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Pediatric Antifungal Agents

Michael Cohen-Wolkowicz, MD, Cassandra Moran, DO, Daniel K. Benjamin Jr., MD, MPH, PhD, and P Brian Smith, MD, MHS

Department of Pediatrics, Duke University; Duke Clinical Research Institute

Abstract

Purpose of review—In immunocompromised hosts, invasive fungal infections are common and fatal. In the past decade, the antifungal armamentarium against invasive mycoses has expanded greatly. The purpose of this report is to review the most recent literature addressing the use of antifungal agents in children.

Recent findings—Most studies evaluating the safety and efficacy of antifungal agents are limited to adults. However, important progress has been made in describing the pharmacokinetics and safety of newer antifungal agents in children, including the echinocandins.

Summary—Dosage guidelines for newer antifungal agents are currently based on adult and limited pediatric data. Because important developmental pharmacology changes occur throughout childhood impacting the pharmacokinetics of these agents, antifungal studies specifically designed for children are necessary.

Keywords

infant; immunocompromised host; child; mycoses; neutropenia

Introduction

Invasive fungal infections (IFI) in the immunocompromised host are common and often fatal. In recent years, the antifungal armamentarium used to treat IFIs has expanded. Clinicians now have the opportunity to choose from several antifungal classes with decreased risk of compromising patient safety. However, most of the pharmacokinetics (PK), safety, and efficacy data published to date are limited to adults. The purpose of this report is to provide a concise review of recent trials of antifungal agents used in the pediatric population. Systemic (non-topical) antifungal agents will be discussed with an emphasis on studies published within the last 12 months. Pediatric dosing recommendations are summarized in Table 1.

POLYENES

The polyene macrolides represent the oldest class of antifungal agents; the major systemically administered drug in this group is amphotericin B.

Amphotericin B deoxycholate—Amphotericin B deoxycholate works by binding to fungal membrane ergosterols resulting in increased membrane permeability and cell death. Amphotericin B deoxycholate is a broad spectrum antifungal agent active against *Candida* spp. (excluding *Candida lusitanae*), *Aspergillus* spp., and Zygomycetes. The recommended

dose is 1.0–1.5 mg/kg/day. In adults, amphotericin B deoxycholate has a long terminal elimination half-life of up to 15 days.(1) Although a similar elimination half-life has been described for premature infants, they have a greater potential for substantial drug accumulation and inter-individual variability.(2) Adults and infants also differ with respect to cerebrospinal (CSF) penetration. In adults, CSF values reach 2–4% of serum concentrations(3), but in premature infants CSF penetration may be as high as 40%.(2)

Acute and chronic toxicities of amphotericin B deoxycholate limit its use; up to 80% of patients receiving the drug develop infusion-related toxicity or nephrotoxicity.(4) Nephrotoxicity is generally less severe in infants and children. In addition to conventional amphotericin B deoxycholate, three lipid-based formulations associated with less toxicity are available: amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (L-amphotericin B). The lipid formulations are indicated for neutropenic patients with persistent fever despite broad-spectrum antibiotic therapy and patients with systemic mycoses who are intolerant of, or refractory to, amphotericin B deoxycholate.(5) Despite extensive use of liposomal formulations in infants, there is very limited published experience. One review of L-amphotericin B use in infants showed the agent is well tolerated.(6) Although amphotericin B deoxycholate and its lipid formulations are active against most IFIs, their use in most pediatric clinical settings is decreasing because newer agents with improved safety profiles have emerged.

TRIAZOLES

Triazole antifungal agents have broad antifungal coverage like amphotericin but are associated with less toxicity. They work by inhibiting the fungal specific enzyme, cytochrome P450_{14DM}. This enzyme inhibition prevents cell membrane ergosterol synthesis leading to altered membrane permeability and cell death.(7, 8) Agents of this class include: fluconazole, active against most *Candida* species but not *Aspergillus* and itraconazole, voriconazole, posaconazole, and ravuconazole active against both *Candida* and *Aspergillus* species.

Fluconazole—Fluconazole is used in children for oropharyngeal candidiasis, invasive candidiasis, cryptococcal meningitis, and *Candida* prophylaxis in immunocompromised hosts. In recent years, fluconazole has been evaluated in the intensive care nursery for prophylaxis. Two randomized controlled trials showed that premature infants who received fluconazole for 4–6 weeks had a decrease in fungal colonization and development of IFI compared to placebo.(9, 10) While results of fluconazole prophylaxis studies in premature infants are encouraging, the universal implementation of prophylaxis is discouraged until outcomes of larger studies incorporating the influence of *Candida* infection incidence and neurodevelopmental follow up are known.(11) A multicenter trial is underway to evaluate the impact of fluconazole prophylaxis on mortality, IFI, and neurodevelopmental outcomes among infants < 750 g birth weight.

