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Update on antifungal agents for paediatric patients

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Abstract

Paediatric age groups display important differences in host biology, predisposing conditions, epidemiology and presentation of fungal infections relative to the adult population. During the past decade, several new antifungal agents have been developed. Although not all of these agents are yet approved for children, the paediatric development of antifungal agents has moved forwards in an exemplary manner. Invasive fungal infections will remain important causes of morbidity and mortality in immunocompromised paediatric patients. Whereas the availability of new therapeutic options is an important advance, antifungal therapy has become increasingly complex, and a thorough understanding of the available antifungal armamentarium is essential for the successful management of the individual patient. This article provides an update on the pharmacokinetics, safety and dosing of antifungal agents in paediatric patients, and their clinical indications.

Keywords: 5-Fluorocytosine, amphotericin B deoxycholate, anidulafungin, caspofungin, fluconazole, intraconazole, lipid formulations of amphotericin B, micafungin, posaconazole, review, voriconazole

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Introduction

Invasive fungal infections have evolved into important causes of morbidity and mortality in children with severe underlying illnesses. Irrespective of age and underlying condition, these infections remain difficult to diagnose, and responses to treatment depend on early diagnosis and prompt initiation of appropriate treatment. Apart from a better understanding of both the pharmacology and clinical indications of existing antifungal agents, recent years have witnessed the development of new broad-spectrum triazoles and the advent of the new class of echinocandins (Fig. 1). Children, in particular neonates and young infants, represent a unique patient population, in particular with regard to the disposition of antifungal agents and safety issues; however, antifungal pharmacodynamics may also be different, as emerging data on treatment approaches for central nervous system infections in premature neonates suggest. This article provides a brief update on the pharmacokinetics, safety and dosing of antifungal agents in paediatric patients, their clinical indications in the management of opportunistic fungal infections, and the current status of regulatory approval, with a focus on recent developments.

Established Antifungal Agents

Amphotericin B deoxycholate

The pharmacokinetics of amphotericin B deoxycholate in paediatric patients are characterized by high inter-individual variability, but are not different from those observed in adults [1]. Infusion-related reactions, although rarely observed in neonates, and, even more, nephrotoxicity often limit treatment with amphotericin B deoxycholate [2–8]. In countries where alternative options are available, few indications are therefore left for antifungal treatment with amphotericin B deoxycholate. These include neonatal invasive candidiasis and induction therapy for cryptococcal meningitis. The recommended daily dosage in these settings ranges from 0.7 to 1.0 mg/kg daily administered over 2–4 h as tolerated;

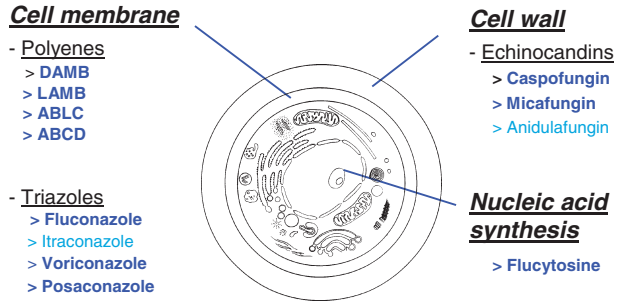

FIG. 1. Overview of current antifungal agents available for the management of invasive fungal infections and their cellular targets. Agents approved for paediatric patients are in bold type. ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; DAMB, amphotericin B deoxycholate; LAMB, liposomal amphotericin B.

treatment should be started at the full target dosage with careful clinical monitoring.

Lipid formulations of amphotericin B

The lipid formulations of amphotericin B (amphotericin B colloidal dispersion (Amphocil or Amphote), amphotericin B lipid complex (Abelcet) and liposomal amphotericin B (AmBisome) allow for the safe delivery of higher dosages of the parent compound [9]. Each of the lipid formulations possesses distinct physicochemical and pharmacokinetic properties. Whether and how these distinct features translate into different pharmacodynamics *in vivo* is not well characterized.

The available pharmacokinetic and safety data for the lipid formulations of amphotericin B in paediatric age groups indicate no fundamental differences relative to the adult population [4,10–21] (48th ICAAC, Abstract A-005, Walsh T, 2008) (Table 1). Taken together, the lipid formulations have less renal toxicity as defined by development of azotaemia than conventional amphotericin B; distal tubular toxicity also may be somewhat reduced. Infusion-related side effects of fever, chills and rigor are substantially less frequent with liposomal amphotericin B only, whereas the infusion-related reactions of amphotericin B colloidal dispersion and amphotericin B lipid complex appear to be similar to those of amphotericin B deoxycholate. Mild increases in serum bilirubin and alkaline phosphatase can be observed with all three formulations, and mild increases in serum transaminases with liposomal amphotericin B [9,22].

Currently, amphotericin B colloidal dispersion is licensed for treatment of patients with invasive aspergillosis refractory to, or who are intolerant to, amphotericin B deoxycholate, and amphotericin B lipid complex for treatment of patients with invasive *Candida* and *Aspergillus* infections refractory to, or who are intolerant to, amphotericin B deoxycholate; amphotericin B lipid complex may also be indicated for first-line treatment of zygomycosis [22]. Liposomal amphotericin B has approved first-line indications for empirical therapy of persistently neutropenic patients and for treatment of invasive mycoses, including invasive aspergillosis [23] and invasive candidiasis [24]. The recommended therapeutic dosages are 3–4 mg/kg per day for amphotericin B colloidal dispersion, 5 mg/kg daily for amphotericin B lipid complex, and 3 (to 5) mg/kg daily for liposomal amphotericin B [22]. The therapeutic dosage for treatment of zygomycosis should not be <5 mg/kg daily. As for to amphotericin B deoxycholate, treatment should be started with the full target dosage at the infusion rate recommended by the manufacturer.

5-Fluorocytosine

5-Fluorocytosine is a fungus-specific synthetic base analogue that has useful antifungal activity against *Candida* and *Cryptococcus* species [22,25]. An established indication for 5-fluorocytosine is its use in combination with amphotericin B deoxycholate for induction therapy for cryptococcal meningitis [26,27]. The combination with amphotericin B may also be an option for the treatment of *Candida* infections involving deep tissues [25] including *Candida* meningitis [28–30]; however, the optimal management of *Candida* meningitis and meningoencephalitis is unknown [31].

Although separate pharmacokinetic data for infants and children are lacking, extreme inter-individual variability in

TABLE 1. Pharmacokinetic parameters of amphotericin B lipid formulations

	ABCD		ABLC		LAMB	
	P (5)	A (7)	P (3)	A (8)	P (5)	A (9)
Dose (mg/kg)	7–7.5	7–7.5	2.5	2.5	5	5.0
C_{max} (μg/mL)	NA	NA	1.69	2.41	57	83
AUC_{0-24} (μg/mL/h)	7.10	9.60	11.9	6.77	482	555
V_D (L/kg)	4.57	4.21	NA	105	0.53	0.10
CLt (L/kg/h)	0.144	0.111	0.218	0.300	0.017	0.011

AUC_{0-24}, area under the concentration-time curve from 0–24 hours; C_{max}, peak plasma concentrations; CLt, total clearance; NA, not available; V_D, volume of distribution.
Depicted are mean values after multiple dosing in padiatric (P) relative to adult (A) patients. Compiled from references [4,10–21] and 48th ICAAC, Abstract A-005.

