the FDA approved anidulafungin for treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in children aged 1 month and older (see [Drug Dosing Table](#)). Although dosing in adults differs by treatment indication for candidemia (200-mg load, then 100 mg once daily thereafter) versus esophageal candidiasis (100-mg load, then 50 mg once daily thereafter), a separate pediatric dosing for esophageal candidiasis is not FDA approved.⁸⁰ One PK study of anidulafungin in 25 neutropenic children without HIV 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 daily and 100 mg daily, respectively.¹⁴⁰ A PK study of 15 neonates and infants indicated that neonates and infants receiving 1.5 mg/kg/day of anidulafungin have exposures similar to children receiving similar weight-based dosing and adults receiving 100 mg/day.¹⁴⁹ 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 daily of anidulafungin was successful in treating the infection.¹⁴¹ In a prospective, open-label noncomparative, multicenter, international study to evaluate safety, efficacy, and PK of anidulafungin for treatment of invasive candidiasis, 49 participants aged 2 years to <18 years receiving anidulafungin (3 mg/kg Day 1, 1.5 mg/kg daily thereafter for 10–35 days, followed by optional fluconazole) had 8.2% probability of all-cause mortality (4/49) by end of IV therapy and 14.3% (7/49) by Week 6 follow-up. No deaths were considered treatment related, and global response was 70.8% at end of IV therapy.¹⁵⁰ Under the same protocol, 19 participants aged 1 month to <2 years received anidulafungin for 5 to 25 days; PK were similar to adult participants, and global success was 68.8% at end of IV therapy.¹⁵⁰ Rezafungin is approved in adults only; therefore, no pediatric dosing is available.¹⁵¹

Polyenes

Conventional amphotericin B (sodium deoxycholate complex, AmB-D) 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 **(CIII)**.¹⁵²⁻¹⁵⁴ 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 AmB-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 with rapid tissue penetration.^{155,156} 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.¹⁵⁷ 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 for candidiasis. 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.¹⁵⁸ 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.⁴⁹ Flucytosine has been used in combination with amphotericin B in some children with severe invasive candidiasis, particularly in those with CNS 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 (CIII).^{159,160}

For a summary of fungal species, antifungal drugs, activity, route, clearance, CSF penetration, drug monitoring targets, and AEs, refer to the [American Academy of Pediatrics Red Book 2024–2027 chapter on Antifungal Drugs for Systemic Fungal Infections](#).

Monitoring Response to Therapy and Adverse Events, Including IRIS

All medications, including antifungals and antiretrovirals, should be checked for contraindications, warnings, precautions, and administration instructions prior to prescribing, particularly for newer drugs and formulations. For example, administration of the posaconazole PowderMix formulation with alcohol is not recommended, and posaconazole PowderMix and anidulafungin are contraindicated in individuals with known or suspected hereditary fructose intolerance (see corresponding [FDA label](#)).

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.

Azoles

The azole drugs have relatively low toxicity, but because of their ability to inhibit the CYP-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. Potential azole-related drug–drug interactions are pertinent to certain drugs from many ARV classes, including protease inhibitors, non-nucleoside reverse transcriptase inhibitors, an integrase strand transferase inhibitor (i.e., elvitegravir), a CCR5 antagonist (i.e., maraviroc), and pharmacokinetic boosting agents (e.g., ritonavir or cobicistat). Most nucleos(t)ide reverse transcriptase inhibitors in current use have no major drug–drug interactions, but itraconazole may increase exposures and AEs from tenofovir disoproxil fumarate and tenofovir alafenamide. Most integrase strand transferase inhibitors (i.e., dolutegravir, bictegravir, raltegravir, cabotegravir) do not require dose adjustments with most azoles, but elvitegravir has drug–drug interactions with many azoles. Lenacapavir has possible drug–drug interactions with many azoles, but no dose adjustments are recommended. The potential for drug–drug interactions should be carefully evaluated before initiation of therapy (**AII***).¹⁶¹