Fluconazole has excellent bioavailability (>90%); CSF penetration is approximately 80%(12); it is predominantly cleared as by the kidneys(13); and clearance is more rapid in children with a mean plasma half-life of approximately 20 hours versus 30 hours in adults. (13) Children > 3 months of age require 6–12 mg/kg/day in order to achieve comparable adult exposures. In premature infants a population PK study showed that a maintenance dose of 12 mg/kg/day is necessary to achieve exposures similar to older children and adults.(14) In addition, a loading dose of 25 mg/kg will achieve steady state concentrations sooner than the traditional dosing scheme. The loading dose strategy is being evaluated in pediatric clinical trials. Side effects of fluconazole are uncommon and include gastrointestinal upset (7.7%) or a skin rash (1.2%).(15)

Itraconazole—Widespread use of itraconazole in children is limited by erratic oral absorption, high PK variability, significant drug interactions, and availability of more efficacious and reliable triazoles. However, it is efficacious against oropharyngeal candidiasis in HIV infected children, including patients with fluconazole-resistant isolates(16) and has been used successfully in children following hematological stem cell transplantation to prevent IFI.(17) The use of itraconazole over fluconazole in this population is attractive because of its activity against *Aspergillus* species. Pediatric dosing for itraconazole is not exact, but usually higher than adult doses and approximately 3–10 mg/kg/day. Itraconazole has a long half-life of 25–50 hours allowing once-daily dosing(18) and oral solution in children produces lower maximum concentrations and similar half-life when compared to adults.(19) Side effects of itraconazole are relatively few and include nausea and vomiting (10%), elevated transaminases (5%), and peripheral edema. However, given the limitations described above, newer triazole agents (i.e. voriconazole) are first line of therapy against invasive mold infections.

Voriconazole—Voriconazole, a derivative of fluconazole, is a second-generation triazole with a broad spectrum of activity against yeast and moulds; notably, it is fungicidal against *Aspergillus*.(20) Clinical indications of voriconazole in children include first line therapy for invasive aspergillosis(21, 22) and esophageal candidiasis in the immunocompromised host(23). Premature infants with primary cutaneous aspergillosis have been treated successfully with voriconazole.(24) However, appropriate voriconazole dosing in premature infants has not been established and the drug should be used with caution because of concern of toxicity to the developing retina.

Voriconazole has a high bioavailability (90%); it is extensively metabolized by the liver cytochrome P450 2C19; and genetic polymorphisms of this enzyme play a role in its PK. (25, 26) In adults, voriconazole exhibits saturable non-linear PK with a half-life of approximately 6 hours.(27) However, a pediatric PK study showed that elimination of voriconazole in children is linear, without significant accumulation after multiple doses. This study also showed, that the PK are most affected by body weight and CYP2C19 phenotype and exposures in immunocompromised pediatric patients are similar at 4 mg/kg every 12 hours when compared to 3 mg/kg in adults.(26) A recent population PK study involving 82 pediatric patients 2–12 years of age determined that intravenous doses of 7 mg/kg every 12 hours produced exposures similar to that observed in adults.(28) Voriconazole side effects include visual disturbances (13%); elevated hepatic transaminases; and skin photosensitization.

Posaconazole—Posaconazole is FDA approved for the prophylaxis and treatment of disseminated candidiasis and aspergillosis in severely immunocompromised patients and for the treatment of oropharyngeal candidiasis; it is available as an oral formulation; and its antimicrobial spectrum is wider than voriconazole including activity against zygomycetes. The use of posaconazole in the pediatric population is very limited. In a study that included 7 patients 9 to 18 years of age with chronic granulomatous disease and proven invasive mould infection refractory to standard therapy, posaconazole (400 mg orally twice per day) was reported to be well tolerated.(29)

Posaconazole has a half-life of 25 hours(30); steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration(31); exposure varies according to dietary fat content (i.e high fat diets increase systemic exposure)(32); and the drug is not a substrate for the cytochrome P-450 enzymatic system. In a PK study of oral posaconazole (200 mg three times per day) including 7 pediatric patients with hematological malignancies, the maximum posaconazole concentration at steady state was not different between children and adults.(33)

Ravuconazole—Ravuconazole is a new triazole with fungicidal activity against *Candida* spp. and moulds. It has a bioavailability of >50% and demonstrates linear PK(34) with a half-life of approximately 100 hours.(35) Ravuconazole does not induce CYP isoenzymes. No clinical trials of ravuconazole have been conducted in children, and the FDA has not approved it.

