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Antifungal agents and therapy for infants and children with invasive fungal infections: a pharmacological perspective

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Invasive fungal infections, although relatively rare, are life-threatening diseases in premature infants and immunocompromised children. While many advances have been made in antifungal therapeutics in the last two decades, knowledge of the pharmacokinetics and pharmacodynamics of antifungal agents for infants and children remains incomplete. This review summarizes the pharmacology and clinical utility of currently available antifungal agents and discusses the opportunities and challenges for future research.

Introduction

Despite recent advances in antifungal diagnostics and therapeutics, the attributable mortality of invasive fungal disease in neonates and children remains unacceptably high [1]. There exists, therefore, a clinical and regulatory imperative to establish safe and effective antifungal regimens for neonates and children. Much of the available data supporting paediatric dosing strategies for current antifungal compounds are gathered from studies designed to achieve drug exposures comparable with those for which efficacy and safety have been established in adults. Clinically significant differences exist, however, in both the pathophysiology of fungal infection and pharmacokinetics in paediatric populations compared with that of adults. The optimal treatment of fungal infection in this special population requires a detailed understanding of these differences, and studies to examine pharmacokinetics, safety and efficacy of antifungal therapies in neonates and children.

Principles of antifungal pharmacology for neonates and children

The impact of size on antifungal pharmacokinetics

The relationships between many physiological and morphological parameters and size are frequently non-linear. For example, Figure 1 shows the absolute estimates of clearance for caspofungin in a range of species that vary in size by approximately four orders of magnitude (data compiled from [2–5]). As demonstrated, this relationship is not linear, but better described using a power function. Power functions have been used to describe the pharmacokinetics of many agents in neonates and children [6], including the antifungal agents micafungin, fluconazole and amphotericin B lipid complex (see for example [7–9]). Such an approach is crucial to accurately predict drug behaviour over a wide range of sizes. The use of power functions does not imply the pharmacokinetics are necessarily non-linear

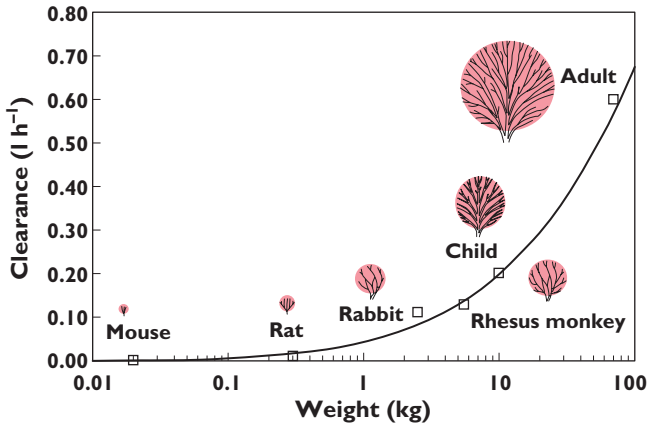


Figure 1

Schematic demonstrating the non-linear relationship between size (estimated using weight) and absolute value for clearance of caspofungin in mice, rats, rabbits, monkeys and humans. Clearance is higher in larger species and best described by a power function with an exponent of 0.75. Illustrations represent the increasing complexity of the fractal-based transport networks associated with an organ of increasing size. (Data compiled from [2–5])

for an individual patient, merely that drug exposure and hence dosing change in a non-linear way across a range of weights.

A theoretical explanation for the non-linear relationship between size (most often estimated with weight) and pharmacokinetic behaviour rests with the fact that the vasculature systems required to transport drugs to functional tissues (i.e. metabolically active cells such as hepatocytes) consume an increasing proportion of space within the organ as size increases [10]. The relationship between the size of an organ and its ever-diminishing weight-adjusted functional capacity is often best described using a scaling exponent of 0.75. An example of the impact of size on pharmacokinetic behaviour and consequently on dosing is shown in Figure 2.

Ontological changes in neonates

The maturation of hepatic clearance mechanisms and renal function is especially rapid in neonates and can have a significant impact upon the pharmacokinetics of many agents. Appropriate dosing can change very quickly. Neonates have comparatively less adipose tissue and more total body water compared with older children and adults. Furthermore, metabolic pathways mature in distinct sequential patterns. Isoform specific maturation of CYP enzymes occurs in the following phases: foetal (e.g. CYP3A7 and CYP4A1), early neonatal (e.g. CYP2D6, CYP2E1) and late neonatal (CYP3A4, CYP1A2). Glomerular filtration rate increases rapidly in early life, but in a non-linear manner. These changes may be difficult to predict because estimation of GFR is often problematic (in the first days of life creatinine reflects maternal circulating concentrations and subsequently rapidly changing muscle mass).