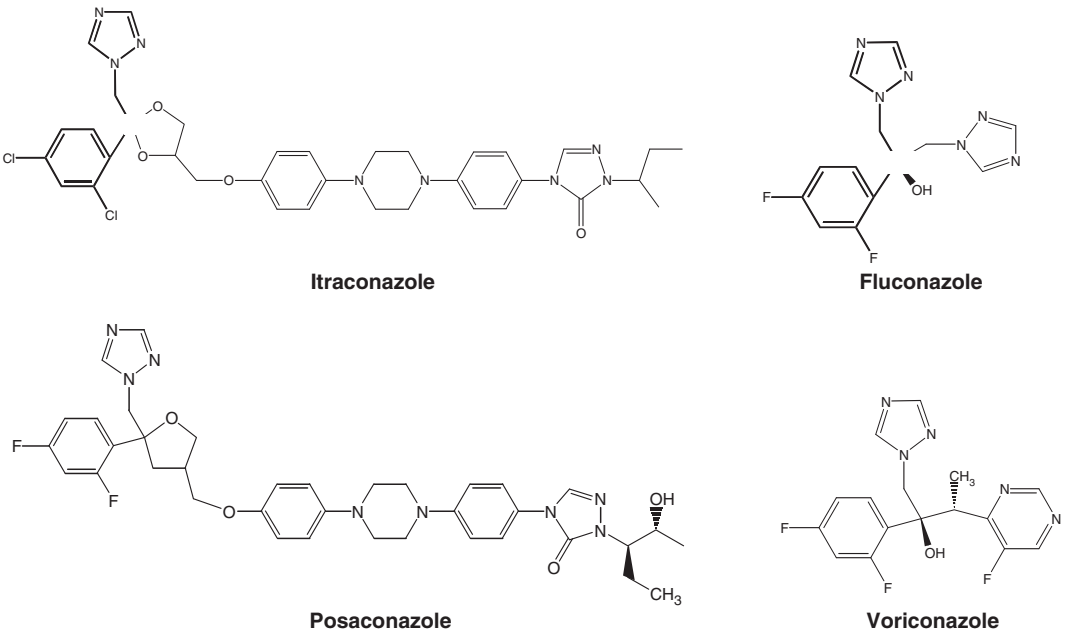

FIG. 2. Chemical structures of the antifungal triazoles. Whereas voriconazole is structurally related to fluconazole, posaconazole is related to itraconazole.

clearance and distribution volume has been reported in neonates [32]. Although recent analyses of therapeutic drug monitoring (TDM) data in children and pharmacokinetic bridging models suggest that lower dosages may be more appropriate [33,34], the approved starting dosage of 100 mg/kg daily divided into three or four doses is currently recommended for both adults and children. TDM is advised; peak plasma levels between 40 and 60 μg/mL correlate with antifungal activity, but are seldom associated with marrow toxicity [35].

TABLE 2. Pharmacokinetic parameters of fluconazole in pediatric patients

Age group	V_{Dss} (L/kg)	Cl (L/h/kg)	$t_{1/2}$ beta (h)
Preterm <1500 g			
Day 1	1.18	0.010	88
Day 6	1.84	0.019	67
Day 12	2.25	0.031	55
Term neonates	1.43	0.036	28
Infants >1–6 months	1.02	0.037	19
Children 5–15 years	0.84	0.031	18
Adult volunteers	0.65	0.015	30

Data represent mean values and are compiled from [36–38].
Cl, total plasma clearance; $t_{1/2}$ beta, elimination half-life; V_{Dss}, apparent volume of distribution at steady state.

Antifungal triazoles

The antifungal triazoles have become an important component of the antifungal armamentarium. Whereas fluconazole and itraconazole have been available for more than a decade, voriconazole and posaconazole have entered clinical practice only recently [25] (Fig. 2).

Fluconazole. With the exception of premature neonates, where clearance may be decreased during the first days of life, paediatric patients tend to have greater normalized plasma clearance and a shorter half-life than adults [36–39] (Table 2). Therefore, relative to weight, higher dosages are required in children to achieve comparable exposures.

In paediatric patients, at dosages of up to 12 mg/kg daily, fluconazole is generally well tolerated [40]. The most common reported side effects include gastrointestinal disturbances (8%), increases in hepatic transaminases (5%) and skin reactions (1%); toxicity-related discontinuations occur in approximately 3% of patients [40]. Severe side effects, including relevant hepatotoxicity and exfoliative skin reactions, have been reported anecdotally [25].

Fluconazole may be used for invasive *Candida* infections caused by susceptible organisms in paediatric patients of all ages who are in a stable condition and who have not received prior azole therapy [22, 41–47]. The recommended dosage range beyond the neonatal period is 6–12 mg/kg daily; in view of the faster clearance rate and the absence of population pharmacokinetics, however, 12 mg/kg daily may be the most appropriate dosage. For infants, population-based pharmacokinetics and Monte Carlo simulation showed that for the treatment of invasive candidiasis, a dose of at least 12 mg/kg daily in the first 90 days after birth is needed

to achieve an area under the concentration curve/MIC index >50 for *Candida* species with MIC <8 mg/L in ≥90% of <30-week-gestation infants and 80% of 30–40-week-gestation infants, respectively; according to the model, infants with serum creatinine ≥1.3 mg/dL have a slower clearance rate, and dose adjustment is indicated if creatinine does not improve within 96 h [39,48].

Further potential therapeutic and prophylactic indications for fluconazole, including those for cryptococcal disease, are similar to those in adults. In low-birthweight infants, fluconazole has been shown to reduce *Candida* infections [49,50]; on the basis of these studies, fluconazole prophylaxis is a valid option for centres with a high frequency (>10%) of invasive *Candida* infections in premature infants of <1000 g birthweight or in the setting of a nosocomial outbreak with a fluconazole-susceptible *Candida* species. Population pharmacokinetics and Monte Carlo simulation support a dose of 3 or 6 mg/kg twice weekly during the first 42 days of life for early prevention of candidiasis in 23–29-week infants, and a 6 mg/kg dose every 72 h or 3 mg/kg daily for late prevention [39,48].

Itraconazole. The safety and pharmacokinetics of cyclodextrin itraconazole oral solution in immunocompromised paediatric patients ≥2 years of age have been studied in two phase II clinical trials [51,52] in children with cancer, liver transplantation or human immunodeficiency virus infection who received the compound for treatment of oropharyngeal candidiasis or as prophylaxis. On the basis of safety and efficacy, a dosage of 2.5 mg/kg twice daily was recommended for the treatment of oropharyngeal candidiasis [52]. Population-based pharmacokinetics in paediatric cystic fibrosis and allogeneic bone marrow transplant patients receiving the oral solution or the capsule formulation as antifungal prophylaxis, however, suggest a starting dose of 5 mg/kg twice daily and TDM to maintain a target trough level of >0.5 μg/mL [53]. Information on the intravenous hydroxypropyl-β-cyclodextrin formulation is limited to a single-dose pharmacokinetic study in 33 children who received itraconazole at 2.5 mg/kg over 1 h. There was no safety issue, and analysis of pharmacokinetic parameters suggests that the compound can be administered with a weight-normalized dosing approach [54].

