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Pharmacokinetics and Pharmacodynamics of Antifungals in Children: Clinical Implications

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Abstract

Invasive fungal disease (IFD) remains life-threatening in premature infants and immunocompromised children despite the recent development of new antifungal agents. Optimal dosing of antifungals is one of the few factors clinicians can control to improve outcomes of IFD. However, dosing in children cannot be extrapolated from adult data because IFD pathophysiology, immune response, and drug disposition differ from adults. We critically examined the literature on pharmacokinetics (PK) and pharmacodynamics (PD) of antifungal agents and highlight recent developments in treating pediatric IFD.

To match adult exposure in pediatric patients, dosing adjustment is necessary for almost all antifungals. In young infants, the maturation of renal and metabolic functions occurs rapidly and can significantly influence drug exposure. Fluconazole clearance doubles from birth to 28 days of life and, beyond the neonatal period, agents like fluconazole, voriconazole, and micafungin require higher dosing than in adults due to faster clearance in children. As a result, dosing recommendations are specific to bracketed ranges of age.

Pharmacodynamics principles of antifungals mostly rely on *in vitro* and *in vivo* models but very few pharmacodynamics studies specifically address IFD in children. Exposure-response relationship may differ in younger children compared with adults, especially in infants with invasive candidiasis who are at higher risk of disseminated disease and meningoencephalitis, and by extension severe neurodevelopmental impairment. Micafungin is the only antifungal agent for which a specific target of exposure was proposed based on a neonatal hematogenous *Candida* meningoencephalitis animal model.

In this review, we found that pediatric data on drug disposition of newer triazoles and echinocandins are lacking, dosing of older antifungals such as fluconazole and amphotericin B products still need optimization in young infants, and that target PK/PD indices need to be clinically validated for almost all antifungals in children. A better understanding of age-specific PK and PD of new antifungals in infants and children will help improve clinical outcomes of IFD by informing dosing and identifying future research areas.

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Introduction

Invasive fungal diseases (IFD) cause significant mortality and morbidity in children. *Candida* sp. occur more commonly in children than adults and are a major cause of IFD [1] with a high mortality of 34% in very-low-birth-weight infants [2]. Invasive aspergillosis (IA) is another important cause of IFD in immunocompromised children, resulting in unacceptably high mortality despite antifungal therapy (nearly 50%) [3].

Therapeutic options for IFD are evolving, and several antifungal classes are available to clinicians. Pharmacokinetics (PK), pharmacodynamics (PD), and safety data are predominantly available in adults. However, IFD pathophysiology may differ in children; for example, one of the characteristics of neonatal candidiasis is the high frequency of meningoencephalitis reported in 8 to 28% of neonates with invasive candidiasis, likely due to immature immune system and more permeable blood brain barrier [4-6]. This incidence, however, is underreported given the difficulties in growing *Candida* in the microbiology laboratory and lack of available brain tissue samples for culture. In addition to pathophysiology differences, change in PK in children compared with that in adults might lead to suboptimal drug exposure or increase in toxicity. In this review, we critically examined the literature on PK and PD of systemic antifungal agents in the pediatric population. A better understanding of these pharmacological concepts will help optimize and personalize antifungal therapy in children and identify areas of future research. The following sources were searched: MEDLINE, clinicaltrials.gov, dailymed.nlm.nih.gov, ema.europa.eu and international proceedings and abstracts from the earliest record to 15 November 2013. The search strategy included the following key words: ‘pharmacokinetics’, ‘pharmacodynamics’, ‘antifungal’, amphotericin B’, ‘liposomal amphotericin B’, ‘deoxycholate amphotericin B’, ‘amphotericin B lipid complex’, ‘amphotericin B colloidal dispersion’, ‘fluconazole’, ‘itraconaozle’, ‘voriconazole’, ‘posaconazole’, ‘triazoles’, ‘ravuconazole’, ‘isavuconazole’, ‘albaconazole’, ‘echinocandins’, ‘micafungin’, ‘caspofungin’, ‘anidulafungin’, ‘aminocandin’, ‘5-flucytosine’, ‘flucytosine’, ‘children’, ‘infants’, ‘neonates’. Electronic searches were supplemented by hand-searching the reference lists of previous systematic reviews. The search was restricted to trials published in English.

1. Polyenes

The polyene macrolide class includes amphotericin B deoxycholate (AmB) and newer lipid-based formulations: amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (L-AmB). Although these agents are among the oldest class of antifungals and are associated with frequent toxicity, they still play a major role in the treatment of IFD in children [7]. The biggest advantage of polyenes is their wide spectrum of activity.

1.1. Amphotericin B Deoxycholate

By binding ergosterol, a component of the fungus cell wall, AmB increases membrane permeability and induces cell death [8, 9]. In vitro fungicidal activity has been demonstrated against a wide spectrum of fungi, including *Candida* sp., *Aspergillus* sp., *Zygomycetes*, and

dimorphic fungi [10]. Although occasional resistance has been reported for multiple fungi species, clinically significant resistance is rare and is mostly encountered in *A. terreus, C. lusitaniae, Trichosporon* sp., *Scedosporium* sp., and *Fusarium* sp. [11-14].

AmB activity is concentration-dependent with a prolonged post-antifungal effect (PAFE>12h) [15]. In vitro, its fungicidal effect was observed when maximum concentration (Cmax) was 4 times greater than minimum inhibitory concentration (MIC) for *C. albicans*, whereas in candidiasis murine models, maximal activity occurred at Cmax:MIC of 2.4 [10, 16, 17]. In vitro susceptibility testing has been correlated with clinical outcome in adults with invasive aspergillosis, but no correlation was established in adults with invasive candidiasis [18, 19]. No PK/PD indices are validated in children.

Due to poor oral absorption [20], systemic AmB is administered parenterally. AmB circulates in plasma highly bound to lipoproteins and is taken up by reticulo-endothelial organs, especially the liver [21]. In adults, cerebrospinal fluid (CSF) penetration is limited (2–4% of serum concentrations) [22]. Immaturity in the blood-brain barrier can lead to enhanced central nervous system (CNS) penetration in premature infants where CSF: plasma ratios can reach 40– 90% [23]. AmB is slowly excreted in urine and bile, and metabolism pathways are not well defined [21]. PK in children is characterized by a lower volume of distribution (V) (0.4–3.1 L/kg) and faster clearance (CL) (0.03–0.22 L/kg/h) compared with adults (V: 4L/kg; CL: 0.03 L/kg/h) (Table 1) [23-27]. Although most PK studies in children support a dosage regimen of 0.5–1 mg/kg/day [23-25, 27], a population PK analysis suggested that younger children might be underexposed with 1 mg/kg/day while older children may be overdosed at the same regimen [26].