Dosing strategies

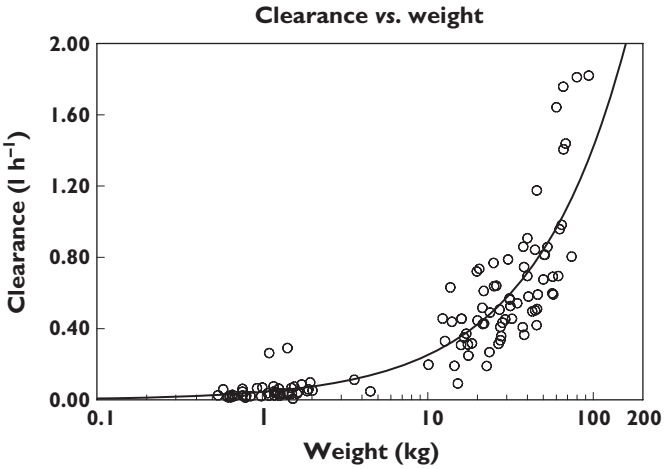
A number of approaches have been used to dose paediatric patients. Dosing on a 'mg kg^{-1}' basis is the simplest strategy, but there is a significant risk that neonates and infants may be under-dosed if adult weight-based dosages are used. Dosing can be assigned on the basis of bracketed ranges of weights and/or ages (for example, micafungin dosing regimens, see Table 1). A potential disadvantage of this method is that dosing at the boundaries of these brackets will likely be inaccurate. Drugs can also be administered on the basis of total body surface area and this has been used for caspofungin (see Table 1). This method works reasonably well because of the non-linear relationship between weight and body surface area, where surface area is proportional to weight$^{0.66}$ (in comparison with the 'true' relationship between clearance and weight, where clearance is proportional to weight$^{0.75}$). While this approach often works well for older children, estimates for surface area in neonates are difficult and frequently imprecise.

Clinical pharmacology of currently available antifungal agents

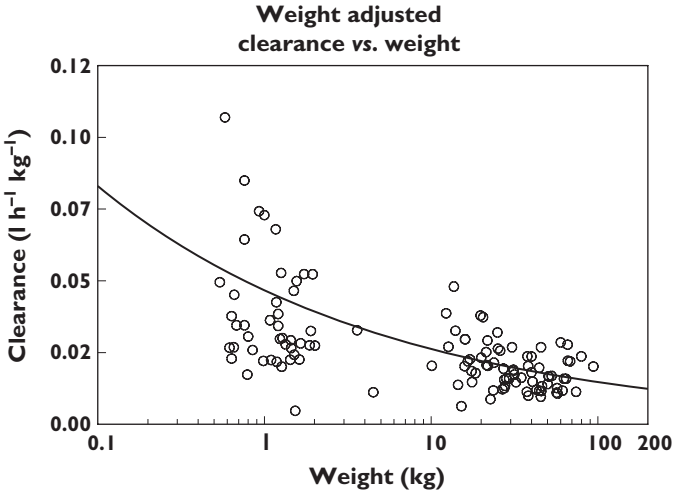
Polyenes

Introduction Amphotericin B, a natural product of *Streptomyces nodosus* [11], is the only polyene available for parenteral use. Amphotericin B is active against a majority of medically important *Candida* spp. and most *Aspergillus* spp., with the possible exceptions of *Aspergillus terreus* and *Aspergillus nidulans*. Solubilization of amphotericin B for parenteral administration was first achieved using the bile salt deoxycholate (amphotericin B deoxycholate) and later via incorporation into various lipid structures (e.g. amphotericin B lipid complex and liposomal amphotericin B). The molecular and clinical pharmacology of each these formulations are distinct and remain relatively poorly characterized (see for example [12–14]).

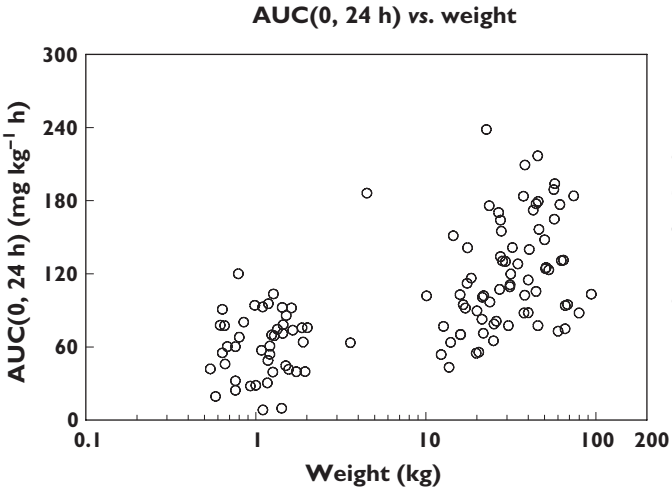
Amphotericin B formulations for neonates and children Amphotericin B deoxycholate, liposomal amphotericin B, amphotericin B lipid complex and amphotericin B colloidal dispersion have all been used to treat invasive fungal infections in neonates [13, 15–17]. There are several considerations relevant for the use of amphotericin B in this patient population: (i) all amphotericin B formulations penetrate the CNS (but not the CSF), which is important for the treatment of haematogenous *Candida* meningoencephalitis (HCME) [18]. A preclinical model of HCME suggests that all formulations have fungicidal activity in the CNS [13], which is also supported by at least some clinical data [19–21], (ii) amphotericin B does not achieve effective urinary concentrations, and may, therefore be ineffective for treatment of