Vomiting (12%), abnormal liver function tests (5%) and abdominal pain (3%) were the most common adverse effects considered to be related to cyclodextrin itraconazole solution in an open study in 103 neutropenic paediatric patients who received the drug at 5 mg/kg daily for antifungal prophylaxis; 18% of patients withdrew from the study because of adverse events [55]. Safety data on the intravenous cyclodextrin formulation in paediatric patients are limited to a single-dose pharmacokinetic trial [54]; similarly, only anecdotal reports have been published on the use of itraconazole in the neonatal setting.

Therapeutic and prophylactic indications for itraconazole in the settings of superficial and invasive mycoses have been reviewed elsewhere [25]. Itraconazole is not approved for use in individuals <18 years of age, and can therefore only be used off-label. On the basis of published pharmacokinetic and safety data, the starting dosage range for the oral solution of itraconazole in paediatric patients beyond the neonatal period is 5 mg/kg daily in two divided doses. The recommended target trough level is >0.5 μg/mL of the parent itraconazole by HPLC [25]. Multiple-dose pharmacokinetic data for intravenous itraconazole are currently lacking; the dosage regimen utilized in the published adult studies is 200 mg twice daily for 2 days, followed by 200 mg daily for a maximum of 12 days [56].

New Agents and Current Status of Paediatric Development

New antifungal triazoles

Voriconazole. Voriconazole is a synthetic oral and parenteral antifungal triazole with activity against a wide spectrum of clinically important yeasts and moulds (Fig. 2; Table 3). Voriconazole is currently approved for the treatment of invasive aspergillosis, fusariosis and scedosporiosis, and for the primary treatment of invasive candidiasis in non-neutropenic patients. For patients aged 12 years and above, the recommended intravenous dosages are 6 mg/kg twice daily on day 1, followed by 4 mg/kg twice daily; the oral dosages are 400 mg twice daily on day 1 (<40 kg, 200 mg twice daily), followed by 200 mg twice daily (<40 kg, 100 mg twice daily).

Paediatric patients 2–11 years of age have a higher capacity for elimination of voriconazole per kilogram of bodyweight than healthy adult volunteers, resulting in a lower,

TABLE 3. Principal pharmacokinetic properties of the new antifungal triazoles posaconazole and voriconazole

	Posaconazole	Voriconazole
Formulation	Oral/intravenous	Oral/intravenous
Dose linearity	Yes	No
Oral bioavailability (%)	>50	>90
Protein binding (%)	>95	58
Volume of distribution (L/kg)	>5	2
Elimination half-life (h)	25	6
Substrate/inhibitor of CYP450	3A4	3A4, 2C9, 2C19
Elimination via:		
Faeces (%/% metabolites)	77/–	<20/?
Urine (%/% metabolites)	14/14	80/78

Data compiled from [57,66].

potentially non-therapeutic, exposure at similar dosages [57]. *In vitro* studies with liver microsomes suggest that this differential clearance is attributable to faster action of CYP2C19 and flavin-containing monooxygenase 3 in N-oxidizing voriconazole in children [58]. In the interim, an intra-individual dosage escalation study has been completed; on the basis of the population-based analysis of the dataset of this and the initial dose-finding study, an intravenous dosage of 7 mg/kg twice daily and an oral dosage of 200 mg twice daily (oral suspension) without loading dosages has been approved in the European Union for children 2–11 years of age [59]. A very recent population-based analysis in 46 patients with a median age of 12 years (range, 0.8–20.5 years) found a pharmacodynamic association between a voriconazole trough concentration of >1000 ng/mL and survival; simulations predicted that an intravenous dose of 7 mg/kg or an oral dose of 200 mg twice daily would achieve a trough >1000 ng/mL in most patients, including those ≥12 years of age [60]. Taken together, these data raise questions, as in adults, about the optimal dose, the dosing target and the need for TDM of voriconazole in paediatric patients aged ≥2 years. It is of note that for children <2 years of age, no systematic pharmacokinetic data exist, so that dosing is empirical [61].

Data for larger cohorts of voriconazole-treated paediatric patients are quite limited. Of 58 immunocompromised children with invasive fungal infections, 26 (45%) had a complete or partial response; in four patients (7%), the drug was discontinued because of intolerance. A total of 23 patients had voriconazole-related adverse events, most commonly elevations of hepatic transaminases or bilirubin (n = 8), skin rash (n = 8), abnormal vision (n = 3) and photosensitivity reactions (n = 3) [62]. In a retrospective cohort study in 37 immunocompromised children and adolescents who received the drug for a mean duration of 174 days, grade I or II adverse events were observed in 19 patients (51%); the most frequent events included transient increases in hepatic transaminases (19) and transient visual disturbances (five). Four patients experienced grade III/IV adverse events, and in three (8%) the drug was permanently discontinued [63]. It is of note that, apart from more serious hepatic adverse events, a possible link between long-term use of voriconazole, immunosuppression and chronic phototoxicity with aggressive squamous cell carcinoma has been reported in adult and paediatric patients [64]. Further clinical trials in paediatric patients initiated by the manufacturer are currently underway to collect supportive data on dosing, safety and antifungal efficacy.

Posaconazole. Posaconazole is a novel oral antifungal triazole with potent and broad-spectrum activity against opportunistic, endemic and dermatophytic fungi *in vitro* (Fig. 2; Table 3). Importantly, posaconazole also possesses activity against zygomycetes both *in vitro* and *in vivo*, distinguishing it from all available azoles [65].

Posaconazole has been approved in the European Union in patients ≥18 years of age for second-line treatment of aspergillosis, fusariosis, chromoblastomycosis and coccidioidomycosis. In addition, posaconazole is approved for prophylaxis in high-risk patients with acute myeloid leukaemia/myelodysplastic syndrome and in haematopoietic stem cell transplant patients with graft-versus-host disease. The recommended daily dosage for salvage treatment is 400 mg twice daily given with food; for patients not tolerating solid food, a dosage of 200 mg four times daily is recommended, preferably together with a nutritional supplement. The dosage for prophylaxis is 200 mg three times daily [65].

The pharmacokinetics of posaconazole in paediatric patients <18 years of age have not yet been studied systematically. Limited data obtained in 12 paediatric subjects ≥8 years of age indicate no fundamental differences in trough plasma concentrations as compared with adults [66]. Successful salvage treatment with posaconazole has been reported in 5/11 and 6/10 paediatric subjects with invasive fungal infections, which appears to be similar to the outcome in the adult population (15th ECCMID, Abstract P774; 67, Blune J, 2005). A paediatric development programme has been initiated by the manufacturer to define dosages, safety and tolerance in paediatric patients beyond the neonatal period.