TDM should be used to optimize management of itraconazole, voriconazole, and posaconazole. The benefits of TDM are likely greatest in treatment of severe disease, such as invasive candidiasis, but TDM may be considered in other circumstances for ensuring appropriate azole exposures to improve effectiveness and/or decrease toxicity. Generally, itraconazole trough levels ≥ 0.5 $\mu\text{g/mL}$ (prophylaxis) or ≥ 1 $\mu\text{g/mL}$ (treatment) are ideal, and trough levels >3 to 4 $\mu\text{g/mL}$ may be associated with increased toxicity. Target voriconazole trough levels are ≥ 0.5 $\mu\text{g/mL}$ for prophylaxis and ≥ 1 $\mu\text{g/mL}$ to 2 $\mu\text{g/mL}$ for treatment, with a trough toxicity ceiling of 4 to 5.5 $\mu\text{g/mL}$. Posaconazole target trough levels for prophylaxis are ≥ 0.5 $\mu\text{g/mL}$ to 0.7 $\mu\text{g/mL}$ with treatment targets ≥ 1 $\mu\text{g/mL}$ to 1.5 $\mu\text{g/mL}$; the trough toxicity ceiling is >3 $\mu\text{g/mL}$ to 3.75 $\mu\text{g/mL}$.¹¹¹ Note that these targets are based in large part on adult data from a variety of invasive fungal infections, not necessarily on *Candida* PK/pharmacodynamic targets; for example, voriconazole targets were based primarily on studies of invasive aspergillosis.

The most frequent adverse effects of the azole drugs are gastrointestinal, including nausea and vomiting (10% to 40% of recipients). 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 recipients). 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 people receiving voriconazole.¹⁶² 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.¹⁶³ Voriconazole administration has been associated with fluorosis. Voriconazole is a tri-fluorinated agent with up to 16% fluoride and can result in excess fluoride accumulation in the recipient after prolonged exposure. Recipients will often present with non-specific bone pain and have periosteal reaction seen on radiographs.¹⁶⁴ 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.^{165,166} Voriconazole should not be administered intravenously to people with renal impairment, including people with creatinine clearance <50 mL/min, or people who require hemodialysis or continuous venovenous hemodiafiltration (see [voriconazole's FDA label](#)). This is not due to the drug itself, but because intravenous administration of voriconazole requires coadministration with sulphobutylether- β -cyclodextrin (SBECD) as an excipient. SBECD can accumulate in people with impaired renal function.

Polyenes

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 usually occurs 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.

Echinocandins

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 three participants had AEs potentially related to the drug (hypokalemia in all three children, elevated bilirubin in two children, and decreased hemoglobin and elevated alanine aminotransferase in one child).¹³² 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%) participants experienced one or more drug-related clinical AEs, including one patient each with fever, diarrhea, phlebitis, proteinuria, and transient extremity rash. One or more drug-related laboratory AEs were reported in two participants, including one patient each with hypokalemia and increased serum aspartate transaminase. None of the drug-related AEs in this study were considered serious or led to discontinuation of caspofungin.¹³² In a prospective multicenter trial for primary or salvage treatment of *Candida* or *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 AEs occurring in 26.5% and 34.7% of participants, respectively, similar to proportions seen in adults. Drug-related clinical AEs 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 AEs led to therapy interruption or discontinuation.⁸⁹

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 participants who weighed 40 kg, and 100 mg for participants who weighed >40 kg, was well tolerated. AEs were similar for both treatment arms and reflected those experienced by people with comorbid conditions. These AEs included sepsis, fever, vomiting, diarrhea, anemia, thrombocytopenia, and hypokalemia. Participants in the micafungin group experienced significantly fewer AEs 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 participants receiving micafungin experienced serious AEs, including a worsening of renal failure, a preexisting condition, and a moderate increase in serum creatinine resulting in discontinuation of therapy. Participants 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.⁹⁵