Panel A. The absolute estimates for clearance for neonates and children aged 2-17 years. This estimates (open circles) were obtained after the Bayesian step by fitting a population pharmacokinetic model to the entire dataset (*n* = 117) of patients receiving micafungin. Clearance was parameterized in the following way: Clearance=Constant×(weight/70)$^{0.75}$. The solid line is the fit of the model to the data and is given by Clearance=1.085×(weight/70)$^{0.75}$. Of note clearance increases with weight, but in a non-linear manner.



Panel B. The estimates for clearance have now been adjusted for weight. Because of the non-linear relationship between clearance and weight, adjusting for weight does not provide a correction. Neonates have higher weight adjusted clearances compared with heavier children (even though their absolute estimates for clearance are much lower, as shown in A.



Panel C. Because AUC is inversely proportional to clearance (where: AUC=Dose (mg)/Clearance (l h^{-1}), the administration of a fixed weight-based dosage (2 mg kg^{-1} in this example) to all 117 patients results in lower AUCs in neonates. To achieve a comparable AUC to heavier children, neonates require higher weight-based dosages.

Figure 2

A) the non-linear relationship between weight and drug clearance following administration of micafungin. B) relationship between weight and weight-adjusted clearance of micafungin where a linear relationship between weight and clearance is assumed. C) resultant lower drug exposure (AUC) at lower weights following administration of micafungin per unit weight

candiduria and renal fungal balls [22] and (iii) the pharmacokinetics of amphotericin B deoxycholate are exceedingly variable in neonates, and this may lead to unexpected treatment failure or toxicity [23–25].

A dosage of amphotericin B deoxycholate 0.1 mg kg^{-1} results in undetectable serum concentrations [23]. The administration of 0.25 mg kg^{-1}, with escalation to 0.75–1 mg kg^{-1} to infants results in lower serum concentrations