ECHINOCANDINS

The echinocandins are agents that interfere with cell wall biosynthesis by inhibition of fungal 1,3 β -D-glucan synthase.(34, 36) Echinocandins are fungicidal *in vitro* against *Candida* spp.(34, 37), but appear to be fungistatic against *Aspergillus*. As a class, these agents are not hepatically metabolized lessening the potential for drug interactions and side effects. Three compounds in this class (caspofungin, micafungin, and anidulafungin) are FDA-approved for use in adults.

Caspofungin—In children, the use of caspofungin has been limited to refractory cases of invasive candidiasis and as salvage or combination therapy in other IFI including aspergillosis.(38, 39) A retrospective review of children who received caspofungin as empirical therapy for fever and neutropenia showed that 79% of caspofungin courses resulted in an overall favorable response.(40) A prospective, open-label, efficacy trial in children (3 months to 17 years of age) with suspected or proven IFI showed that success at end of therapy was achieved in 50% (5/10) of patients with invasive aspergillosis and 80% (30/37) of patients with invasive candidiasis.(41) Two small retrospective studies of caspofungin in infants with disseminated candidiasis showed that the drug was well tolerated and that most patients had a sterile blood culture within 3 days of starting therapy. (42, 43) In adults, caspofungin is administered as a loading dose (70 mg) followed by a daily maintenance dose (50 mg daily)(44). Caspofungin demonstrates linear PK and is hepatically metabolized with a terminal half-life of about 10 hours.(45) Renal insufficiency has little effect on its PK(46, 47), however, dose reductions are necessary in patients with hepatic insufficiency.(46) Caspofungin clearance is increased in children as demonstrated by lower exposures and shorter half-life when compared to adults. A study evaluated the PK of caspofungin in children (2–17 years) with neutropenia and showed that in patients receiving 50 mg/m²/day, systemic exposure was similar to that seen in adults receiving 50 mg/day and was consistent across age ranges.(48) Importantly, weight based dosing (1 mg/kg/day) was suboptimal when compared to body surface area regimens.(48) In infants and toddlers with fever and neutropenia, a daily caspofungin dose of 50 mg/m² produced similar steady state exposures as older children and adults receiving 50 mg/m²/day and 50 mg/day, respectively. (49) Similar findings were observed when infants < 3 months of age (gestational age 24–41 weeks) were given 25 mg/m²/day.(50) Additional studies of caspofungin in the pediatric population are necessary in order to assess its efficacy. Prior to its widespread use in infants, additional PK studies are needed.

Micafungin—Micafungin, an echinocandin lipopeptide compound, is fungicidal against *Candida* spp. and fungistatic *in vitro* against *Aspergillus*(51); Micafungin is efficacious in the treatment of IFI (including aspergillosis) in immunocompromised adults(52, 53) and as prophylaxis in stem-cell transplant patients.(54) In a pediatric sub-study (n=106, ages 0–16 years including 14 infants) conducted as part of a double blind, randomized, multinational trial comparing micafungin (2 mg/kg/day) with L-amphotericin B (3 mg/kg/day) as rst-line treatment for invasive candidiasis, the rate of overall treatment success was similar for micafungin (72.9%, 35/48) when compared to L-amphotericin B (76.0%, 38/50).(55) Micafungin was better tolerated than liposomal amphotericin B as evidenced by the fewer adverse events that led to discontinuation of therapy.(55) When stratified by age group,

however, amphotericin B deoxycholate outperformed micafungin in all groups except the infants. This observation could be related to the low micafungin dose used in this trial.