Echinocandin lipopeptides

The echinocandins are a distinct class of intravenous semisynthetic amphiphilic lipopeptides that act by inhibiting the synthesis of 1,3-β-D-glucan in the fungal cell wall. Over the past decade, three compounds with similar spectra, pharmacokinetics, safety and antifungal efficacies have been developed: anidulafungin (Eraxis), caspofungin (Cancidas) and micafungin (Mycamine) (Fig. 3; Table 4).

Anidulafungin. Anidulafungin is licensed in the European Union for primary therapy in non-neutropenic adult patients (≥18 years of age) with invasive *Candida* infections. The recommended dose regimen consists of 100 mg (day 1, 200 mg), administered at a rate not exceeding 1.1 mg/min.

A paediatric phase I/II multicentre study on the pharmacokinetics and safety of anidulafungin has been completed in 19 granulocytopenic children with cancer. Patients were divided into two age cohorts (2–11 and 12–17 years) and were enrolled into sequential groups to receive 0.75 or 1.5 mg/kg daily [68]. No drug-related serious adverse events were recorded. Pharmacokinetic parameters were similar across

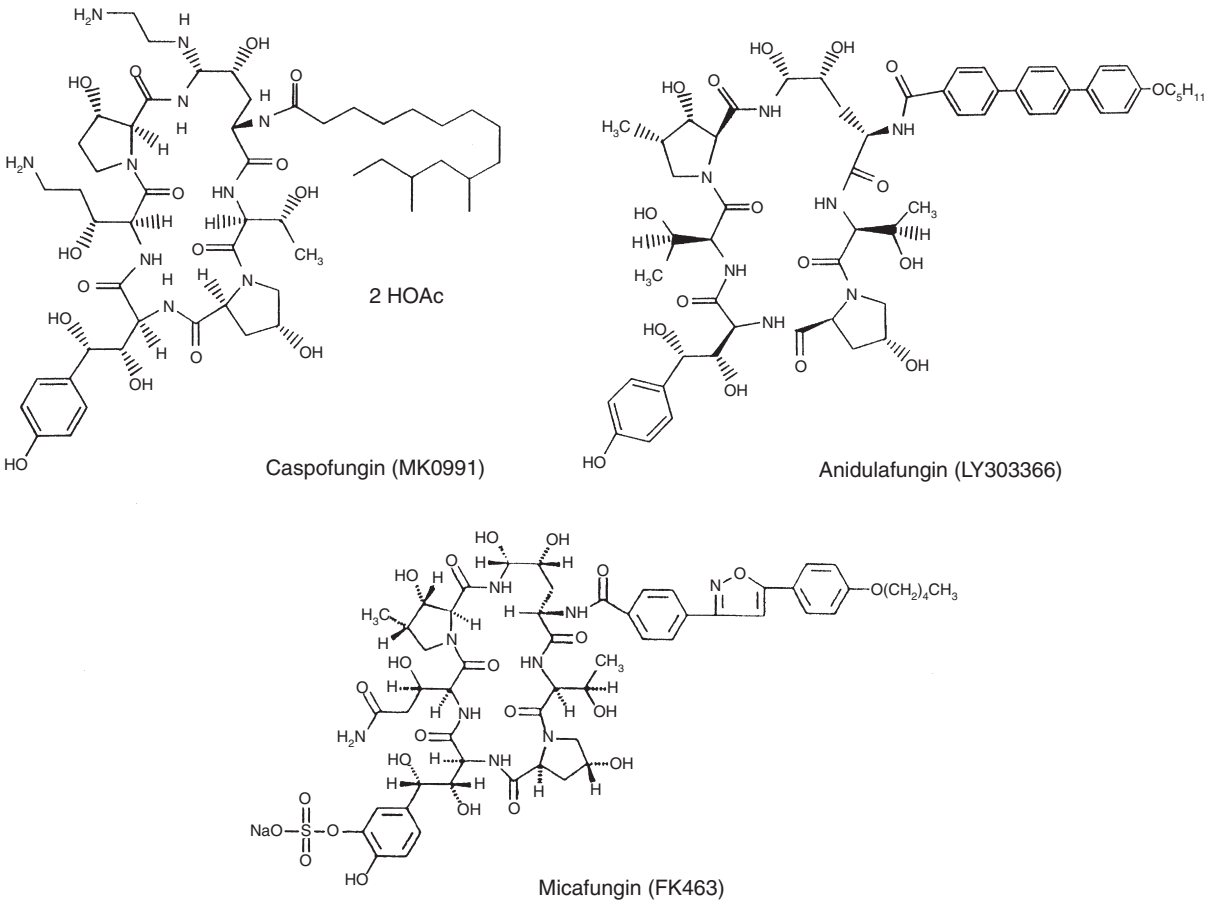

FIG. 3. Chemical structures of anidulafungin, caspofungin and micafungin. The echinocandins are amphoteric cyclic lipopeptides with a hexapeptide core that is linked to a variably configured lipid side chain.

TABLE 4. Principal pharmacokinetic properties of the echinocandin lipopeptides caspofungin, anidulafungin and micafungin

	Caspofungin	Anidulafungin	Micafungin
Formulation	Intravenous	Intravenous	Intravenous
Dose linearity	Yes	Yes	Yes
Oral bioavailability (%)	NA	NA	NA
Protein binding (%)	97	84	99
Volume of distribution (L/kg)	NA	0.7–0.9	0.24
Elimination half-life (h)	8–10	24	15
Substrate/inhibitor of CYP450	NA	NA	NA
Routes of elimination	Degradation/metabolism, urine > faeces	Degradation only, faeces	Metabolism, faeces > urine

Data compiled from [67,71,78].
NA, not applicable.

age groups and dosage cohorts, and similar to those in adult subjects. Following single and multiple daily doses of 0.75 and 1.5 mg/kg, plasma concentration data corresponded to those in adults following a daily 50-mg and 100-mg dose, respectively. The manufacturer's paediatric development programme is at an advanced stage.

Caspofungin. Caspofungin is licensed in the European Union for adult and paediatric patients, including neonates, for second-line therapy of invasive aspergillosis, for primary therapy in non-neutropenic patients with invasive *Candida* infections, and for empirical antifungal therapy in persistently febrile granulocytopenic patients. The recommended dose regimen in adults consists of a single 70-mg loading dose on day 1, followed by 50 mg daily thereafter, administered over 1 h [69].

In children and adolescents 2–17 years of age, the pharmacokinetics and safety of caspofungin were investigated with

either a weight-based or a body surface area regimen. Whereas 1 mg/kg daily achieved suboptimal exposure, dosing with 50 mg/m^2 daily provided similar or slightly higher as in adults [70]. In conjunction with similar pharmacokinetic data obtained in small children [71], the dosage of 50 mg/m^2 daily (day 1, 70 mg/m^2 daily; maximum daily dose, 70 mg) was selected for paediatric patients between 3 months and 17 years of age. This dosing regimen has been confirmed by a population-based pharmacokinetic study including 124 paediatric patients 3 months to 17 years enrolled in four clinical trials (48th ICAAC, Abstract A-006, Lee J, 2008). In neonates up to a postnatal age of 3 months, limited pharmacokinetic data obtained in a small cohort of patients suggest that a dosage of 25 mg/m^2 daily results in similar exposures as 50 mg/m^2 daily in older patients [72].