Table 1

Antifungal agents currently available for use in paediatric patients

Drug	Formulation	Adult regimen	Neonatal regimen	Paediatric regimen	Current EMA licence
Amphotericin B	Amphotericin B Deoxycholate i.v. injection	0.6–1 mg kg^{-1} daily	0.5–1.5 mg kg^{-1}	0.6–1.5 mg kg^{-1} daily	- Severe systemic and deep fungal infections.
Amphotericin B	Liposomal amphotericin B i.v. injection	3–5 mg kg^{-1} daily	1–5 mg kg^{-1} daily	1–5 mg kg^{-1} daily	- Treatment of severe systemic and/or deep mycoses - Treatment of visceral leishmaniasis in immunocompetent patients including both adults and children. - Empirical treatment of presumed fungal infections in febrile neutropenic patients, where the fever has failed to respond to broad spectrum antibiotics and investigations have failed to define a bacterial or viral cause.
Amphotericin B	Amphotericin B lipid complex i.v. injection	3–5 mg kg^{-1} daily	1–5 mg kg^{-1} daily	1–5 mg kg^{-1} daily	- Treatment of severe invasive candidiasis. - Second line therapy for the treatment of severe systemic fungal infections in patients who have not responded to conventional amphotericin B or other systemic antifungal agents, in those who have renal impairment or other contra-indications to conventional amphotericin B, or in patients who have developed amphotericin B nephrotoxicity. - Second line treatment for invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients, fusariosis, coccidiomycosis, zygomycosis and blastomycosis.
Fluconazole	Capsule, oral suspension and i.v. injection	Prophylaxis: 200 mg daily Treatment: 400–800 mg daily	Newborn (0–14 days) maximum dose 12 mg kg^{-1} every 72 h Newborn (15–27 days) maximum dose 12 mg kg^{-1} every 48 h Consideration given to a loading dose 25 mg kg^{-1}	Infants and children 6–12 mg kg^{-1} daily	- Treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. - Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence.
Itraconazole	Capsule, oral cyclodextrin suspension and i.v. cyclodextrin injection	200 mg twice daily	Very limited data with a single report describing the use of 5 mg kg^{-1} twice daily	2.5–5 mg kg^{-1} twice daily	- Other antifungal agents recommended due to paucity of data. - For the treatment of oral and/or oesophageal candidosis in HIV-positive or other immunocompromised patients. - As prophylaxis of deep fungal infections anticipated to be susceptible to itraconazole, when standard therapy is considered inappropriate, in patients with haematological malignancy or undergoing bone marrow transplant, and who are expected to become neutropenic. - Insufficient clinical efficacy data in the prevention of aspergillosis.
Voriconazole	Capsule, oral suspension and i.v. cyclodextrin injection	Oral dosing: 400 mg twice daily for two doses, then 200 mg twice daily i.v. dosing: 6 mg kg^{-1} twice daily for two doses, then 4 mg kg^{-1} twice daily	Very limited data with dosages ranging from 3.4–14.7 mg kg^{-1}	Oral dosing: 9 mg kg^{-1} (maximum 350 mg in 12 h) i.v. dosing: 9 mg kg^{-1} twice daily for two doses, then 8 mg kg^{-1} twice daily	- Only licenced for children >2 years. - Treatment of invasive aspergillosis. - Treatment of candidaemia in non-neutropenic patients. - Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*). - Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.
Posaconazole	Oral suspension	Prophylaxis: 200 mg 8 hourly Treatment: 400 mg twice daily	Very limited information in this setting	Adult regimen used for children aged 8–17 years	- No licence for patients <18 years of age.
Caspofungin	I.v. injection	70 mg loading dose, followed by 50 mg daily	Limited data for use of caspofungin in neonates and younger children with doses of 25 mg m^{-2} daily (<3 months) and 50 mg m^{-2} daily (3–11 months).	Children 12 months–17 years loading dose 70 mg m^{-2} followed by 50 mg m^{-2} daily (maximum dose 70 mg)* *Increased to 70 mg m^{-2} daily if clinical response inadequate.	- Treatment of invasive candidiasis in adult and children. - Treatment of invasive aspergillosis in adult or paediatric patients refractory to or intolerant of amphotericin B and/or itraconazole. (Refractory disease is defined as progression of infection or failure of clinical improvement after a minimum of 7 days of therapeutic doses of effective antifungal therapy). - Empirical therapy for presumed fungal infections (*Candida* or *Aspergillus)* in febrile, neutropenic adult or paediatric patients.
Micafungin	I.v. injection	Treatment of invasive candidiasis: 100 mg daily, increased to 200 mg daily if clinical response inadequate Treatment of oesophageal candidiasis: 150 mg daily Prophylaxis: 50 mg day^{-1}	4–10 mg kg^{-1}* *Higher dosages may be required for CNS infection	Body weight >40 kg: adult dosing Body weight <40 kg: Invasive candidiasis 2 mg kg^{-1} daily** Oesophageal candidiasis 3 mg kg^{-1} daily Prophylaxis of *Candida* infection 1 mg kg^{-1} daily **Increased to 4 mg kg^{-1} daily if clinical response inadequate	- Treatment of invasive candidiasis in children <16 years, including neonates. - Prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia for 10 or more days.
Anidulafungin	I.v. injection	200 mg loading dose, 100 mg daily	*1.5 mg kg^{-1} day^{-1} *Higher dosages may be required for CNS infection, although safety remains to be confirmed	0.75–1.5 mg kg^{-1}	- No licence for patients <18 years of age.

compared with similar dosages in adults [24]. A dosage of 1 mg kg^{-1} results in significantly higher weight-corrected estimates for clearance in infants and younger children compared with older children [26]. This is one potential reason amphotericin B deoxycholate is better tolerated in neonates compared with adults [24] and may provide an explanation for the observation that a massive overdose in a neonate only led to transitory renal dysfunction [27]. Despite these studies and decades of clinical experience, the optimal dosage of amphotericin B deoxycholate for neonates is not known.

The various lipid formulations of amphotericin B are increasingly used in place of amphotericin B deoxycholate, predominantly because of their more favourable toxicity profiles. Liposomal amphotericin B (dosage range 1–7 mg kg^{-1} day^{-1}; [16, 17, 28, 29]) and amphotericin B lipid complex (ABLC; dosage range 3.2–6.5 mg kg^{-1} [9, 30]) are the most commonly used compounds in the USA and Europe. Despite relatively extensive information on clinical usage and safety, the pharmacokinetics of these compounds are poorly characterized in both neonates and children. There are no pharmacokinetic studies of liposomal amphotericin B in neonates, and only a single study of ABLC that used 2.5–5 mg kg^{-1} day^{-1} [9]. While a dosage of liposomal amphotericin B 5 mg kg^{-1} is probably reasonable, this is not supported by pharmacokinetic studies that enable equivalence of drug exposure to be established.