Similar to adults, AmB use in children is associated with infusion-related toxicities (fever, chills rigors), nephrotoxicity, and electrolyte disturbances [25]. AmB is often believed to be better tolerated in children than in adults due to decreased number of co-morbidities and comedication. However, in infants, renal toxicity rates vary across studies from 0 to 44% whereas a rate of 53% was described in adults with invasive aspergillosis [28-31]. On the other hand, up to 50% of adults experience fever during infusions whereas this toxicity is rarely described in infants [28, 30, 32].

1.2. Lipid-based Amphotericin B Preparations

Lipid-associated formulations have the same mechanism of action and antifungal spectrum as AmB, but higher dosages are required for equivalent antifungal efficacy in vitro and in animal models [33-35]. In a murine candidiasis model, AmB was 5–8-fold more potent than L-Amb and ABLC in the kidneys [33]. Nonetheless, in adults with hematologic malignancies, no difference in therapeutic efficacy has been demonstrated between the 2 formulations [36, 37]. In a cohort of children (median age 7 years) with proven IFD caused by *C. albicans*, *Aspergillus* sp., or *Scedosporium* sp., Cmax:MIC was statistically higher in children with a complete response compared with children with partial response (median Cmax:MIC of 68 vs. 40, p=0.02) [38]. Other than in this small cohort, no further correlation between PK and PD has been established in children.

Compared with AmB, the newer lipid-based formulations have different pharmacological properties. ABLC at a dosage of 2.5 mg/kg/day showed a lower Cmax (2.1 mg/L) and faster CL (0.218 L/kg/h) than conventional AmB in children with invasive candidiasis (Cmax of 2.9 mg/L and CL of 0.040 L/kg/h after dosing of 1–1.5 mg/kg/day of AmB) [24, 39]. ABLC was also investigated in neonates with invasive candidiasis (age 8–89 days; gestational age [GA] of 24–41 weeks), showing a clearance rate at the upper range of adults values (0.4 L/kg/h) [40, 41]. This neonatal population analysis led to dosing recommendations of 2.5–5 mg/kg/day (Table 2). In contrast to ABLC, a population PK study of L-Amb in 39 children (age 0.2–17 years) revealed a higher Cmax (11.4–44.2 mg/L) compared with similar AmB (Table 1) [38]. In this study, LAmB also had a lower V and CL, presumably due to a slower tissue distribution [38]. PK estimates for each of these lipid-based formulations were nonetheless comparable to adult values. No published data were found on ABCD PK in children.

There have been concerns that amphotericin lipid formulations penetrate kidneys and CNS at a lesser extent than AmB [42]. For infants, this characteristic is of special interest because *Candida* commonly disseminates in those two compartments. In animals, *Candida* kidney infection models showed decreased penetration and potency of lipid formulations compared to AmB [33, 42]. Despite these findings, neonates treated with ABLC demonstrated urine amphotericin concentrations higher than the MIC of many *Candida* isolates [41]. In the CNS, studies in animal models demonstrated that AmB and L-AmB had higher penetration than ABLC and ABCD, consistent with clinical findings in which neonates treated with ABLC had low or undetectable amphotericin concentrations in CSF [41, 43]. The clinical significance of these findings is not well established. The largest comparative effectiveness study between AmB and lipid-formulation in infants consisted of a cohort study (730 infants, <120 days old) in which there was increased mortality and therapeutic failure with lipid-formulations compared with AmB [44]. These findings are consistent with lower lipid products penetration to the kidneys and CNS in animal models, but this observational study failed to adjust for renal function and other clinical data and these results could also be due to confounding by indication.

In terms of safety, the lipid-based formulations offer the advantage of reduced toxicity compared with AmB, with the exception of ABCD for which the frequency of infusion-related symptoms in adults is similar [45]. In infants, uncontrolled studies demonstrated favorable safety for L-Amb with mild increases in liver enzymes (0–37%) and serum creatinine (0–5%), and decrease in potassium (0–5%) [46-49]. No serious AEs were reported in those studies For ABLC, 2 large safety studies were conducted in children [50, 51]. The first study involved 111 children (21 days –16 years) who received ABLC at a dosing of 5 mg/kg/day and demonstrated no drug-related adverse events [50]. The second involved 548 children (0–20 years) who received 5 mg/kg/day of ABLC and showed an increase of serum creatinine of 2.5x baseline in 8.8% of children [51].

Given extensive clinical experience with AmB and broad-spectrum activity, amphotericin B compounds are widely used for IFD therapy in pediatric populations. Lipid-based formulations PK data are limited in infants, and there are concerns of insufficient penetration in the urinary tract and CNS in this population [44]. As a result, AmB is

generally the first line polyene agent in young infants unless urine infection and meningoencephalitis are excluded. Further comparative data on efficacy and safety of AmB vs lipid-based formulations are needed in infants. Appropriate plasma concentrations have not been defined for safety and efficacy, and therapeutic drug monitoring (TDM) is therefore not recommended.

2. Triazoles

Triazole agents inhibit the cytochrome P450 (CYP) that synthesizes ergosterol, which is a major cell membrane component of most fungi [52]. This mechanism of action inhibits cell growth and replication. In humans, because triazole agents are inhibitors of CYP enzymes (particularly CYP3A4), this class is prone to significant drug-drug interactions. Despite this characteristic, clinical efficacy of triazoles has been demonstrated for the prophylaxis and treatment of many IFD.

2.1. First-generation Triazoles

Fluconazole and itraconazole constitute the first generation in this class. They are active against *Candida* sp., *Cryptococcus neoformans*, and dimorphic fungi. Exceptions include *C. glabrata* and *krusei*, which are often resistant to fluconazole (MIC_{90} of 32 mg/L and 64 mg/L, respectively) [53]. Only itraconazole provides coverage of *Aspergillus* sp. Both agents are available as oral and parenteral formulations.

2.1.1. Fluconazole—Fluconazole exhibits in vitro fungistatic activity [54], which does not correlate well with concentration and is more dependent on duration of exposure (time-dependent). In vivo infection models demonstrated that a ratio of area under the concentration-time curve (AUC) over MIC (AUC:MIC) of 18 was associated with 80% survival in the murine candidiasis models [55, 56]. In adults with *Candida* infection, a ratio (AUC: MIC) <11.5, and MIC≤64 mg/L were associated with increased mortality or therapeutic failure [57, 58]. For a *Candida* sp. with an MIC of 32 mg/L, AUC:MIC >12 corresponds to an $AUC_{0\text{-}24}$ of 400 mg*h/L, which is often cited as the exposure target for adults. In immunocompromised patients and premature infants, an $AUC_{0\text{-}24}$ of 800 mg*h/L is typically targeted, probably to cover a broader range of *Candida* spp. MICs. In children, there is no established relationship between PK and PD, and exposure target is usually extrapolated from adults ($AUC_{0\text{-}24}$ from 400–800 mg*h/L).