Caspofungin is well tolerated in paediatric patients. In the above-mentioned phase I/II dose-finding trials, none of the patients developed a serious drug-related adverse event or had the drug discontinued because of toxicity [70–72]. In a phase III comparative estimation trial with safety as the primary objective, 82 patients between the ages of 2 and 17 years with persistent fever and neutropenia were randomly assigned to receive caspofungin or liposomal amphotericin B (3 mg/kg daily) in a 2 : 1 ratio. Rates of drug-related adverse events were similar (clinical, 48.2% vs. 46.2%; laboratory, 10.7% vs. 19.2%); serious drug-related adverse events occurred in 1.8% of caspofungin-treated and in 11.5% of amphotericin B-treated patients. Overall success rates were not different [18]. In the combined analysis of caspofungin safety in all five clinical registration trials involving 171 paediatric patients aged 1 week to 17 years, the most common drug-related adverse events were fever (11.7%), increased alanine transaminase (6.5%), and rash (4.7%); few events were serious (0.6%) or required treatment discontinuation (1.2%) [73]. A favourable safety profile has also been reported in immunocompromised paediatric patients who received the compound for various indications outside of clinical registration trials, mostly in combination with other antifungal agents [74,75], and in neonates with refractory invasive candidiasis [76,77].

Micafungin. Micafungin is licensed in the European Union for neonates, children and adults for the treatment of invasive candidiasis and as prophylaxis for *Candida* infections in patients with allogeneic haematopoietic stem cell transplantation and those with prolonged neutropenia; it is also licensed for the treatment of oesophageal candidiasis in individuals 16 years and older. The recommended dosage is 100 mg daily for invasive candidiasis (≤40 kg bodyweight, 2 mg/kg) with the option of dose escalation to 200 mg daily or 4 mg/kg daily, 150 mg daily for oesophageal candidiasis (≤40 kg, 3 mg/kg), and 50 mg daily (≤40 kg, 1 mg/kg) for prevention.

The pharmacokinetics of micafungin have been studied in 70 children and adolescents in an open-label, sequential group, dose escalation study of empirical therapy in febrile granulocytopenic children aged 2–17 years. At dosages ranging from 0.5 to 3.0 mg/kg daily, the pharmacokinetics were linear and the pharmacokinetic parameters were similar to those observed in adults [78]. Population-based pharmacokinetic modelling of the data revealed that clearance in smaller children was higher than predicted on the basis of weight alone, requiring a relative dosage increase to ensure exposure comparable to that in older children; however, dosages of 2 and 4 mg/kg in the children achieved at least similar exposures as 100 and 200 mg, respectively, in adults [79]. The pharmacokinetics in neonates were explored in a phase I, single-dose, multicentre, open-label, sequential dose trial of micafungin (0.75, 1.5 and 3.0 mg/kg) in 18 premature infants weighing >1000 g. On average, the half-life was shorter and the clearance was more rapid than in older children and adults [80]. Population pharmacokinetic modelling of the neonatal pharmacokinetic data and Monte Carlo simulation suggest that a larger neonatal dose is required to produce drug exposure comparable to those predicted on the basis of weight in children and adults; additional population pharmacokinetics based on open-label pharmacokinetic studies with doses up to 15 mg/kg daily support a target dose of 10 mg/kg for neonates, particularly in view of the substantial risk of secondary brain involvement [81–84]. Although the treatment results in the pivotal candidaemia study showed no sign of decreased efficacy at dosages between 2 and 4 mg/kg in this population [17], we recommend a dose of at least 4 mg/kg in neonates with invasive candidiasis and a dose of 10 mg/kg in the case of central nervous system involvement.

The comparative safety of micafungin was investigated in the paediatric subpopulation of a double-blind, phase III trial in patients with invasive candidiasis or candidaemia. Patients were randomized to receive intravenous micafungin (2 mg/kg daily) or liposomal amphotericin B (3 mg/kg daily) for a minimum of 14 days. There was no difference in the success rates (69.2% vs. 74.1%). The incidence of serious adverse events (3.8% vs. 9.3%) and the rate of patients discontinuing therapy because of an adverse event (3.8% vs. 16.7%) were lower in micafungin-treated patients [17]. In a pooled analysis of adverse event data from six clinical trials including 296 patients (median daily dose, 1.7 mg/kg (range: 0.4–8.6 mg/kg); median treatment duration, 15 days (range: 1–425 days), 26.7% of patients had a treatment-related adverse event and

TABLE 5. Summary of current concepts for management of invasive fungal infections in paediatric patients[a]

Condition	Treatment recommendation	Comments
Candidaemia and deeply invasive candidiasis	First-line options approved by the FDA and/or the EMA: Liposomal amphotericin B (3 mg/kg daily) Fluconazole (8–12 mg/kg daily) Caspofungin (50 mg/m^2 daily; day 1, 70 mg/m^2) Micafungin (<40 kg, 2–4 mg/kg; ≥40 kg, 100–200 mg daily)	Patients who have received azole prophylaxis, are haemodynamically unstable or granulocytopenic, are colonized with *Candida glabrata* or *Candida krusei* or are admitted to institutions with a high frequency of these organisms should receive a polyene or echinocandin up front
	Second-line options: Amphotericin B lipid complex (5 mg/kg daily) Voriconazole (4 mg/kg twice daily in children ≥12 years)	Central venous catheters should be removed promptly if feasible Neutropenic patients should receive colony-stimulating factors, and in immunosuppressed patients, steroids should be reduced, discontinued or replaced
	Treatment of other forms of invasive candidiasis (endocarditis, peritonitis and meningitis) is ill-defined and based on pharmacological considerations such as a cidal mode of action and water solubility, and always includes the evaluation of surgical interventions. The additional use of flucytosine has a role in these situations	The recommended duration of therapy for uncomplicated candidaemia is 14 days after clearance from the bloodstream and resolution of all symptoms Following clearance from the bloodstream and clinical stabilization, oral consolidation with fluconazole is feasible for susceptible isolates Fundoscopy is mandatory prior to end of treatment, to rule out endophthalmitis
Invasive aspergillosis	First-line options approved by the FDA and/or the EMA: Voriconazole (4 mg/kg twice daily in children ≥12 years; 7 mg/kg twice daily ≥2 to 11 years) Liposomal amphotericin B (3 mg/kg daily)	Adjunctive surgical interventions need consideration in skin and soft tissue infections, sinus infections, impeding erosion of pulmonary arteries, and operable CNS and lung lesions
	Second-line options: Amphotericin B lipid complex (5 mg/kg daily) Caspofungin (50 mg/m^2 daily; day 1, 70 mg/m^2)	G-CSF or GM-CSF is indicated in neutropenic patients, and reduction, discontinuation or replacement of steroids in immunosuppressed patients
	Voriconazole is currently recommended for *Aspergillus terreus* infections and infections affecting the CNS	The duration of therapy is individual and determined by the clinical and microbiological response
	In settings with a high frequency of zygomycosis, voriconazole may not be a choice for pre-emptive therapy	Clinical stabilization and at least a partial response provided; treatment can be consolidated with oral therapies
	Dose escalation of liposomal amphotericin B to 10 mg/kg daily for the initial 14 days of treatment was not beneficial in a randomized comparative trial	
	Combination of standard doses of either voriconazole or liposomal amphotericin B with caspofungin is promising, but valid clinical data are currently lacking	
Emerging fungal pathogens	Amphotericin B is used as primary therapy for zygomycosis; posaconazole has shown encouraging clinical activity in the second-line setting	Treatment of infections by the emerging fungal pathogens is an interdisciplinary challenge and needs to be individualized on the basis of the isolate, the site of the infection, and the patient's response to treatment
	Limited and uncontrolled data indicate an important role of both voriconazole and posaconazole for treatment of *Scedosporium* and *Fusarium* infections	
Empirical antifungal therapy	Options approved by the FDA and/or the EMA in this indication: Liposomal amphotericin B (1–3 mg/kg daily) Caspofungin (50 mg/m^2 daily; day 1, 70 mg/m^2)	Empirical antifungal therapy is an established standard of care in haemato-oncological patients with prolonged neutropenia (ANC <500 for ≥10 days) and refractory or new fever that provides targeted prevention in a high-risk setting
Antifungal prophylaxis	Prophylactic fluconazole (8–12 mg/kg daily) remains a standard post-allogeneic haematopoietic stem cell transplantation; alternatives may include the use of voriconazole or micafungin (1 mg/kg daily)	–
	In patients with GVHD and increased immunosuppression, posaconazole (200 mg three times daily) has been shown to prevent IFIs and invasive aspergillosis	Posaconazole may be given to children >12 years with high-risk haematological malignancies, or used for augmented immunosuppression for GVHD and voriconazole in younger children. Alternatives include liposomal amphotericin B (1 mg/kg every other day) or micafungin (1 mg/kg daily)
	In adults with AML/MDS, posaconazole (200 mg three times daily) had a significant impact on the frequency of IFIs and, in particular, invasive aspergillosis, coupled with an overall survival benefit	
Prophylaxis in very low birthweight preterm neonates	Four randomized controlled trials, including a multicentre study, consistently reported significant decreases in colonization and infection by *Candida* spp. in the treated infants. On pooling of the results, fluconazole reduced IFI risk by 75%, and all-cause mortality by 24%	Fluconazole may be given as antifungal prophylaxis in institutions with a substantial incidence (>5% to 10%) of invasive candidiasis in very low birthweight infants or in outbreak situations