With the advent of newer agents and formulations, amphotericin B deoxycholate is now used less commonly in older children. A dosage of 0.5–1 mg kg^{-1} and 1 mg kg^{-1} day^{-1} is generally used for invasive candidiasis and invasive aspergillosis, respectively [31]. Population pharmacokinetic models have incorporated non-linear scaling terms to describe the behaviour of the drug in children, and demonstrated that smaller children receiving 1 mg kg^{-1} have significantly lower AUCs compared with heavier children [32]. Thus there is a potential danger of under dosing smaller children using a weight-based regimen designed for adults. The pharmacokinetics of amphotericin B deoxycholate depend on whether the drug is administered in dextrose or in a lipid emulsion (the latter results in higher estimates for clearance and volume) [32]. However, the clinical consequences of these pharmacokinetic differences are not known. A clinical study did not suggest any differences in efficacy or toxicity when amphotericin B deoxycholate was administered in these different ways [33].

The pharmacokinetics of liposomal amphotericin B have been described in children [34]. These analyses suggest that both volume and clearance are affected by weight. Further studies are required to design appropriate regimens for smaller children. The clinical efficacy and safety of ABLC have been studied in children using dosages of 1–5 mg kg^{-1} daily (see Table 1). Further pharmacokinetic studies and analyses of lipid amphotericin B formulations in children are urgently required to identify regimens that achieve comparable drug exposures to those observed in adults receiving 3 mg kg^{-1} day^{-1}.

Flucytosine (5FC, 5-flurocytosine)

Introduction Flucytosine is a fluorinated pyrimidine analogue that interferes with fungal nucleic acid synthesis. This compound was discovered in the late 1950s in the course of antineoplastic drug discovery programmes where it was found to have activity against yeasts [11]. Flucytosine is invariably administered in combination with other antifungal agents because of the potential for rapid emergence of drug resistance when administered alone. Perhaps the most useful attribute of flucytosine is its extensive penetration into tissues and fluids (including CSF and urine), which makes it a potentially useful adjunct for other first line agents, especially for treatment of cryptococcal meningitis or *Candida* infections at sanctuary sites (e.g. central nervous system candidiasis and urinary candidiasis [35–37]). The most significant adverse event related to flucytosine use is concentration-dependent myelotoxicity. Peak concentrations >100 mg l^{-1} are associated with toxicity in adults, but there are no specific data for children [38].

Flucytosine for neonates and children Flucytosine is still occasionally used for neonates with disseminated candidiasis and involvement of the central nervous system and/or urinary tract. There is, however, uncertainty as to whether flucytosine is beneficial for HCME [18]. Furthermore, flucytosine is poorly tolerated and severe gastrointestinal upset can delay early oral feeding in neonates. Therefore, the decision to use flucytosine for neonates requires a careful assessment of the potential risks and benefits.

As a result of the relatively low GFR in infancy, and lower clearance rates than predicted on the basis of weight alone, neonates require a lower dosage of flucytosine compared with older children to achieve comparable systemic drug exposure. A dosage of 25–100 mg kg^{-1} daily in one to three divided dosages is recommended [39]. Extreme pharmacokinetic variability is observed and is a further reason therapeutic drug monitoring and dosage adjustment should be considered in this population [39]. Flucytosine is rarely used in children. The currently recommended dose in children older than 1 month is 100–150 mg kg^{-1} in four divided dosages (i.e. adult dosing).

Triazoles

Introduction The triazoles revolutionized the treatment of invasive fungal infections by providing orally bioavailable alternatives to the polyenes and echinocandins. The triazoles interfere with the fungal specific enzyme 14-alpha-demethylase required for sterol synthesis. These compounds have a common triazole ring, but different side arms that account for differences in the spectrum of activity, clinical pharmacology and toxicity [11].

Fluconazole is the only triazole that is routinely used in the nursery. There is little role for the routine use of other extended spectrum triazoles with anti-*Aspergillus* activity (i.e. itraconazole, voriconazole, posaconazole) in this setting where *Candida albicans* and *Candida parapsilosis* are the predominant pathogens [40]. Mould-active triazoles (itraconazole, voriconazole, posaconazole) are extensively used in children. While the overall rates of triazole resistance remain low, there are increasing reports of resistance in *Aspergillus* spp. especially in Europe [41, 42]. Fluconazole has no inherent activity against *Aspergillus* spp., which is an occasional pathogen in neonates [43]. Breakthrough infections caused by fluconazole-resistant organisms have been described [44]. Fluconazole penetrates the central nervous system (including CSF) and the urine, and may therefore be useful for treatment of infections at these sites [45–47].