Fluconazole has high oral bioavailability (92%) [59]. Consistent with its low protein-binding, fluconazole shows good penetration into tissues and body fluids, especially in the urine, and concentrations in CSF achieve 80% of blood levels [60, 61]. Fluconazole does not undergo significant metabolism and is predominantly excreted unchanged in urine. After filtration, fluconazole is highly reabsorbed by the kidney [62]. Dosing should be reduced in subjects with renal impairment; however, continuous renal replacement therapy might result in lower concentrations than expected because of the lack of renal reabsorption in this setting [63].

In neonates, a population PK model developed with a cohort of 55 infants <120 days of age (23–40-week-gestation) revealed the importance of gestational age and postnatal age in

fluconazole disposition [64]. Based on this PK model, simulations predicted that a daily dose of 12 mg/kg in infants <30 weeks of gestation achieved a median 24h-AUC close to the target of 800 mg*h/liter, whereas infants >30 weeks of gestation achieved a lower median 24h-AUC of 400 mg*h/L [64]. In contrast, dosing of 6 mg/kg daily in adults is sufficient to achieve a 24h-AUC of 400 mg*h/L in more than 85% of the subjects [57]. In the population PK model involving infants described above, fluconazole achieved steady state therapeutic AUC in 5-7 days [64]. As a result, administration of a loading dose has been suggested in vulnerable populations such as infants [7]. In a small cohort of 10 infants < 60 days old, a fluconazole loading dose of 25 mg/kg was safe and achieved the therapeutic target more rapidly than traditional dosing which may lead to decreased morbidity [65].

Beyond the neonatal period, the PK in children is characterized by a higher CL (0.030 L/kg/h) and a larger V (0.95 L/kg in children aged 2–12 years) compared with adults (CL of 0.016 L/kg/h and V of 0.7 L/kg) as demonstrated in a study involving 100 children (ages 0–18 years) (Table 1) [60, 66]. Consequently, children require a proportionately higher dose to match adult exposures. Finally, although limited, assessment of oral absorption after 2 years of age suggested similar bioavailability as adults (>80%) [66].

Fluconazole is a potent inhibitor of CYP2C9 and CYP3A4 leading to increased plasma concentration of other drugs metabolized by those metabolic enzymes when co-administered with fluconazole. Such compounds include tacrolimus or cyclosporine, which are commonly used in the pediatric population at high risk for invasive fungal infection [67]. Beside safety concerns related to drug-drug interactions, fluconazole is well tolerated in children as evidenced by a safety analysis in 562 children (0–17 years of age) following oral and intravenous administration [68]. The most common treatment-related adverse events (AEs) were gastrointestinal symptoms (7.7%) and skin rash (1.2%). In this study, overall, 18 of 562 children (3.2%) discontinued fluconazole due to AEs [68].

Fluconazole is widely used for the prevention and treatment of invasive candidiasis in children and infants. It is also used for treatment and secondary prophylaxis of cryptococcal meningitis. PK and safety are well defined across a wide age range. Moreover, its reliable penetration into CSF and the urinary tract makes fluconazole a useful agent against neonatal invasive candidiasis [69, 70]. Children generally require higher dosing per unit of weight to match adult exposure. However, target exposure is extrapolated from adults, and age-specific PD indices have not been established.

2.1.2. Itraconazole—Similar to fluconazole, itraconazole is fungistatic against yeast-like fungi [71], while only itraconazole has fungicidal activity against molds [72]. Given the time-dependent PD demonstrated for both yeasts and *Aspergillus* sp. [71, 73], separating the daily dose in 2 appears more appropriate (Table 2) [74]. PD modeling revealed that AUC:MIC, Cmax:MIC, and minimum plasma concentration (Cmin):MIC equally correlated with antifungal efficacy for the treatment of oropharyngeal candidiasis in human immunodeficiency virus (HIV)-infected children [74].

Itraconazole circulates in blood highly protein-bound and undergoes extensive hepatic metabolism into several metabolites. One of those metabolites, hydroxyl-itraconazole, has

similar activity to the parent drug. Itraconazole is excreted through the liver and kidneys. Oral absorption is variable, but acidic gastric environment, food, and administration in oral solutions enhance its absorption [75]. Dosing of 5 mg/kg/day with oral solution results in lower exposure in children compared with adults (mean AUC_{0-24} of 8.7 mg.h/L vs. 22.7 mg.h/L, and mean Cmax of 0.6 mg/L vs. 1.5 mg/L) [76, 77]. These differences were not found with lower dosing (2.5 mg/kg/dose twice a day), which produced similar exposure in adults and children [78]. These findings highlight the non-linearity of itraconazole's PK profile and the possible dose-dependent bioavailability. PK parameters in children >5 years of age are otherwise relatively similar to adults [74, 76, 79].

Itraconazole is well tolerated in children, and the most commonly reported AEs are gastrointestinal symptoms (8–12%) [74, 80]. In adults, trough concentrations above 17 mg/L (measured by bioassay) are significantly associated with toxicity (mainly fluid retention and gastrointestinal symptoms) [81]. The main safety concern for itraconazole is the potential for drug-drug interactions due to inhibition of CYP3A enzymes [82]. Co-medication with itraconazole may result in increased plasma concentration of drugs metabolized by CYP3A4 enzymes, such as cisapride or oral midazolam [83]. Enhanced vincristine neurotoxicity is a well-documented drug interaction with itraconazole in both adults and children [84, 85]. In a retrospective study of 20 children with acute lymphoblastic leukemia, those receiving vincristine in combination with azole treatment (predominantly itraconazole) experienced significantly more peripheral neurotoxicity ($p<0.05$) [85].

Itraconazole use is limited in children due to erratic, dose-dependent oral bioavailability, high PK variability, and the availability of more reliable alternatives [86]. Given an established target trough concentrations in adults, TDM is standard practice (target trough concentrations >0.5 mg/L when measured by HPLC [57] and <17 mg/L when measured by bioassay [81]). No age-specific target concentrations have been identified in children.

2.2. Second-generation Triazoles

Second generation triazoles are active against a wide spectrum of clinically important fungi including yeast, molds, and dimorphic fungi. Members of this class of triazoles include voriconazole, posaconazole, and newer compounds such as ravuconazole.