AML, acute myeloid leukaemia; ANC, absolute neutrophile count; CNS, central nervous system; EMA, European Medicines Agency; FDA, Food and Drug Administration; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; GVHD, graft-versus-host disease; IFI, invasive fungal infection; MDS, myelodysplastic syndrome.

[a]Modified from Dornbusch *et al.* [85]. For details on the selected treatment options, please consult the text.

2.4% had a treatment-related adverse events that led to treatment discontinuation. No trends were seen with respect to dose or duration of treatment, and the types and rates of events were similar to those observed in adults (47th ICAAC, Abstract M-1162, Avvieta A, 2007).

In Europe, the Summary of Product Characteristics for micafungin recommends careful monitoring of liver function, and early discontinuation in the presence of significant and persistent elevation of alanine transaminase/aspartate transaminase values. It also recommends that micafungin treatment should be conducted with a careful risk–benefit assessment, particularly in patients with liver diseases or receiving concomitant hepatotoxic/genotoxic therapies (Mycamine SPC; http://www.ema.europa.eu/ena/index.jsp.curl=pages/medicines/human/medicines/000734/human_med_0009 (last accessed 14 May 2010)). This recommendation is based on exposure-dependent development of foci of altered hepatocytes (significant) and liver tumours (non-significant) in a long-term exposure model in rats. The human relevance of this finding is presently not known. Similar, comparable preclinical studies for anidulafungin and caspofungin are not in the public domain.

Conclusions

Paediatric age groups display important differences in host biology, predisposing conditions, epidemiology and presentation of fungal infections relative to the adult population. During the past decade, several new antifungal agents have been developed. Although not all of these agents are yet approved for children, the development of antifungal agents for paediatric use has moved forwards in an exemplary manner. Invasive fungal infections will remain important causes of morbidity and mortality in immunocompromised paediatric patients. Whereas the availability of new therapeutic options is an important advance, antifungal therapy has become increasingly complex (Table 5), and a thorough understanding of the available antifungal armamentarium is essential for the successful management of the individual patient.

Transparency Declaration

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References

1. Nath CE, Shaw PJ, Gunning R, McLachlan AJ, Earl JW. Amphotericin B in children with malignant disease: a comparison of the toxicities and pharmacokinetics of amphotericin B administered in dextrose versus lipid emulsion. *Antimicrob Agents Chemother* 1999; 43: 1417–1423.
2. Nath CE, McLachlan AJ, Shaw PJ, Gunning R, Earl JW. Population pharmacokinetics of amphotericin B in children with malignant diseases. *Br J Clin Pharmacol* 2001; 52: 671–680.
3. Kingo AR, Smyth JA, Waisma D. Lack of evidence of amphotericin B toxicity in very low birth weight infants treated for systemic candidiasis. *Pediatr Infect Dis J* 1997; 16: 1002–1003.
4. Prentice HG, Hann IM, Herbrecht R *et al.* A randomized comparison of liposomal versus conventional amphotericin B for the treatment of pyrexia of unknown origin in neutropenic patients. *Br J Haematol* 1997; 98: 711–718.
5. Le J, Adler-Shohet FC, Nguyen C, Lieberman JM. Nephrotoxicity associated with amphotericin B deoxycholate in neonates. *Pediatr Infect Dis J* 2009; 28: 1061–1063.
6. Butler KM, Rench MA, Baker CJ. Amphotericin B as a single agent in the treatment of systemic candidiasis in neonates. *Pediatr Infect Dis J* 1990; 9: 51–56.
7. Leibovitz E, Iuster-Reicher A, Amitai M, Mogilner B. Systemic candidal infections associated with use of peripheral venous catheters in neonates: a 9-year experience. *Clin Infect Dis* 1992; 14: 485–491.
8. Glick C, Graves GR, Feldman S. Neonatal fungemia and amphotericin B. *South Med J* 1993; 86: 1368–1371.
9. Groll AH, Muller FM, Piscitelli SC, Walsh TJ. Lipid formulations of amphotericin B: clinical perspectives for the management of invasive fungal infections in children with cancer. *Klin Padiatr* 1998; 210: 264–273.
10. Amantea MA, Bowden RA, Forrest A, Working PK, Newman MS, Mamelok RD. Population pharmacokinetics and renal function-sparing effects of amphotericin B colloidal dispersion in patients receiving bone marrow transplants. *Antimicrob Agents Chemother* 1995; 39: 2042–2047.
11. Sandler ES, Mustafa MM, Tkaczewski I *et al.* Use of amphotericin B colloidal dispersion in children. *J Pediatr Hematol Oncol* 2000; 22: 242–246.
12. Walsh TJ, Whitcomb P, Piscitelli S *et al.* Safety, tolerance, and pharmacokinetics of amphotericin B lipid complex in children with hepatosplenic candidiasis. *Antimicrob Agents Chemother* 1997; 41: 1944–1948.
13. Walsh TJ, Seibel NL, Arndt C *et al.* Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J* 1999; 18: 702–708.
14. Wiley JM, Seibel NL, Walsh TJ. Efficacy and safety of amphotericin B lipid complex in 548 children and adolescents with invasive fungal infections. *Pediatr Infect Dis J* 2005; 24: 167–174.
15. Wurthwein G, Groll AH, Hempel G, Adler-Shohet FC, Lieberman JM, Walsh TJ. Population pharmacokinetics of amphotericin B lipid complex in neonates. *Antimicrob Agents Chemother* 2005; 49: 5092–5098.
16. Hong Y, Shaw PJ, Nath CE *et al.* Population pharmacokinetics of liposomal amphotericin B in pediatric patients with malignant diseases. *Antimicrob Agents Chemother* 2006; 50: 935–942.
17. Queiroz-Telles F, Berezin E, Leverger G *et al.* Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. *Pediatr Infect Dis J* 2008; 27: 820–826.
18. Maertens JA, Madero L, Reilly AF *et al.* A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for

empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. *Pediatr Infect Dis J* 2010; 29: 415–420.
19. Kolve H, Ahlke E, Fegeler W, Ritter J, Jürgens H, Groll AH. Safety, tolerance and outcome of treatment with liposomal amphotericin B in paediatric patients with cancer or undergoing haematopoietic stem cell transplantation. *J Antimicrob Chemother* 2009; 64: 383–387.
20. Juster-Reicher A, Leibovitz E, Linder N *et al.* Liposomal amphotericin B (AmBisome) in the treatment of neonatal candidiasis in very low birth weight infants. *Infection* 2000; 28: 223–226.
21. Juster-Reicher A, Flidel-Rimon O, Amitay M, Even-Tov S, Shinwell E, Leibovitz E. High-dose liposomal amphotericin B in the therapy of systemic candidiasis in neonates. *Eur J Clin Microbiol Infect Dis* 2003; 22: 603–607.
22. Groll AH, Ritter J. Diagnosis and management of fungal infections and pneumocystis pneumonitis in pediatric cancer patients. *Klin Padiatr* 2005; 217 (suppl 1): S37–S66.
23. Cornely OA, Maertens J, Bresnik M *et al.* Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis* 2007; 44: 1289–1297.
24. Kuse ER, Chetchotisakd P, da Cunha CA *et al.* Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet* 2007; 369: 1519–1527.
25. Groll AH, Piscitelli SC, Walsh TJ. Clinical pharmacology of systemic antifungal agents: a comprehensive review of agents in clinical use, current investigational compounds, and putative targets for antifungal drug development. *Adv Pharmacol* 1998; 44: 343–500.
26. Bennett JE, Dismukes WE, Duma RJ *et al.* A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptoccal meningitis. *N Engl J Med* 1979; 301: 126–131.
27. van der Horst CM, Saag MS, Cloud GA *et al.* Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med* 1997; 337: 15–21.
28. Smego RA Jr, Perfect JR, Durack DT. Combined therapy with amphotericin B and 5-fluorocytosine for Candida meningitis. *Rev Infect Dis* 1984; 6: 791–801.
29. Fernandez M, Moylett EH, Noyola DE, Baker CJ. Candidal meningitis in neonates: a 10-year review. *Clin Infect Dis* 2000; 31: 458–463.
30. McCullers JA, Vargas SL, Flynn PM, Razzouk BI, Shenep JL. Candidal meningitis in children with cancer. *Clin Infect Dis* 2000; 31: 451–457.
31. Benjamin DK Jr, Stoll BJ, Fanaroff AA *et al.* Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics* 2006; 117: 84–92.
32. Baley JE, Meyers C, Kliegman RM, Jacobs MR, Blumer JL. Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990; 116: 791–797.
33. Soltani M, Tobin CM, Bowker KE, Sunderland J, MacGowan AP, Lovering AM. Evidence of excessive concentrations of 5-flucytosine in children aged below 12 years: a 12-year review of serum concentrations from a UK clinical assay reference laboratory. *Int J Antimicrob Agents* 2006; 28: 574–577.
34. Hope WW, Warn PA, Sharp A *et al.* Optimization of the dosage of flucytosine in combination with amphotericin B for disseminated candidiasis: a pharmacodynamic rationale for reduced dosing. *Antimicrob Agents Chemother* 2007; 51: 3760–3762.
35. Francis P, Walsh TJ. Evolving role of flucytosine in immunocompromised patients: new insights into safety, pharmacokinetics, and antifungal therapy. *Clin Infect Dis* 1992; 15: 1003–1018.
36. Lee JW, Seibel NL, Amantea M, Whitcomb P, Pizzo PA, Walsh TJ. Safety and pharmacokinetics of fluconazole in children with neoplastic diseases. *J Pediatr* 1992; 120: 987–993.
37. Brammer KW, Coates PE. Pharmacokinetics of fluconazole in pediatric patients. *Eur J Clin Microbiol Infect Dis* 1994; 13: 325–329.
38. Saxen H, Hoppu K, Pohjavuori M. Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. *Clin Pharmacol Ther* 1993; 54: 269–277.
39. Wade KC, Wu D, Kaufman DA*et al.*. Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother* 2008; 52: 4043–4049.
40. Novelli V, Holzel H. Safety and tolerability of fluconazole in children. *Antimicrob Agents Chemother* 1999; 43: 1955–1960.
41. Pappas PG, Rex JH, Sobel JD *et al.* Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004; 38: 161–189.
42. Fasano C, O'Keeffe J, Gibbs D. Fluconazole treatment of neonates and infants with severe fungal infections not treatable with conventional agents. *Eur J Clin Microbiol Infect Dis* 1994; 13: 351–354.
43. Bilgen H, Ozek E, Korten V, Ener B, Molbay D. Treatment of systemic neonatal candidiasis with fluconazole. *Infection* 1995; 23: 394.
44. Driessen M, Ellis JB, Muwazi F, De Villiers FP. The treatment of systemic candidiasis in neonates with oral fluconazole. *Ann Trop Paediatr* 1997; 17: 263–271.
45. Driessen M, Ellis JB, Cooper PA *et al.* Fluconazole vs. amphotericin B for the treatment of neonatal fungal septicemia: a prospective randomized trial. *Pediatr Infect Dis J* 1996; 15: 1107–1112.
46. Wainer S, Cooper PA, Gouws H, Akierman A. Prospective study of fluconazole therapy in systemic neonatal fungal infection. *Pediatr Infect Dis J* 1997; 16: 763–767.
47. Huttova M, Hartmanova I, Kralinsky K *et al.* Candida fungemia in neonates treated with fluconazole: report of forty cases, including eight with meningitis. *Pediatr Infect Dis J* 1998; 17: 1012–1015.
48. Wade KC, Benjamin DK Jr, Kaufman DA *et al.* Fluconazole dosing for the prevention or treatment of invasive candidiasis in young infants. *Pediatr Infect Dis J* 2009; 28: 717–723.
49. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N Engl J Med* 2001; 345: 1660–1666.
50. Manzoni P, Stolfi I, Pugni L *et al.* A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *N Engl J Med* 2007; 356: 2483–2495.
51. de Repentigny L, Ratelle J, Leclerc JM *et al.* Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children. *Antimicrob Agents Chemother* 1998; 42: 404–408.
52. Groll AH, Wood L, Roden M *et al.* Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis. *Antimicrob Agents Chemother* 2002; 46: 2554–2463.
53. Hennig S, Wainwright CE, Bell SC, Miller H, Friberg LE, Charles BG. Population pharmacokinetics of itraconazole and its active metabolite hydroxy-itraconazole in paediatric cystic fibrosis and bone marrow transplant patients. *Clin Pharmacokinet* 2006; 45: 1099–1114.
54. Abdel-Rahman SM, Jacobs RF, Massarella J *et al.* Single-dose pharmacokinetics of intravenous itraconazole and hydroxypropyl-beta-cyclodextrin in infants, children, and adolescents. *Antimicrob Agents Chemother* 2007; 51: 2668–2673.
55. Foot AB, Veys PA, Gibson BE. Itraconazole oral solution as antifungal prophylaxis in children undergoing stem cell transplantation or intensive chemotherapy for haematological disorders. *Bone Marrow Transplant* 1999; 24: 1089–1093.
56. Caillot D, Bassaris H, McGeer A *et al.* Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. *Clin Infect Dis* 2001; 33: e83–e90.
57. Walsh TJ, Karlsson MO, Driscoll T *et al.* Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob Agents Chemother* 2004; 48: 2166–2172.