Use of fluconazole for neonates and children Fluconazole is widely used for the prevention and treatment of invasive *Candida* infections in the nursery. Routine use in high-risk babies (e.g. <28 weeks gestation or <1000 g) with 3–6 mg kg^{-1} every 24–72 h results in fewer invasive fungal infections, but may not decrease overall mortality [31, 48]. In other clinical settings, the decision to use fluconazole is frequently embedded in a risk stratification strategy where a variety of risk factors for the development of invasive candidiasis are also considered (e.g. presence of a central line, use of third generation cephalosporins, isolation of *Candida* at a non-sterile site).

The regimen for fluconazole prophylaxis for premature neonates was initially based on preliminary pharmacokinetic studies that suggested 6 mg kg^{-1} resulted in concentrations 72 h post-dose that were above the MIC of *Candida parapsilosis* [49]. The half-life in this patient population is approximately 48–72 h [49]. The pharmacokinetics of fluconazole in the first weeks of life are affected by the relatively high total body water and low glomerular filtration rate (GFR) [50]. The impact of these physiological changes on pharmacokinetics is further compounded by drug-induced renal impairment [8]. The prolonged serum half-life and relative renal insufficiency of prematurity is the principal reason for using a longer dosing interval in the first weeks of life (i.e. 48–72 h). Clearance progressively increases with increasing gestational age [8], and also doubles in the first 4 weeks of life. Consequently, progressive alterations in fluconazole regimen (dosage escalation and/or more frequent administration) may be required to achieve desired target AUC : MIC values (see, for example, dosing regimens in clinical trials examining the utility of fluconazole for prevention of fungal infections in neonates where the schedule of administration changes with increasing post-natal age [51, 52]).

Fluconazole can also be used for the treatment of invasive candidiasis in premature infants [46, 53]. A dose of 5–6 mg kg^{-1} daily has been used for this indication. A higher neonatal dosage of 12 mg kg^{-1} daily administered to infants <29 weeks gestation results in a median AUC of ~700 mg l^{-1} h (adults receiving 800 mg day^{-1} have a mean AUC of ~800 mg l^{-1} h [54]). A loading dose of 25 mg kg^{-1} can be considered, and enables the desired AUC : MIC pharmacodynamic target to be achieved as early as possible [55]. Further safety data are required and currently being collected for these elevated dosages. While advocated by some, therapeutic drug monitoring for fluconazole is generally not considered or performed [53]. Importantly, however, a validated assay is available [56], and measurement of serum concentrations could be performed to ensure optimal dosing, especially in the circumstance of rapidly changing physiology where there is considerable uncertainty about the most appropriate regimen.

Fluconazole is used extensively for older children for the prevention and treatment of disseminated candidiasis. The pharmacokinetics are linear following the administration of 2, 4 and 8 mg kg^{-1} day^{-1} [57]. A dosage of 8 mg kg^{-1} day^{-1} produces an AUC of ~200 mg l^{-1} h [57], which is comparable to an average adult receiving ~200 mg day^{-1} [54]. Of note, this is a lower drug exposure than expected in adults receiving 400–800 mg day^{-1}, which is the usual dosage used for the treatment of disseminated candidiasis, and therefore suggests some children may be inadvertently under-dosed, especially for treatment of an organism with reduced susceptibility (i.e. an isolate with an MIC around the breakpoint of 8 mg l^{-1}). Dosage escalation may therefore be reasonable in selected cases.

Itraconazole for neonates and children Itraconazole is an orally bioavailable triazole with broad-spectrum activity against a range of medically important fungi. There are a number of formulations including a capsule (not generally used in children), cyclodextrin oral solution and an intravenous preparation. The clearance of itraconazole occurs through hepatic oxidation and results in the production of an active metabolite (hydroxyitraconazole), which has antifungal potency comparable with the parent compound, and is responsible for discordant measurement of serum concentrations with high performance liquid chromatography and bioassay. The ratio $AUC_{itraconazole}$: $AUC_{hydroxyitraconazole}$ is approximately 1:2 in serum [58]. The pharmacokinetics are non-linear in adults [59], and limited data suggest that the same is true for children [58]. Itraconazole is generally well tolerated, although the oral suspension is exceedingly unpalatable, which may have an impact upon compliance.

Itraconazole is not generally used in the nursery. A dose of 5 mg kg^{-1} twice daily has been used with apparently favourable clinical outcomes, but serum concentrations were not estimated [60]. There are only limited pharmacokinetic data for itraconazole administered to children aged >6 months. A single intravenous dosage of 2.5 mg kg^{-1} day^{-1} in children aged 7 months–17 years is well tolerated, but results in trough concentrations <

0.25 mg l^{-1} [61]. Similarly, an oral solution of itraconazole 2.5 mg kg^{-1} 12 hourly results in trough concentrations that progressively increase in the first 30 days of therapy and are approximately 1 mg l^{-1} after that period [58, 62]. A dosage of 5 mg kg^{-1} day^{-1} results in lower concentrations in children aged 6 months–2 years compared with children >2 years [63], suggesting a non-linear relationship between weight and clearance, and meaning smaller children may require higher weight-based dosages. A regimen of 2.5 mg kg^{-1} 12 hourly is effective for treatment of oropharyngeal candidiasis in HIV positive children [58], and for prevention of invasive fungal infection in children with neutropenia [64].