2.2.1. Voriconazole—Voriconazole is available in oral and intravenous formulations and is the primary therapy for invasive aspergillosis. It is structurally similar to fluconazole but has extended antifungal spectrum against *Aspergillus* sp. Despite its broad-spectrum activity against yeast and molds, voriconazole is not active against zygomycetes [12, 87]. In vitro, fungicidal and fungistatic activity against *Aspergillus* sp. and *Candida* sp., respectively, are time-dependent [88, 89]. Near maximal effect against *Candida* sp. was observed at concentrations 3 times the MIC at different time points [89]. In murine candidiasis models, AUC: MIC was strongly predictive of treatment success with a suggested target of free concentration AUC_{0-24}:MIC of 20 [90]. Consistent with voriconazole time-dependent effect, Cmin >1-2 mg/L was a good predictor of successful clinical outcome in both adults and children [91, 92]. In children, Cmin <1 mg/L was associated with increased odds of death (odds ratio [OR] 2.6; 95% confidence interval [CI] 1.6, 4.8) [91].

Voriconazole is 58% protein-bound, distributes well into tissues and CSF [93, 94], and is extensively metabolized by hepatic CYP2C19. Allelic variations contribute to high inter-subject PK variability in adults and children [95, 96]. In contrast to adults, children have a linear PK at dosing of 3–4 mg/kg intravenously (IV) [97]. Elimination becomes nonlinear over the range of 4 mg/kg to 8 mg/kg every 12 hours [98]. Children <12 years of age have greater clearance of voriconazole and require almost twice the dose to match adult systemic exposure (7–9 vs. 4 mg/kg IV twice a day) [95, 98, 99]. Children also have a lower oral bioavailability than adults (45–65% vs. 96%) [95, 98]. This difference is not completely understood but may relate to greater first-pass metabolism in children.

Voriconazole side effects include visual disturbances; elevated hepatic transaminases, and skin photosensitization (13–30%) [97, 98, 100, 101]. In adults, trough concentrations above 4–5.5 mg/L correlate with toxicity [6, 102, 103]. In a small pediatric cohort, oral administration of more than 6 mg/kg/dose twice a day was associated with an increased risk of phototoxic skin reactions, but no correlation was described with trough concentrations [101]. For other forms of toxicity, no relationship to exposure has been determined in children [104].

Multiple pediatric PK studies recently helped determine optimal dosing in children down to 1 year of age, but voriconazole currently has European Medicines Agency (EMA) and Food and Drug Administration (FDA) labeling for children over 2 and 12 years of age, respectively [105, 106]. In infants, PK and safety still need to be characterized, and voriconazole use is discouraged in this population. Efficacy has been well established in adults with aspergillosis, and it is the primary recommended therapy for invasive aspergillosis [107]. TDM is recommended, given a high inter-subject variability, and has proven useful in adults for which a randomized controlled trial showed better outcome and reduced toxicity with target Cmin between 1 and 5.5 mg/L [108]. In children, Cmin≥1 mg/L was also retrospectively associated with decreased mortality from IFD, but as opposed to adults, no upper bound of target trough concentration has been identified, and this question warrants further study [91].

2.2.2. Posaconazole—Posaconazole has broad antifungal activity against the majority of yeasts and azole-resistant *Candida* sp. In addition to *Aspergillus* sp., posaconazole is also active against other molds, including zygomycetes, as opposed to voriconazole. Similar to other triazoles, posaconazole is fungicidal in vitro with time-dependent killing against most Candida species and molds [63, 75]. In animal models, the duration of exposure to plasma concentrations above the MIC is the most important parameter for optimum efficacy [109].

Posaconazole is only available as an oral formulation and should be taken with high-fat meals to enhance absorption [110]. Protein-binding is high, and the primary route of elimination is through feces with renal clearance playing a minor role [111]. Posaconazole prophylaxis and treatment have been described in children, but the PK is not well characterized. No specific dose recommendations exist, and its use in children is off-label [112-115]. A twice-daily dosing algorithm based on allometric scaling (body weight-based) delivered adequate exposure in 12 children with chronic granulomatous disease (mean trough concentration of 1.54 mg/L) [115]. In adults, the PK is linear, and the long half-life

(25 hours) produces stable plasma concentrations over time [110]. Steady-state concentrations are achieved 7–10 days after initiating therapy, suggesting that this agent might be suboptimal for induction therapy or a loading dose may be required. Posaconazole is well tolerated, and the most common side effect is gastrointestinal symptoms in 25% of patients [113, 114].

Exposure-response relationship analyses in adults suggest the need for TDM with a target trough concentration of 0.5 mg/L to 1 mg/L for prophylaxis and therapy, respectively [116, 117]. There is no correlation between exposure and toxicity [116].

Posaconazole PK/PD in children is scarce and needs better characterization. It is not licensed for use in children under 12 years of age by regulatory agencies [17, 35]. An ongoing trial will address posaconazole dosing in children (NCT01716234). Availability of an intravenous formulation will attract interest from the pediatric community; however, PK studies will need to be conducted to evaluate optimal dosing in children.

2.2.3. Other Triazoles—Ravuconazole, isavuconazole, and albaconazole are the newest antifungal triazoles with in vitro and in vivo fungicidal activity against a wide spectrum of clinically important fungi. They are active against *Candida* sp. including fluconazole-resistant strains, *Cryptococcus* sp., and *Aspergillus* sp. [90, 118-121]. Activity against *Fusarium* sp., *Scedosporium* sp., and *Mucor* sp. remains limited [53, 121, 122]. Similar to other triazoles, animal models show that antifungal efficacy is time-dependent [90, 123]. All 3 agents are available orally and have high oral bioavailability, but only ravuconazole and isavuconazole are available intravenously [124, 125]. Clinical experience is still limited in adults, but PK studies reveal a prolonged half-life from 75– 117 hours [124, 126, 127]. These new triazoles are well tolerated, and the most frequently reported AEs are headaches, rhinitis, and gastrointestinal symptoms [124, 126, 127]. No clinical trials have been completed in children, and so these agents are not currently recommended.

3. Echinocandins

Agents from the echinocandins class are only available in parenteral form and include micafungin, caspofungin, anidulafungin and the more recent aminocandin. They act by inhibiting (1,3)-β-D-glucan synthase, a fungus-specific enzyme crucial to the biosynthesis of glucan in the fungal cell wall [128]. They exhibit fungicidal activity against most *Candida* spp, including fluconazole-resistant species (C. albicans, C. parapsilosis, C. glabrata, C. tropicalis, and *C. krusei*) and fungistatic activity against *Aspergillus* sp. [129, 130]. Echinocandins are not active against *Cryptococcus neoformans*, zygomycetes, and dimorphic fungi. Advantages of echinocandins include low toxicity and minimal drug interactions due to the fungus-specific mechanism of action. Disadvantages include the lack of oral formulation and the reduced activity against non-Candida species.