A multicenter, ascending-dosage study of anidulafungin in 25 children with neutropenia, without HIV and aged 2 years to 17 years, showed anidulafungin to be well tolerated and observed no drug-related serious AEs. 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.¹⁴⁰ In a prospective, open-label, noncomparative, multicenter international study of participants aged 2 years to <18 years old receiving anidulafungin followed by optional fluconazole, the most common treatment-emergent AEs (>10%) were vomiting, diarrhea, pyrexia, epistaxis, headache, abdominal pain, alanine transaminase (ALT) increased, and hypotension. Most were mild or moderate in severity, but five severe AEs occurred in one patient each: neutropenia, gastrointestinal hemorrhage, increased transaminases, hyponatremia, and myalgia. Five participants (10.2%) discontinued treatment due to AEs, and AEs were considered related to anidulafungin in four participants (increased transaminases in two cases, vomiting, generalized pruritis); two participants (4.1%) underwent infusion rate reduction or temporary discontinuation due to AEs. Serious AEs were observed in 23 participants (46.9%) with two reported as related to anidulafungin (increased transaminases and gastrointestinal hemorrhage).¹⁶⁷ Under the same protocol, in 19 participants aged 1 month to <2 years, the most frequent treatment-emergent AEs (>10%) were anemia, diarrhea, pyrexia, vomiting, increased ALT, increased aspartate transaminase, bacteremia, pancytopenia, rash, sepsis, and thrombocytopenia. Most treatment-emergent AEs were mild to moderate with 10 severe treatment-emergent AEs in 7 (36.8%) participants. Five AEs were considered serious (abdominal sepsis, coagulopathy, diarrhea, pancytopenia, and urinary tract infection), of which one event of diarrhea was considered related to anidulafungin and led to discontinuation.¹⁵⁰

Immune reconstitution inflammatory response syndrome (IRIS) associated with *Candida* infection has not been described in children with HIV. However, evidence suggests that candidiasis (other than *Candida* esophagitis) occurs with increased frequency in adults during the first 2 months after initiation of ART.¹⁶⁸

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***).^{59,60,68}

Approximately 50% to 60% of people with fluconazole-refractory OPC and 80% of people with fluconazole-refractory esophageal candidiasis will respond to itraconazole solution.^{65,67,68,169,170} Therefore, itraconazole solution is recommended to treat fluconazole-refractory OPC and fluconazole-refractory esophageal candidiasis (**AI***). Posaconazole is a second-generation orally bioavailable triazole that has been effective in adolescents and adults with HIV who have azole-refractory OPC or esophageal candidiasis.⁶² Although experience in children is still limited, newer posaconazole formulations provide more consistent absorption and drug exposures or the option of IV therapy. Thus, posaconazole is recommended for OPC in children with fluconazole-refractory disease (**AI***).^{61-63,171} Similarly, voriconazole has supporting RCT data in immunocompromised adults (most with HIV) demonstrating that voriconazole is at least as effective as fluconazole in treatment of biopsy-proven esophageal candidiasis, but AEs with voriconazole were more frequent.⁶⁶ Given supporting pediatric PK and dosing data, as well as efficacy data in a limited number of immunocompromised children, voriconazole may also be considered for treatment of esophageal candidiasis in fluconazole-refractory disease (**AI***).⁶⁹ Randomized clinical trials in adults with HIV have demonstrated good treatment response when using an echinocandin for esophageal candidiasis, but relapse is more frequent, particularly for OPC.^{70,72,75,76,172} Pediatric studies evaluating echinocandin PK and safety have determined appropriate dosing of echinocandins and support their good safety profile at these doses. Thus, echinocandins may be considered alternative treatment options when IV therapy is necessary for azole-refractory esophageal candidiasis and possibly for azole-refractory OPC (**BI***).

Amphotericin B has historically been used in treatment of esophageal candidiasis with efficacy as a comparator in adult RCTs of esophageal candidiasis, but toxicities are frequent. Thus, amphotericin B is recommended as an alternative agent for esophageal candidiasis (**BI***).^{71,73,81} An amphotericin B dose of 1 mL given orally four times daily of a 100-mg/mL suspension sometimes has been effective in people with OPC who do not respond to itraconazole solution; however, this product is not commercially available in the United States and requires compounding by pharmacies (**CIII**).^{68,173,174} Lipid formulations of amphotericin B IV may be considered if needed.¹⁷⁵ Although lower dosing for pediatric OPC or esophageal candidiasis has not been established, the recommended adult dosing range of 3 to 4 mg/kg/day would fall within the standard pediatric dosing range. Low-dose IV amphotericin B (0.3–0.5 mg/kg/day) has been effective and may be considered in children with refractory OPC or esophageal candidiasis (**BII***),^{49,68,81,176} while some adult sources recommend a dose of 0.3 mg/kg/day for OPC and dosing of 0.3 to 0.7 mg/kg/day for esophageal candidiasis.^{34,175}