Micafungin has a half-life of approximately 12 hours and it exhibits linear PK with the highest drug concentrations detected in the lung, liver, spleen, and kidney. Micafungin is undetectable in the CSF(56), but in animal models the drug penetrates and cures invasive fungal infections in the central nervous system tissue.(57) Of the echinocandins, the PK of micafungin is the best described across all pediatric age groups and it is the only product for which elevated dosing has been described in premature infants. Elevated dosing in the premature infant is thought to be important to drive the antifungal agent into the central nervous system. In children with fever and neutropenia, micafungin (0.5 to 4 mg/kg per day) demonstrated linear PK and clearance was inversely related to age.(58) In order to achieve micafungin exposures equivalent to adults children require dosages higher than 3 mg/kg.(59) A PK study in 18 premature infants (mean gestational age 26.4 $\pm$ 2.4 weeks) showed that micafungin demonstrated linear PK; displayed a shorter half-life (8 hours); and had a more rapid clearance compared with older children and adults.(60) PK data obtained in 12 premature infants (mean gestational age 27 weeks) suggest that a micafungin dose of 15 mg/kg/day achieves similar exposures to those in adults receiving 5 mg/kg/day.(61). A second study of micafungin (7–10 mg/kg/day) administered to 13 premature infants suggests that 10 mg/kg/day is the correct dose for premature infants.(62) In therapeutic and prophylaxis clinical trials against IFI, patients treated with micafungin demonstrated fewer adverse events versus L-amphotericin B and fluconazole. The most common adverse events related to micafungin include gastrointestinal tract manifestations (nausea, diarrhea); hypersensitivity reactions; and elevation of liver enzymes.(63)

Anidulafungin—Anidulafungin has proven efficacy in the treatment of adults with esophageal and systemic candidiasis(64–66) It has fungistatic activity against *Aspergillus* spp. and fungicidal activity against *Candida* spp.(67) Anidulafungin demonstrates linear PK with the longest half-life of all the echinocandins (approximately 18 hours)(68) Because it degrades in the blood, neither end-stage renal impairment, dialysis, nor mild to moderate hepatic failure alter its PK.(69) Anidulafungin tissue concentrations after multiple dosing are highest in lung, liver, spleen and kidney, with measurable concentrations in the brain tissue.

There is only one study evaluating the PK of anidulafungin in pediatric patients.(70) Children ages 2 to 17 years with neutropenia given anidulafungin (1.5–3 mg/kg loading dose, 0.75–1.5 mg/kg/day maintenance dose) had exposures similar to adults patients receiving the same weight-adjusted dose and achieved steady-state plasma concentrations after administration of the loading dose.(70) Anidulafungin safety and PK in infants younger than 2 years is under investigation; a preliminary PK analysis of the first 7 patients enrolled in the study suggests that systemic exposure in young infants is similar to older children and adults receiving maintenance doses of 1.5 mg/kg/day.(71) Anidulafungin is well tolerated; the most commonly reported adverse event is transient liver function test elevations.(72) However, given lack of evidence and expertise of its use in children, it is currently not recommended for use in this population. In addition, the current anidulafungin formulation requires reconstitution with ethanol and its safety among pediatric populations with decreased ethanol metabolizing capacity (i.e. premature infants) has not been established.

Conclusions

Over the past decade the number of antifungal agents in development and ongoing clinical trials has grown exponentially. However, most of the studies conducted to date have primarily included adults. Pediatric studies are necessary because extrapolation of adult data has failed to predict accurate drug disposition in children.

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Table 1

Pediatric Antifungal Agents.

Drug	Susceptible species			Formulation	Pediatric dose	Infant dose
	<i>Candida sp.</i>	<i>Aspergillus sp.</i>	Zygomycetes			
Polynes						
Amphotericin B	X ^a	X	X	IV	0.5–1 mg/kg/day	1 mg/kg/day
Triazoles						
Fluconazole	X ^c	-	-	IV, PO	6–12 mg/kg/day	12 mg/kg/day
Itraconazole	X	X	-	IV, PO	3–10 mg/kg/day 14 mg/kg/day	N/A
Voriconazole	X	X	-	IV, PO	divided every 12 hours	N/A
Posaconazole	X	X	X	PO	N/A	N/A
Echinocandins						
Caspofungin	X	X	-	IV	50 mg/m ² /day	25 mg/m ² /day [*]
Micafungin	X	X	-	IV	8 mg/kg/day	10 mg/kg/day
Anidulafungin	X	X	-	IV	1.5 mg/kg/day (loading dose 3 mg/kg once)	N/A

IV: intravenous; PO: oral; N/A: not available;

^{*} not enough data supporting universal dosing recommendations; -: no activity;

^a not active against *C. lusitanae*;

^b Blastomyces dermatitidis, Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum, Paracoccidioides brasiliensis, Sporotrix schenckii;

^c not active against *C. krusei*, *C. glabrata*;

^d C. neoformans, B. dermatitidis, H. capsulatum, C. immitis, P. brasiliensis;

^e B. dermatitidis, H. capsulatum, C. immitis, P. brasiliensis;

^f Fusarium, B. dermatitidis, H. capsulatum, C. immitis, Malassezia species, Scedosporium, dematiaceous moulds;

^g Fusarium, H. capsulatum, C. immitis, Zygomycetes, dematiaceous moulds.