3.1. Micafungin

Micafungin displays concentration-dependent fungicidal killing, and in animal models, efficacy correlates best with AUC:MIC ratios [131]. Analysis of adult clinical data for the treatment of invasive candidiasis found that an AUC:MIC ratio over 3,000 predicts better

mycological response [127]. In neonates who are at greater risk of meningoencephalitis caused by *Candida* sp., a different exposure target (AUC_{0-24} =166.5 mg*/L) has been proposed based on a rabbit model of neonatal hematogenous *Candida* meningoencephalitis [132].

Micafungin is highly bound to protein and distributes well into tissues including lung, liver, and spleen. Although penetration into the CNS and eye are generally limited in adults, high-dose micafungin successfully treated neonatal animal models of hematogenous *Candida* meningoencephalitis [132, 133]. Micafungin undergoes only limited phase 1 metabolism, and the parent drug is mostly excreted via the biliary system [134].

Micafungin PK is well described in pediatric patients aged 4 months to 16 years, and 229 patients were included in population PK analyses in support of recent U.S. pediatric labeling [135]. The half-life is approximately 12 hours, and the PK is linear at doses of 1–3 mg/kg [136]. Several PK studies show an age effect demonstrated by an inverse relationship between weight and CL, such that as body weight decreases, higher dosages of micafungin (on a mg/kg basis) are required to achieve equivalent drug exposure [137]. In a study of 77 neutropenic children, doses of 3–4.5 mg/kg/day for 2–8-year-olds and 2–3 mg/kg/day for 9–17-year-olds achieved adult exposure [138].

Four PK studies demonstrated that younger infants (GA of 24–40 weeks and postnatal age of 2–119 days) have higher clearances and therefore need higher dosing than children and adults [123, 126, 139, 140]. Moreover, this population requires reliable micafungin CNS penetration because of a higher risk of *Candida* meningoencephalitis. Based on a population PK model, PK simulation analyses showed that 83% of neonates receiving 10 mg/kg/day would achieve an AUC0-24h of 166.5 mg*/L, a specific target for neonatal *Candida* meningoencephalitis [125, 132]. These preliminary PK/PD analyses led to the dose selection for an ongoing phase 3, randomized controlled trial comparing micafungin to amphotericin B deoxycholate (NCT00815516).

Pooled data from 6 pediatric studies show that micafungin has a favorable safety profile [141]. The most common treatment-related AEs are transient and include liver enzyme elevations and decreased potassium (3%) [141]. In a trial comparing micafungin and L-Amb in 106 children with invasive candidiasis, both drugs had equivalent efficacy, but micafungin was better tolerated [142]. No maximum tolerated dose has been identified, and high doses of 15 mg/kg have been safely used in premature neonates [140].

Overall, micafungin dosing is well-defined in children, and regulatory agencies have labeled its use in the pediatric population [143, 144]. The EMA product license includes dosing of 2 mg/kg/day for all children <16 years of age, including neonates. On the other hand, the U.S. FDA product label includes dosing of 2 and 3 mg/kg/day in children <30 kg for treatment of invasive candidiasis and esophageal candidiasis, respectively. Unlike EMA, FDA label restricts its use to children ≥ 4months of age. For infants ≤ 3 months, PK studies and age-specific exposure targets suggest that dosing up to 10 mg/kg/day are required. Clinical efficacy and safety data with newly proposed dosing in this population needs further evaluation.

3.2. Caspofungin

Caspofungin is recommended for therapy of invasive candidiasis, salvage therapy of invasive aspergillosis, and as empirical therapy in febrile neutropenia in children >3 months of age. It demonstrates in vitro fungicidal activity against *Candida* sp. with a concentration-dependent effect and prolonged PAFE (12 hours) [15, 75, 145]. In vitro PD properties suggest optimal killing when concentration is 4x the MIC [145, 146]. Murine candidiasis models demonstrate reduced activity against *C. parapsilosis* and *C. guillermondii*. The clinical significance of this reduced activity is unclear, but clinicians should be aware of the possibility of reduced efficacy. Caspofungin is generally classified as fungistatic against Aspergillus sp, however, evidence of killing in vitro was shown by change in cells staining pattern but this phenomenon did not translate into reduction in the number of CFU from standard killing curve measurements [147]. In a PK trial of 32 children aged 3 months to 17 years with confirmed or suspected IFD (*Candida* sp. and *Aspergillus* sp.), the exposure-response analyses revealed no association with clinical outcome and PK/PD parameters [148].

Caspofungin is metabolized by the liver with a half-life of 7–10 hours and demonstrates linear PK in children.[149, 150] Similar to other agents in this class, caspofungin urine concentrations are low [151]. However, this poor renal penetration has not translated into treatment failure of candiduria in adults [152]. Specific to caspofungin, weight-based dosing does not provide consistent steady-state concentrations across ages, whereas dosing based on body surface area does [150]. In infants and children with neutropenia, 50 mg/m^2/day dosing produces systemic exposures similar to adults receiving 50 mg/day [149, 150]. In young infants, although the PK has not been fully characterized, a study involving 18 infants <3 months old with suspected invasive candidiasis showed that 25 mg/m^2/day was required to achieve adult plasma levels [153].

Dose-limiting toxicities have not been seen in adults [154]. Multiple clinical trials in children found that caspofungin is well tolerated; fever, rash, hypokalemia, and elevated liver enzymes are the most frequently reported AEs but do not usually require therapy discontinuation [148, 150, 153, 155, 156]. The incidence of AEs does not correlate with concentration [148]. In young infants, safety data are limited to 2 small cohorts (total N=22) in which AEs were described without a comparator group [157, 158].

Caspofungin is recommended for pediatric IFD and is particularly useful against invasive candidiasis caused by azole-resistant isolates. Its PK has been adequately characterized in children down to 3 months of age. However, PK, safety, and efficacy are inadequately defined in young infants [157, 158].

3.3. Anidulafungin

The spectrum of anidulafungin activity is wide with fungicidal effect against *Candida* sp. including fluconazole-resistant strains, and fungistatic effect against *Aspergillus* sp. [118, 159-161]. Fungicidal activity was demonstrated in neutropenic murine models for which both Cmax:MIC and AUC:MIC ratios strongly predict successful treatment of systemic

candidiasis [162]. In *Aspergillus* animal models, anidulafungin therapy reduces *Aspergillus* antigenemia but is unable to clear the infection, consistant with its fungistatic activity [118].