Posaconazole may also be considered as a possible alternative for fluconazole- or itraconazole-refractory esophageal candidiasis (**CII***).^{62,177} Isavuconazole is another alternative treatment due to promising Phase 2 efficacy and safety data for treatment of uncomplicated esophageal candidiasis in adults with bridging pharmacokinetic data of IV and oral options in children (**CII***).^{82,83}

Invasive Disease

As noted above, the treatment of choice for invasive disease in children with HIV 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; however, there is extensive clinical experience with echinocandins in children. Invasive candidiasis associated with neutropenia in people undergoing hematopoietic stem cell 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 **(AI*)**.

Various amphotericin B formulations exist for management of refractory disease. Lipid amphotericin B formulations appear to be at least as effective as conventional amphotericin B for treating serious fungal infections,^{178,179} and one efficacy trial including 98 children in the modified intention-to-treat analysis had comparable treatment success between liposomal amphotericin B (76.0%) and micafungin (72.9%), although participants with liposomal amphotericin B (16.7%) had more AEs leading to treatment discontinuation than micafungin (3.8%).^{95,175} Further, the lipid formulations have less acute and chronic toxicity. An RCT of 702 participants, including 75 children aged 2 through 12 years, compared liposomal amphotericin B versus conventional amphotericin for empirical therapy in participants with persistent febrile neutropenia. Liposomal amphotericin B demonstrated similar efficacy but fewer breakthrough fungal infections, less infusion-related toxicity, and less nephrotoxicity.⁹⁶ Thus, lipid formulations of amphotericin B are preferred over amphotericin B deoxycholate, although amphotericin B deoxycholate is an acceptable alternative when a lipid formulation is not available **(AI)**. Two lipid formulations are used: ABLC and liposomal amphotericin B lipid complex.^{96,180,181}

For invasive candidiasis, ABLC is administered as 5 mg/kg body weight IV once daily over 2 hours.^{96,180,182} 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 (1) treatment of recurrence is typically effective; (2) there are risks of compounding toxicities; (3) the potential exists for development of resistance; (4) there are concerns for drug–drug interactions; (5) additional chronic medications may add to ART adherence challenges; and (6) prophylaxis can prove costly **(AII*)**. Although similar considerations apply to esophageal candidiasis, providers should weigh that esophageal disease typically causes more significant morbidity and is associated with more severe immune suppression. In all cases of candidiasis in children living with HIV, immune reconstitution with ART children should be a priority. Indeed, all infants and children with HIV should be initiated on ART, particularly those who develop candidiasis **(AI** for children aged <3 months, **AI*** for older children).¹⁸³⁻¹⁸⁵ See the [Pediatric Antiretroviral Guidelines](#) for more information. However, when recurrences are frequent and severe despite ART, secondary prophylaxis may be considered on a case-by-case scenario.^{57,186-192} Data from studies of adults with HIV on ART suggest that suppressive therapy with systemic azoles, either with oral fluconazole, considered first-line therapy **(AI*)**, or itraconazole solution, voriconazole, or posaconazole as alternatives **(BII*)**, can be effective and may be considered.^{59,66,177,190,193}

Experience with adults with HIV suggests that in children or adolescents 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 and may be considered **(BII*)**.

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 and other

OIs, discontinuation of secondary prophylaxis can be considered when a patient's CD4 count or percentage has risen to CDC HIV stage 2 (moderate immunosuppression) or 1 (no or mild immunosuppression) with evidence of immune reconstitution **(BII*)**.¹⁹⁴⁻¹⁹⁸ HIV infection staging (see [HIV Infection Staging Table](#) for more information) classifies severity of HIV disease primarily according to CD4 cell count (or CD4 percentage, if CD4 cell count is missing), age (as CD4 norms vary by age), and other clinical factors (e.g., acute/early HIV or most AIDS-defining OIs).