Therapeutic drug monitoring of itraconazole should be considered as a matter of routine. Drug concentration targets of trough >0.5 mg l^{-1} measured using HPLC and >5 mg l^{-1} using bioassay, but <17 mg l^{-1} (measured using bioassay) are currently used, although these targets have been directly extrapolated from studies in adults [65–67].

Voriconazole for neonates and children Voriconazole is a structural congener of fluconazole that was specifically engineered to extend the antifungal spectrum of fluconazole to *Aspergillus* spp [11]. Voriconazole is a first line agent for the treatment of infections in adults caused by *Aspergillus* spp., *Scedosporium apiospermum* and *Fusarium* spp. (see Table 1). On occasions, voriconazole may be a potentially useful agent for the treatment of *Candida* spp. with reduced or frank resistance to fluconazole (e.g. *C. glabrata, C. krusei*) [68].

There are several reports describing the use of voriconazole in the nursery. In general, voriconazole does not offer significant advantages over fluconazole in this clinical setting, but may be useful for the treatment of rare cases of invasive aspergillosis [43, 69]. Dosages in the range 3.4–14.7 mg kg^{-1} 12 hourly have been used in preterm infants [69, 70]. Extreme variability in serum concentrations is apparent, with no clear relationship between drug exposure and weight-based dosages [69]. Further carefully designed pharmacokinetic studies are required.

There have been a number of pharmacokinetic studies and population pharmacokinetic models for voriconazole in children [71–74]. The pharmacokinetics of voriconazole in older children and adults are characterized by significant variability in concentration–time profiles and non-linear clearance (i.e. a constant amount rather than a constant fraction of drug is cleared per unit time) [75]. The major clinical consequence of non-linear pharmacokinetics is the disproportionate change in drug exposure (e.g. AUC or trough concentration) with a change in dosage. For younger children, voriconazole pharmacokinetics appear linear when adult weight-based dosages are used (e.g. 4–6 mg kg^{-1}), although non-linear behaviour may be seen at higher dosages.

Population pharmacokinetic models fitted to pharmacokinetic datasets from children have been used to define regimens that produce comparable drug exposures with those observed in adults [76]. There has been a progressive upwards revision of the recommended dosage from 7 mg kg^{-1} twice daily i.v. followed by 200 mg daily by mouth regardless of weight (the regimen initially approved by the EMA) to the currently recommended regimen of 9 mg kg^{-1} twice daily followed by 8 mg kg^{-1} twice daily i.v., based on more recent studies and pharmacokinetic models [72]. All population pharmacokinetic analyses have consistently quantified the considerable pharmacokinetic variability that is apparent in children [71–74]. Such variability in the context of increasingly well-defined concentration–effect and concentration–toxicity relationships for voriconazole in both adults and children provides the basis for therapeutic drug monitoring [74, 77]. A trough concentration target of 1 to 5–6 mg l^{-1} is used in adults [77]. A recent study in children demonstrated a higher probability of death if trough concentrations were <1 mg l^{-1} [74]. The use of an upper concentration bound of 5–6 mg l^{-1} in children is unclear given the lack of correlation between voriconazole drug exposure and hepatotoxicity [72, 74]. While there is little debate amongst clinicians that therapeutic drug monitoring is necessary, there is considerable uncertainty regarding the best time to obtain samples and the best way to adjust dosages. Both of these questions require further study. Nevertheless, a recent population pharmacokinetic model suggests that for every 1 mg kg^{-1} dosage increase in children, the median trough concentrations increases by a fixed amount of 0.52 mg l^{-1}, which provides a guide for dosage adjustment [74].

Posaconazole for neonates and children Posaconazole is a broad-spectrum triazole agent that exhibits structural homology with itraconazole. This agent is only currently available as an oral suspension, although newer formulations are in development. The pharmacokinetics of a solid capsule in a phase I study in adults have recently been described. Unfortunately, however, this formulation (if licensed) will only be potentially suitable for older children and adolescents. Posaconazole has fewer drug–drug interactions than voriconazole [11]. There is an increasing recognition that therapeutic drug monitoring is required [78]. While there is some uncertainty regarding target concentrations, trough concentrations of 0.7 and >1 mg l^{-1} (at steady-state) are probably reasonable for prophylaxis and treatment of established infection, respectively, although both of these values are derived from adults [78].