Anidulafungin is highly protein-bound (>99%) but achieves tissue concentrations above MIC in animal models [51]. Anidulafungin demonstrates linear PK and a longer half-life than other echinocandins (20 hours) [163]. It has a unique elimination pathway among the echinocandins, consisting of slow, non-enzymatic degradation to inactive metabolites. When anidulafungin is given at the same weight-adjusted dose (1.5–3 mg/kg loading dose, 0.75–1.5 mg/kg/day maintenance dose), children 2–17 years old with neutropenia achieve exposures similar to adults [163]. In infants and neonates, 1.5 mg/kg/day produces plasma concentrations comparable to adults [164]. Both prior PK trials demonstrate that anidulafungin is well tolerated with no observed drug-related serious AEs.

Despite available PK data and a favorable safety profile demonstrated in 2 pediatric trials, clinical experience in children remains insufficient to recommend it for use in this population. Anidulafungin is not labeled for children under 16 years in the U.S and <18y in Europe [165, 166].

3.4. Aminocandins

Aminocandin is the newest echinocandin and is available as an intravenous formulation. Similarly to other agents of this class, it is active against *Candida* sp. and *Aspergillus* sp. in vivo [167, 168]. Fungicidal effect against *Candida* sp. best correlates with peak:MIC demonstrating a concentration-dependent activity [168]. Animal models suggest that extended dosing interval (7– 10 days) is effective as treatment and prophylaxis of invasive candidiasis [169]. In healthy volunteers, a phase 1 study also demonstrated a long half-life (48–58 hours) indicating that dosing could be less frequent than once a day [135]. In this small cohort, aminocandin was well tolerated, but no other clinical trials have been published in adults or children.

3.5. Second generation echinochandins

ASP9726, a novel second generation echinocandin is under development. As opposed to other echinocandins, ASP9726 showed *Aspergillus* hyphal growth inhibition and improved MIC against *Candida parapsilosis* and echinocandin resistant-*Candida* in vitro [170]. To our knowledge, no ASP9726 clinical trials have been registered in clinicaltrials.gov at the time of submission.

4. Nucleoside Analogs

5-Flucytosine (5-FC) is an antimetabolite drug that causes RNA miscoding and inhibits DNA synthesis [171]. 5-FC has activity against *Candida* sp. and *Cryptococcus neoformans* [172, 173]. In vitro and in vivo testing demonstrates that flucytosine is fungistatic against yeasts with concentration-independent pharmacodynamics [174, 175]. Moreover, 5-FC exhibits PAFE up to 10 hours [176]. It is never used as monotherapy given rapid emergence of resistance. Its use is limited for the induction therapy of cryptococcal meningitis for which 5-FC in combination with AmB was shown to be efficacious [177].

Only the oral formulation is available in the United States. Oral bioavailability is high in adults (75–95%), and a trial comparing IV and oral 5-FC in adults with HIV-associated cryptococcal meningitis did not detect a difference in fungicidal activity [178]. Protein-binding is negligible, and distribution into tissues and body fluids is reliable. 5-FC is mainly eliminated in active form in urine. The elimination half-life is 3–5 hours, and administration in 3–4 daily doses is required [179]. Data on 5-FC PK in children are limited, but drug clearance appears slower in children compared with adults [23, 180]; as a result, the adult dose of 100 mg/kg/day might lead to overexposure. In addition, the elimination half-life in neonates is nearly twice as long as in adults (4 hours vs. 7 hours) [23, 180], suggesting that the dosing interval should be longer (8 hours to 24 hours).

Dose-limiting toxicities described in up to 44% of adults (hematologic, gastrointestinal, and hepatic) limit the use of 5-FC [181, 182]. Safe target plasma concentrations in adults are established at 40–60 mg/L, but no such data are available for children [181].

Given the narrow therapeutic window, TDM is standard of care for 5-FC with target peak concentrations of 20–50 mg/L [183]. However, target concentrations have not been established in children. Concentration-independent PD suggests that lower dosages could be considered in future research. Clinical use of 5-FC is limited mainly to combination therapy with AmB for the treatment of cryptococcal meningitis. Because of limited PK, safety, and efficacy data, the use of 5-FC in infants is discouraged.

5. Novel Antifungals Agents under development

Two antifungals agents are under development and would each represent a new class of antifungals. T2307, a novel arylamidine showed in vitro and in vivo activities against *Candida* species, *Cryptococcus neoformans*, and *Aspergillus* species [184].The second agent is kakeromycin, which demonstrated good in vitro activity against the same fungal pathogens than T2307 [185]. For those 2 potential antifungal drugs, no clinical data are available thus far.

Conclusion

Effective and safe antifungal therapy depends on optimal drug dosing. With the recent development of new antifungal therapies, specific data in children are needed because prior extrapolations of adult dosing to children have often proved wrong. Thanks to regulatory initiatives and suitable trial designs, the number of PK studies in children has increased and clarified some dosing issues in this vulnerable population. Based on our review of the literature, we present a summary of antifungal dosing recommendations in Table 2. Whenever dose ranges are presented, clinicians should consider the benefits of early initiation of high dose therapy in improving outcomes in the setting of severe IFD.

Despite better evidence on antifungal therapy, morbidity and mortality related to IFD remain unacceptably high and dosing should be optimized, especially in infants. Future research should focus on determining drug disposition of newer antifungals such as newer triazoles and echinocandins in children as they become available for adults. Future research questions should also relate to optimize dosing of older agents such as fluconazole in neonates for

which there is a need to better support the use of a loading dose. We also need better comparison of safety and effectiveness of AmB and lipid formulations of amphotericin B in infants. Finally, clinical validation of PK/PD indices determined in animal models are sparse in humans, even more so in children. Ongoing efforts to characterize the PK and PD of antifungal agents, especially in younger populations, will help inform dosing and improve clinical outcomes of IFD.

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Key Points

- Antifungal pharmacokinetics in children frequently differ from adults, necessitating dosing adjustment to match adult exposure.
- Antifungal target plasma concentrations are still largely extrapolated from adult data; therefore, pharmacokinetics/pharmacodynamics indices specific to children must be better defined.