Dosing Recommendations for Prevention and Treatment of Candidiasis

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 despite ART.</p> <ul style="list-style-type: none"> Fluconazole 6 mg/kg body weight (maximum 200 mg/dose) PO three times weekly 	<ul style="list-style-type: none"> Fluconazole 3–6 mg/kg body weight PO daily (maximum 200 mg/day) Itraconazole oral solution, 2.5 mg/kg body weight/dose PO twice daily 	<p>Secondary Prophylaxis Indicated (Limited Data in Children)</p> <ul style="list-style-type: none"> Frequent or severe recurrences despite ART In patients with initial fluconazole-refractory OPC or esophageal candidiasis that subsequently responded to voriconazole, posaconazole, or an echinocandin, may consider continuation of the effective drug until immune reconstitution <p>Criteria for Discontinuing Secondary Prophylaxis</p> <ul style="list-style-type: none"> When CD4 count or percentage has risen to HIV stage 1 or 2. See HIV Infection Stage Table for more information. <p>Criteria for Restarting Secondary Prophylaxis</p> <ul style="list-style-type: none"> Frequent severe recurrences
Treatment	<p>Oropharyngeal <i>Uncomplicated Infection</i></p> <ul style="list-style-type: none"> Clotrimazole troches, 10-mg troche PO four or five times daily 	<p>Oropharyngeal (Fluconazole-Refractory)</p> <ul style="list-style-type: none"> Itraconazole oral solution 2.5 mg/kg body weight/dose PO twice daily (maximum 200–400 mg/day) for 7–14 days 	<p>Itraconazole oral solution should not be used interchangeably with itraconazole capsules. Itraconazole capsules are generally ineffective for treatment of esophageal disease.</p>

Dosing Recommendations for Prevention and Treatment of Candidiasis

	<ul style="list-style-type: none"> Nystatin suspension 4–6 mL PO four times daily, or one or two 200,000-unit flavored pastilles by mouth four or five times daily <p><i>Moderate to Severe OPC</i></p> <ul style="list-style-type: none"> Fluconazole 3–6 mg/kg/dose PO once daily (maximum dose: 400 mg/day) <p><i>Treatment Duration</i></p> <ul style="list-style-type: none"> 7 to 14 days 	<ul style="list-style-type: none"> Posaconazole PowderMix for delayed-release oral suspension in children age ≥ 2 years and in the weight band for 7–14 days: <ul style="list-style-type: none"> 10 kg to <12 kg: 90 mg PO twice daily on Day 1, followed by 90 mg PO once daily 12 kg to <17 kg: 120 mg PO twice daily on Day 1, followed by 120 mg PO once daily 17 kg to <21 kg: 150 mg PO twice daily on Day 1, followed by 150 mg PO once daily 21 kg to <26 kg: 180 mg PO twice daily on Day 1, followed by 180 mg PO once daily 26 kg to <36 kg: 210 mg PO twice daily on Day 1, followed by 210 mg PO once daily 36–40 kg: 240 mg PO twice daily on Day 1, followed by 240 mg PO once daily Posaconazole delayed-release tablets in children ≥ 2 years old and >40 kg body weight: 300 mg PO twice daily on Day 1, followed by 300 mg PO once daily for 7–14 days Posaconazole oral suspension: 6 mg/kg/dose three times daily for 7–14 days Posaconazole IV: 6 mg/kg/dose (maximum 300 mg) IV twice daily on Day 1, followed by 6 mg/kg/dose (maximum 300 mg) IV once daily for 7–14 days Alternative: Voriconazole: Dosing as per esophageal disease below Alternative: Echinocandins: Dosing as per esophageal disease below Alternative: Lipid formulation amphotericin B 3–4 mg/kg daily. Note: Low-dose lipid formulation amphotericin B dosing has not been established. 	<p>Fluconazole Dosing Considerations</p> <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>
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Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
		<ul style="list-style-type: none"> Alternative: Amphotericin B (deoxycholate) 0.3–0.5 mg/kg body weight IV once daily 	
	<p>Esophageal Disease</p> <ul style="list-style-type: none"> Fluconazole 6 mg/kg/day PO once on Day 1, then 3–6 mg/kg/dose PO once daily (maximum dose: 12 mg/kg/day, 400 mg/day) <p><i>Treatment Duration</i></p> <ul style="list-style-type: none"> 14–21 days 	<p>Esophageal Disease (Intolerance of Oral Therapy)</p> <ul style="list-style-type: none"> Fluconazole 6 mg/kg/day IV once on Day 1, then 3–6 mg/kg/dose IV once daily (maximum dose: 12 mg/kg/day, 400 mg/day) for 14–21 days <p><i>Echinocandins</i></p> <ul style="list-style-type: none"> Anidulafungin <ul style="list-style-type: none"> Aged 1 Month–17 Years: Loading dose of 3 mg/kg body weight/daily and then maintenance at 1.5 mg/kg body weight/dose daily IV (maximum 100 mg/day) Caspofungin <ul style="list-style-type: none"> Infants Aged <3 Months: 25 mg/m² BSA/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 of caspofungin for children should be based on body surface area. Micafungin <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). Neonates: Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations. Ages ≥4 Months and Weight ≤30 kg: 3 mg/kg body weight/dose IV daily 	

Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
		<ul style="list-style-type: none"> o <i>Ages ≥4 Months and Weight >30 kg:</i> 2.5 mg/kg body weight/dose IV daily (maximum dose: 150 mg/day) • Lipid formulation amphotericin B 3–4 mg/kg daily. Note: Low-dose lipid formulation amphotericin B dosing has not been established. • Amphotericin B (deoxycholate) 0.3–0.5 mg/kg body weight IV once daily <p>Esophageal Disease (Fluconazole-Refractory)</p> <ul style="list-style-type: none"> • Itraconazole oral solution 2.5 mg/kg body weight/dose PO twice daily • Voriconazole <ul style="list-style-type: none"> o <i>Ages 2 Years to <12 Years:</i> 4 mg/kg body weight/dose IV every 12 hours. Consider switch to 9 mg/kg/dose (maximum 350 mg) PO every 12 hours only after significant clinical improvement. o <i>Ages 12–14 Years and Weight <50 kg:</i> 4 mg/kg body weight/dose IV every 12 hours. Consider switch to 9 mg/kg/dose (maximum 350 mg) PO every 12 hours only after significant clinical improvement. o <i>Ages 12–14 Years and Weight ≥50 kg:</i> 200 mg PO/IV every 12 hours o <i>Ages ≥15 Years and Weight <40 kg:</i> 100 mg PO/IV every 12 hours o <i>Ages ≥15 Years and Weight ≥40 kg:</i> 200 mg PO/IV every 12 hours • <i>Alternative:</i> Echinocandins: Dosing as above 	

Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
		<ul style="list-style-type: none"> • <i>Alternative:</i> Lipid formulation amphotericin B: Dosing as above • <i>Alternative:</i> Amphotericin B (deoxycholate): Dosing as above • <i>Alternative:</i> Posaconazole: Dosing as above • <i>Alternative:</i> Isavuconazonium sulfate IV (372 mg/vial) <ul style="list-style-type: none"> ○ <i>Ages 1 Year to <3 Years and Weight <18 kg:</i> 15 mg/kg body weight/dose every 8 hours IV loading for six doses (48 hours), followed by 15 mg/kg once daily ○ <i>Ages 3 Years to <18 Years and Weight <37 kg:</i> 10 mg/kg every 8 hours IV loading for 6 doses (48 hours), followed by 10 mg/kg once daily IV ○ <i>Ages 3 Years to <18 Years and Weight ≥37 kg:</i> 372 mg (total dose) every 8 hours IV loading for 6 doses (48 hours), followed by 372 mg (total dose) once daily IV • <i>Alternative:</i> Isavuconazonium sulfate capsules (74.5 mg/capsule) <ul style="list-style-type: none"> ○ <i>Ages 6 Years to <18 Years and Weight 16 kg to <18 kg:</i> 149 mg (2 capsules) PO every 8 hours loading for six doses (48 hours), followed by 149 mg (2 capsules) PO once daily ○ <i>Ages 6 Years to <18 Years and Weight 18 kg to <25 kg:</i> 223.5 mg (3 capsules) PO every 8 hours loading for 6 doses (48 hours), followed by 223.5 mg (3 capsules) PO once daily 	

Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
		<ul style="list-style-type: none"> o Ages 6 Years to <18 Years and Weight 25 kg to <32 kg: 298 mg (4 capsules) PO every 8 hours loading for six doses (48 hours), followed by 298 mg (4 capsules) PO once daily o Ages 6 Years to <18 Years and Weight ≥32 kg: 372 mg (5 capsules) PO every 8 hours loading for six doses (48 hours), followed by 372 mg (5 capsules) PO once daily <p><i>Treatment Duration</i></p> <ul style="list-style-type: none"> • 14–21 days 	
	<p>Invasive Disease: Moderately Severe to Severely Ill</p> <p><i>Echinocandin Recommended</i></p> <ul style="list-style-type: none"> • Anidulafungin <ul style="list-style-type: none"> o Aged 1 Month–17 Years: Load with 3 mg/kg body weight/daily dose IV and then maintenance dose at 1.5 mg/kg body weight once daily (maximum 100 mg/day) • Caspofungin: <ul style="list-style-type: none"> o Infants Aged <3 Months: 25 mg/m² BSA/dose once daily IV o Aged 3 Months–17 Years: 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. 	<p>Invasive Disease</p> <ul style="list-style-type: none"> • Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight IV/PO once daily (maximum 600 mg/day) for minimum 2 weeks after last positive blood culture (if uncomplicated candidemia) o For infants aged ≤3 months and gestational age <30 weeks, maintenance dosing is 9 mg/kg/dose IV/PO daily • Lipid formulations of amphotericin B, 3–5 mg/kg body weight IV once daily • Amphotericin B deoxycholate, 1 mg/kg body weight IV once daily in the neonatal period • Voriconazole: <ul style="list-style-type: none"> o Ages 2 Years to <12 Years: 9 mg/kg body weight/dose every 12 hours IV loading for two doses, followed by voriconazole 8 mg/kg body weight/dose IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg/dose (maximum 350 mg) PO every 12 hours. 	<p>Central venous catheters should be removed, when feasible, in children with HIV with fungemia.</p> <p>The preferred treatment for invasive disease in children with HIV depends on severity of disease, previous azole exposure, and <i>Candida</i> isolate obtained (if known).</p> <p>If a child with uncomplicated invasive candidiasis 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 can be considered when the patient is clinically improved, has isolates susceptible to the oral agent, and have negative repeat blood cultures following initiation of antifungal therapy.</p> <p>Voriconazole can be used in situations in which mold coverage is also warranted.</p>