58. Yanni SB, Annaert PP, Augustijns P, Ibrahim JG, Benjamin DK Jr, Thakker DR. *In vitro* hepatic metabolism explains higher clearance of voriconazole in children versus adults: role of CYP2C19 and flavin-containing monooxygenase 3. *Drug Metab Dispos* 2010; 38: 25–31.
59. Karlsson MO, Lutsar I, Milligan PA. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. *Antimicrob Agents Chemother* 2009; 53: 935–944.
60. Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. *Clin Infect Dis* 2010; 50: 27–36.
61. Shima H, Miharu M, Osumi T, Takahashi T, Shimada H. Differences in voriconazole trough plasma concentrations per oral dosages between children younger and older than 3 years of age. *Pediatr Blood Cancer* 2010; 54: 1050–1052.
62. Walsh TJ, Lutsar I, Driscoll T *et al.* Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. *Pediatr Infect Dis J* 2002; 21: 240–248.
63. Kolve HLT, Ehlert K, Paulussen M *et al.* Safety, tolerance and plasma concentrations of voriconazole in immunocompromised pediatric patients. *Clin Microbiol Infect* 2004; 10: 40–41.
64. Cowen EW, Nguyen JC, Miller DD *et al.* Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. *J Am Acad Dermatol* 2010; 62: 31–37.
65. Groll AH, Walsh TJ. Posaconazole: clinical pharmacology and potential for management of fungal infections. *Expert Rev Anti Infect Ther* 2005; 3: 467–487.
66. Krishna G, Sansone-Parsons A, Martinho M, Kantesaria B, Pedicone L. Posaconazole plasma concentrations in juvenile patients with invasive fungal infection. *Antimicrob Agents Chemother* 2007; 51: 812–818.
67. Lehrnbecher T, Attarbaschi A, Duerken M *et al.* Posaconazole salvage treatment in paediatric patients: a multicentre survey. *Eur J Clin Microbiol Infect Dis*. 2010; 29: 1043–1045.
68. Benjamin DK Jr, Driscoll T, Seibel NL *et al.* Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. *Antimicrob Agents Chemother* 2006; 50: 632–638.
69. Groll AH, Walsh TJ. Caspofungin: pharmacology, safety and therapeutic potential in superficial and invasive fungal infections. *Expert Opin Investig Drugs* 2001; 10: 1545–1558.
70. Walsh TJ, Adamson PC, Seibel NL *et al.* Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. *Antimicrob Agents Chemother* 2005; 49: 4536–4545.
71. Neely M, Jafri HS, Seibel N *et al.* Pharmacokinetics and safety of caspofungin in older infants and toddlers. *Antimicrob Agents Chemother* 2009; 53: 1450–1456.
72. Sáez-Llorens X, Macias M, Maiya P *et al.* Pharmacokinetics and safety of caspofungin in neonates and infants less than 3 months of age. *Antimicrob Agents Chemother* 2009; 53: 869–875.
73. Zaoutis T, Lehrnbecher T, Groll AH *et al.* Safety experience with caspofungin in pediatric patients. *Pediatr Infect Dis J* 2009; 28: 1132–1135.
74. Franklin JA, McCormick J, Flynn PM. Retrospective study of the safety of caspofungin in immunocompromised pediatric patients. *Pediatr Infect Dis J* 2003; 22: 747–749.
75. Groll AH, Attarbaschi A, Schuster FR *et al.* Treatment with caspofungin in immunocompromised paediatric patients: a multicentre survey. *J Antimicrob Chemother* 2006; 57: 527–535.
76. Natarajan G, Lulic-Botica M, Rongkavilit C, Pappas A, Bedard M. Experience with caspofungin in the treatment of persistent fungemia in neonates. *J Perinatol* 2005; 25: 770–777.
77. Odio CM, Araya R, Pinto LE *et al.* Caspofungin therapy of neonates with invasive candidiasis. *Pediatr Infect Dis J* 2004; 23: 1093–1097.
78. Seibel NL, Schwartz C, Arrieta A *et al.* Safety, tolerability, and pharmacokinetics of Micafungin (FK463) in febrile neutropenic pediatric patients. *Antimicrob Agents Chemother* 2005; 49: 3317–3324.
79. Hope WW, Seibel NL, Schwartz CL *et al.* Population pharmacokinetics of micafungin in pediatric patients and implications for antifungal dosing. *Antimicrob Agents Chemother* 2007; 51: 3714–3719.
80. Heresi GP, Gerstmann DR, Reed MD *et al.* The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. *Pediatr Infect Dis J* 2006; 25: 1110–1115.
81. Hope WW, Mickiene D, Petraitis V *et al.* The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous Candida meningoencephalitis: implications for echinocandin therapy in neonates. *J Infect Dis* 2008; 197: 163–171.
82. Smith PB, Walsh TJ, Hope W *et al.* Pharmacokinetics of an elevated dosage of micafungin in premature neonates. *Pediatr Infect Dis J* 2009; 28: 412–415.
83. Hope WW, Smith PB, Arrieta A *et al.* Population pharmacokinetics of micafungin in neonates and young infants. *Antimicrob Agents Chemother* 2010; 54: 2633–2637.
84. Benjamin DK Jr, Smith PB, Arrieta A *et al.* Safety and pharmacokinetics of repeat-dose micafungin in young infants. *Clin Pharmacol Ther* 2010; 87: 93–99.
85. Dornbusch HJ, Manzoni P, Roilides E, Walsh TJ, Groll AH. Invasive fungal infections in children. *Pediatr Infect Dis J* 2009; 28: 734–737.