Table 1

Summary of pharmacokinetic and pharmacodynamic parameters

References	Route of elimination	Protein binding	Bio-availability	N	Age	Dosage	AUC_{0-24}[a] (mg*h/L)	Cmax (mg/L)	Half-life (h)	CL (L/kg/h)[b]	V (L/kg)[b]	PK/PD end point
AmphotericinB												
[10, 17, 23-27, 106, 167, 186]	Kidney; possible metabolic pathway unknown	NR	NR	13	0–2 m GA 24–40 wk	0.5 mg/kg IV q24h	NR	1.0 (0.5–4.0)	15 (5–82)	1 (0.46–4.34)/1.73m^2	1.5 (0.1–17.5)	C_{max}:MIC
				91[c]	3 wk – 18 y	0.25–1 mg/kg IV q24h		2.9	7–63	0.020–0.828	0.4–9.4	
		>90%	<5%	22	Adults	0.6–1 mg/kg IV q24h		0.5–2	24h – 15d	0.02–0.03	4.0	
Liposomal Amphotericin B												
[38, 187, 188]	Kidney; possible metabolic pathway unknown	>90%	NR	12	3 y (0.3–9)	10 mg/kg IV q1 week	AUC_{inf}: 255.3[d]	3.0	56	0.059	4.2	C_{max}:MIC
				39	7 y (0.2–17)	0.8–5.9 mg/kg IV q24h	NR	11.4–44.2[e]	7[f]	0.020	0.2	
				44	Adults 43 y	7.5–15 mg/kg IV q24h	692–554	76–105	6–10.5	0.02	0.2–0.3	
Amphotericin B Lipid Complex												
[39, 143, 183]	Kidney; possible metabolic pathway unknown	NR	NR	28	27 d (8–89) GA 24–41 wk	2.5–5 mg/kg IV q24h	NR	NR	395	0.420	11.1	C_{max}:MIC
				6	10 y (4–17)	2.5 mg/kg IV q24h	11.9	2.1	NR	0.218	NR	
				48	Adults	0.6–5 mg/kg IV q24h	3.29–15.26	0.9–2.7	8–187	0.114–0.408	20.7–131	
Fluconazole												
[60, 64-66, 85, 122]	Kidney			63	1–88 d GA 23–40 wk	3–12 mg/kg IV q24h	347–496	NR	26–80	0.008–0.022	0.9–1.5	AUC_{0-24}: MIC

References	Route of elimination	Protein binding	Bio-availability	N	Age	Dosage	AUC_{0-24}[a] (mg*h/L)	Cmax (mg/L)	Half-life (h)	CL (L/kg/h)[b]	V (L/kg)[b]	PK/PD end point
		NR	NR	88	2–16 y	2–8 mg/kg IV q24h	AUC_{inf} 73.9–230.9[c]	NR	21–22	0.022–0.037[g]	0.7–0.95	
		12%	90%	400	Adults	100–400 mg PO q24h	76.8[h]	4.1–8.1	30	0.01	0.7	
Itraconazole												
[74, 76, 78, 79, 83]	CYP3A4 (main)	NR	NR	25	0.5–5 y	2.5 mg/kg PO q12h 5 mg/kg PO q24h	6.9–16.1	0.5–1.0	31–47	0.714[i]	NR	AUC:MIC C_{max}:MIC C_{min}:MIC
				44	5–18 y	2.5 mg/kg PO q12h 5 mg/kg PO q24h	7.1–23.0	0.6–1.5	28–104	0.601–0.073	5.1–15.5	
		99.8%	55%	32	Adults	100 mg PO q24h 200 mg PO q12h	5.3–39.3 AUC_{0-12} 22.6	0.4–2.3	34–64	0.326[i]	11.4[i]	
Voriconazole												
[62, 97, 98, 189-191]	CYP2C19, CYP2C9, CYP3A4	NR	44–91%	152	2–<12y	3–8 mg/kg IV q12h	4.7–162	1.48–19.2	3.1–29.2	0.142–0.348	1.8–1.9	AUC_{0-24}:MIC
				70	2–<12y	4–18 mg/kg PO q12h	1.70–203.0	0.51–18.0	NR	NR	NR	
			NR	26	12–17 y	LD: 6 mg/kg IV q12h MD: 4 mg/kg IV q12h	AUC_{0-12} 27.9 (6.24–95.3)	3.72 (1.71–9.99)	NR	0.143[g]	1.1[j]	
				22	12–17 y	300 mg PO q12h	AUC_{0-12} 18.7 (1.17–49.7)	2.84 (0.18–5.88)	NR	NR	NR	
		58%	96%	33	Adults	LD: 6 mg/kg IV q12h MD: 4 mg/kg IV q12h	37.6	4.6	NR	0.106 [g]	0.8[j]	

References	Route of elimination	Protein binding	Bio-availability	N	Age	Dosage	AUC$_{0-24}$[a] (mg*h/L)	Cmax (mg/L)	Half-life (h)	CL (L/kg/h)[b]	V (L/kg)[b]	PK/PD end point
				34		200 mg PO q12h	12.8	2.45		NR	NR	
Posaconazole												
[110, 112, 113, 115, 168]	Hepatic glucuro-nidation	NR		38	0.7–15.4 y	4–12 mg/kg PO q12h 800 mg/day PO in div doses	NR	NR	NR	NR	NR	AUC:MIC T>MIC
		>98%	8–47%	36	Adults	50–400 mg POq12h	8.3–73.1	0.4–4.2	20–31	0.147–0.199[k]	4.9–6.9[k]	
Caspofungin												
[87, 92, 148, 153, 192]	Hydrolysis, N-acetylation	NR	NR	18	0–3 m	25 mg/m^2 IV q24h	NR	10.9–11.1		NR		NR
				10	3–24 m	LD: 70 mg/m^2 IV MD: 50 mg/m^2 IV q24h	131.2	17.6	8.8[kl]	0.367[m]	NR	
				35	2–11 y	50 mg/m^2 IV q24h	146.0	2.41	NR	NR	NR	
				33	12–17y	50 mg/m^2 IV q24h	117	12.9	11.2 [l]	0.344[m]	NR	
		97%	Poor	>120	Adults	50–70 mg/m^2 IV q24h	86.9–129.6	8.7–14.0	10	0.009	0.1	
Micafungin												
[119, 123, 125, 126, 138, 140]	Arylsulfatase catechol-*O*-methyltrans–ferase	NR	NR	43	2–119d GA 24–40 wk	0.75–15 mg/kg q24h	19–643.2	2.5–48.1	6.9–20.1	0.015	0.147	AUC$_{0-24}$: MIC
				73	2–17 y	0.5–4 mg/kg q24h	27.9–301.9	6.4–43.5	12.2–13.5	0.014–0.243	0.26–0.42	
		>99%	Poor	62	Adults	12.5–200 mg	11.9–210.6	1.1–22.6	12–20	0.014–0.021	0.23–0.33	
Anidulafungin												
[52, 105, 163, 164]	Chemical degradation			8	2-28 d GA 26-39 wk	LD: 3 mg/kg MD: 1.5 mg/kg q24h	30.4–108.9	2.2–6.7	NR	0.013–0.049	0.5–4.4	AUC:MIC C_{max}:MIC