Dosing Recommendations for Prevention and Treatment of Candidiasis

	<ul style="list-style-type: none"> • Miconazole: <ul style="list-style-type: none"> o 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). o Neonates: Up to 10–12 mg/kg body weight/dose daily IV may be required to achieve therapeutic concentrations. o Infants <15 kg body weight: 5–7 mg/kg/day o Children ≤40 kg body weight and aged 2–8 years: 3–4 mg/kg body weight/dose daily IV o Children ≤40 kg body weight and aged 9–17 years: 2–3 mg/kg body weight/dose daily o Children >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 those with candidemia, treat until 2 weeks after last positive blood culture. <p>Invasive Candidiasis: Mildly to Moderately Ill</p> <p><i>Fluconazole Recommended</i></p> <ul style="list-style-type: none"> • Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily (maximum dose: 600 mg) 	<ul style="list-style-type: none"> o Ages 12–14 Years and Weight <50 kg: 9 mg/kg body weight/dose every 12 hours IV loading for two doses, followed by voriconazole 8 mg/kg body weight/dose IV every 12 hours. Conversion to oral voriconazole should be at 9 mg/kg/dose (maximum 350 mg) PO every 12 hours. o Ages 12–14 Years and Weight ≥50 kg: Load voriconazole 6 mg/kg body weight/dose every 12 hours IV for two doses, followed by 3–4 mg/kg body weight/dose IV every 12 hours. Conversion to oral therapy should be at 200 mg PO every 12 hours. If response is inadequate, may increase to 300 mg PO every 12 hours. o Ages ≥15 Years and Weight <40 kg: Load voriconazole 6 mg/kg body weight/dose every 12 hours IV for two doses, followed by 3–4 mg/kg body weight/dose IV every 12 hours. Conversion to oral therapy should be at 100 mg PO every 12 hours. If response is inadequate, may increase to 150 mg PO every 12 hours. o Ages ≥15 Years and Weight ≥40 kg: Load voriconazole 6 mg/kg body weight/dose every 12 hours IV for two doses, followed by 3–4 mg/kg body weight/dose IV every 12 hours. Conversion to oral therapy should be at 200 mg PO every 12 hours. If response is inadequate, may increase to 300 mg PO every 12 hours. <p><i>Treatment Duration</i></p> <ul style="list-style-type: none"> • Based on presence of deep-tissue foci and clinical response; in those with candidemia, treat until 2 weeks after last positive blood culture. 	
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Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
	<ul style="list-style-type: none"> For infants aged ≤ 3 months and gestational age < 30 weeks, fluconazole maintenance dosing is 9 mg/kg/dose IV daily. Avoid fluconazole for <i>C. krusei</i> and <i>C. glabrata</i>. See dosing for echinocandins above. Use caution with echinocandins 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 those with candidemia, treat until 2 weeks after last positive blood culture. 		
	<p>Invasive Disease: CNS</p> <p><i>Neonates</i></p> <ul style="list-style-type: none"> Initial: Amphotericin B deoxycholate 1 mg/kg body weight/dose IV daily, or liposomal amphotericin B 5 mg/kg body weight/dose IV daily Step-Down (If Fluconazole-Susceptible): Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily <p><i>Children</i></p> <ul style="list-style-type: none"> Initial: Liposomal amphotericin B 5 mg/kg body weight/dose IV daily +/- flucytosine 25 mg/kg body weight/dose PO four times daily 	<p>Invasive Disease: CNS</p> <p><i>Neonates</i></p> <ul style="list-style-type: none"> Amphotericin B deoxycholate 1 mg/kg body weight/dose IV daily, or liposomal amphotericin B 5 mg/kg body weight/dose IV daily, and Flucytosine 25 mg/kg body weight/dose PO four times daily as salvage therapy <p><i>Children</i></p> <ul style="list-style-type: none"> Initial: Amphotericin B deoxycholate 0.7–1 mg/kg body weight/dose IV daily IV daily (maximum 1.5 mg/kg/day) +/- flucytosine 25 mg/kg body weight/dose PO four times daily Step-Down (If Fluconazole-Susceptible): Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily (maximum dose: 800 mg) 	<p>Infected CNS devices should be removed if possible.</p> <p>For patients in whom a ventricular device cannot be removed, amphotericin B deoxycholate could be administered through the device into the ventricle. Intrathecal neonatal doses have ranged from 0.5 mg/day in 2 mL of D5W to 0.6 mg/day in 0.5 mL of D5W (total doses were 0.15 mg to 8.6 mg); doses of 0.125 to 0.25 mg have been administered to children via an Ommaya reservoir.</p> <p>Lipid formulations of amphotericin may not adequately penetrate the kidneys and should only be used with caution in neonates when urinary tract involvement is suspected or confirmed.</p>

Dosing Recommendations for Prevention and Treatment of Candidiasis

Indication	First Choice	Alternative	Comments/Special Issues
	<ul style="list-style-type: none"> • <i>Step-Down (If Fluconazole-Susceptible):</i> Fluconazole 25 mg/kg body weight/dose once IV/PO loading for Day 1, followed by 12 mg/kg body weight/dose IV/PO daily (maximum dose: 800 mg) <p><i>Treatment Duration</i></p> <ul style="list-style-type: none"> • ≥1 month until all signs, symptoms, and CSF and radiographic abnormalities have resolved 		<p>Fluconazole dosing for CNS candidiasis is unknown but based on dosing for <i>Candida</i> invasive disease and maximums from cryptococcal meningitis.</p> <p>In neonates with CNS candidiasis, micafungin 10–15 mg/kg/dose IV daily may be considered as alternative therapy in special circumstances, such as salvage therapy or situations in which toxicity or drug resistance (e.g., <i>C. glabrata</i>) preclude the use of the preferred agents.</p>

Key: ART = antiretroviral therapy; BSA = body surface area; CD4 = CD4 T lymphocyte; CNS = central nervous system; CSF = cerebrospinal fluid; D5W = 5% dextrose in water; IV = intravenous; OPC = oropharyngeal candidiasis; PK = pharmacokinetic; PO = oral

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