References	Route of elimination	Protein binding	Bio-availability	N	Age	Dosage	AUC_{0-24}[a] (mg*h/L)	Cmax (mg/L)	Half-life (h)	CL (L/kg/h)[b]	V (L/kg)[b]	PK/PD end point
		NR	NR	7	50–451d GA 24–40 wk	LD: 3 mg/kg MD: 1.5 mg/kg q24h	30.3–278.0	2.2–14.9	NR	0.005–0.049	0.2–4.4	
				12	2–16 y	LD: 1.5–3 mg/kg MD: 0.75–1.5 mg/kg q24h	16.5–155.7	0.91–12.3	13.9–38.9	0.0094–0.0446	0.319–0.962	
				13	13–16y	LD: 1.5–3 mg/kg MD: 0.75–1.5 mg/kg q24h	31.8–134.1	3.1–8.66	12.0–38.9	0.0095–0.0311	0.163–0.803	
		>99%	Poor	225	Adults	LD: 100–200 mg MD: 50–100mg/kg q24h	42.3–111.8	3.6–8.6	26–52	0.013	0.474	
Flucytosine												
[23, 120, 178]	Kidney	NR	NR	13	2–55 d	25-100 mg/kg q24h	NR	27.7	7.4	2.052 L/h/1.73 m^2	1.1	AUC:MIC T_{tau}>MIC
		2.9–4%	78–89%	>64	Adults	25 mg/kg PO q4h–100 mg/kg q24h	576	70–80	2–5	0.096	1.4	

AUC=area under the concentration-time curve; **AUC_{0-24}**=area under the concentration-time curve from 0 to 24h; **AUC_{inf}**=area under the concentration-time curve from 0 to infinity; **AUC:MIC**=AUC over minimal inhibitory concentration ratio; **Cmax**=maximal concentration; **Cmin**=minimal concentration; **CL**=clearance rate; **GA**=gestational age; **IV**=intravenous; **LD**=loading dose; **MD**=maintenance dose; **MIC**=minimal inhibitory concentration; **N**=number of subjects, can be from multiple studies; **NR**=not reported; **PK/PD**=pharmacokinetics/pharmacodynamics; **PO**=oral; **q**=every; **T_{tau}**= time of dosing interval; **V**=volume of distribution.

[a] AUC0-24h unless specified otherwise.

[b] Adult parameters are weight-normalized dose for a standard adult's weight of 70 kg.

[c] One neonate (17 days old) is excluded with CL of 0.009 L/h/kg; V of 9.4 L/kg and t1/2 of 693 h.

[d] AUC 0 to infinity.

[e] Predicted Cmax based on a population pharmacokinetic model in 11 children.

[f] Half-life estimated based on the following equation: half-life=0.693*V/CL.

[g] Clearance estimated based on the following equation: CL=dose/AUC.

[h] AUC 0-24h after fluconazole oral dosing of 100 mg at steady state.

[i] Clearance and volume after IV administration.

[j] Volume estimated with the following equation: V=dose/Cmax after 7 days of treatment with 4 mg/kg IV q12h.

[k] Apparent clearance or volume of distribution.

[l] β-phase half-life.

[m] Clearance in l/h/m^2.

Table 2

Dosing recommendations of antifungal agents in children

Drug	Dosing			Therapeutic drug monitoring	References
	Neonates (0–30 days)	**Infants (31 days–2 years)**	**Children (2 years–17 years)**		
Polyenes					
Amphotericin B	0.6−1 mg/kg IV q24h	0.6−1 mg/kg IV q24h	0.6−1 mg/kg IV q24h	No	[23-27, 167]
ABLC	2.5−5 mg/kg q24h	Unknown	5 mg/kg IV q24h	No	[39, 50, 51, 183]
ABCD	unknown	Unknown	Unknown	No	
L-AmB	3-5 mg/kg q24h	3–5 mg/kg IV q24h	3–6 mg/kg IV q24h	No	[47-49, 193]
Triazoles					
Fluconazole	Loading dose 25 mg/kg 12 mg/kg q24h (3–6 mg/kg twice weekly for prophylaxis)	12 mg/kg IV q24h (3 mg/kg IV q24h for prophylaxis)	6-12 mg/kg IV or PO q24h (3 mg/kg q24h for prophylaxis)	No	[64-66]
Itraconazole	unknown	Unknown	2.5–5 mg/kg PO q12h (2.5 mg/kg PO q24h for prophylaxis)	Trough >0.5 mg/L[c]	[57, 74-76, 78]
Voriconazole	unknown	Unknown	7–9 mg/kg IV q12h[a] 200 mg PO q12h (2.5 mg/kg PO q12h for prophylaxis)	Trough 1.0-5.5 mg/L	[62, 91, 99, 190]
Posaconazole	unknown	Unknown	200–400 mg PO q6–12 h[b]	Prophylaxis : trough>0.5 mg/L[c] Treatment : trough >1 mg/L[c]	[168]
Ravuconazole **Albaconazole** **Isavuconazole**	unknown	Unknown	unknown	unknown	
Echinocandins					[148-150, 153, 155]
Caspofungin	25 mg/m**2** IV q24h	50 mg/m^2 IV q24h	Load with 70 mg/m^2 IV once, then 50 mg/m^2 IV q24h	No	
Micafungin	10 mg/kg IV q24h	3–4 mg/kg IV q24h	2–4 mg/kg IV q24h (1 mg/kg IV q24h for prophylaxis)	No	[2, 125, 135, 138, 141]
Anidulafungin	Load with 3 mg/kg IV once, then 1.5 mg/kg IV q24h	Load with 3 mg/kg IV once, then 1.5 mg/kg IV q24h	Load with 3 mg/kg IV once, then 1.5 mg/kg IV q24h	No	[105, 163, 164]

Drug	Dosing			Therapeutic drug monitoring	References
	Neonates (0–30 days)	Infants (31 days–2 years)	Children (2 years–17 years)		
Aminocandin	unknown	unknown	unknown	unknown	
Nucleoside analogs					
5-Flucytosine	unknown	unknown	unknown	C_{max} : 20−50 mg/L[c]	[120, 181]

ABCD=amphotericin B colloidal dispersion; **ABLC**=amphotericin B lipid complex; **AUC**=area under the concentration-time curve; **AUC:MIC**=AUC over minimal inhibitory concentration ratio; **C_{max}**=maximal concentration; **div**=divided dose; **EMA**=European Medicines Agency; **FDA**=Food and Drug Administration; **IV**=intravenous; **L-AmB**=liposomal amphotericin B; **MIC**=minimal inhibitory concentration; **PD**=pharmacodynamics; **PO**=oral; **NR**=not reported; **q**=every; **T>MIC**=time concentrations are over the MIC.

[a]Dosing for <12 years old. For children ≥ 12 years old, adult dosing is recommended.

[b]Dosing unknown for children <12 years of age.

[c]Target concentrations in adults.