There are currently no studies examining the pharmacokinetics of posaconazole in neonates. A dosage of 6 mg kg^{-1} 8 hourly has been used without untoward effect in a 610 g neonate with cutaneous aspergillosis as consolidation therapy and this resulted in trough serum concentrations of 1.6 mg l^{-1} after 5 days of therapy [79].

Children aged 8–17 years with proven or probable invasive fungal infections receiving 800 mg day^{-1} posaconazole

due to refractory disease or intolerance to other antifungal agents have median serum concentrations that are comparable with adults [80]. Further studies are required to define appropriate regimens for younger children, especially with the advent of newer formulations. While posaconazole is not licensed for patients <18 years (Table 1), there are at some data supporting efficacy and safety in this population [81].

Echinocandins

Introduction The echinocandins (caspofungin, micafungin and anidulafungin) are large molecular weight semisynthetic lipopeptides that are non-reversible inhibitors of glucan synthase. This enzyme is a membrane-associated protein responsible for the synthesis of 1,3 β-D-glucan, a sugar required for structural integrity of the fungal cell wall. For older children and adults, the echinocandins are increasingly viewed as first line agents for the treatment of candidaemia and disseminated candidiasis [31]. Their role in the nursery is less clear, although accruing evidence suggests they may be safe and effective, especially for the treatment of invasive infections caused by *Candida* spp [82]. In general, there are few clinically or microbiologically relevant differences between these agents, and they may ultimately be used interchangeably. Currently, however, there are significant differences in the clinical experience and licenses for each of these agents (Table 1), which in turn are a reflection of the preclinical and clinical studies that have been performed in neonates and children.

The echinocandins are rapidly fungicidal against *Candida albicans* in murine models of disseminated candidiasis (see, for example, [83]). As a class, they are also active against *Candida glabrata* and some authorities suggest they are the agents of choice for the treatment of invasive infections caused by this pathogen [31]. *Candida parapsilosis* is intrinsically less susceptible to the echinocandins, which is related to the structure of the target protein Fks1. Clinical studies in adults suggest that outcomes from infections caused by *Candida parapsilosis* and treated with an echinocandin are comparable (numerically fewer, but not statistically inferior) with other antifungal agents [84]. Successful treatment of *Candida parapsilosis* infections has been reported in neonates [85]. Nevertheless, it may be prudent to use another antifungal agent for a patient with *Candida parapsilosis* infection who is clinically unstable or failing to respond to therapy with an echinocandin. There are emerging reports of echinocandin resistance in adults infected with *Candida albicans* and *Candida glabrata*, which is related to substitutions of amino acids in the Fks1 subunit of 1,3-β-D-glucan synthase [86, 87]. In general, these mutations render the echinocandins ineffective [83]. PK–PD bridging studies suggest that dosage escalation is unlikely to be an effective therapeutic strategy for overcoming resistance due to such amino acid substitutions in *Candida albicans*. The implications for children and broader public health of these emerging resistance patterns to the echinocandins in *Candida* remain unknown, but are cause for concern.

Echinocandins for neonates The echinocandins may be useful for neonates infected with less common *Candida* spp. (e.g. *Candida lipolytica*, *Candida krusei* [88]), triazole-resistant *Candida albicans* [44] and otherwise susceptible pathogens that are refractory to other first line agents [89, 90]. There are several considerations for the use of echinocandins for neonates. The first is that this class of compounds is generally thought to be ineffective for the treatment of infections in the central nervous system, such as HCME, which is an ever-present consideration in premature babies infected with *Candida* spp. A body of preclinical evidence suggest that this view may be incorrect. All echinocandin agents penetrate the cerebrum (as opposed to the CSF) in a dose-dependent manner, and achieve concentrations that are effective in preclinical models (see for example [91]). Limited clinical data also suggest that the echinocandins may be effective agents for the treatment of central nervous system infections [90]. Second, are concerns related to the predominance of *Candida parapsilosis* in the nursery, and the relatively reduced potency of echinocandins against this pathogen. Some recent epidemiological reports have described *Candida parapsilosis* breakthrough infection in adult patients receiving caspofungin [87]. Thirdly, there has been some debate, especially in Europe, regarding the safety of micafungin. The European Medicines Agency (EMA) suggests that micafungin should not be used if the use of alternative agents is possible. This recommendation is based on the development of hepatic tumours in rats exposed to high dosages of micafungin for prolonged periods. The Food and Drug Administration (USA) has not issued a similar warning. To date, there is no clinical signal to suggest an elevated risk of hepatic injury or neoplasia in humans, despite extensive global usage of this compound. Similar preclinical experiments with either caspofungin or anidulafungin have not been performed. Fourthly, as with the polyenes, the echinocandins do not achieve therapeutic urinary concentrations, and may not be effective agents for the treatment of candiduria [92].

Optimal regimens of caspofungin in neonates remain uncertain. Dosages of 1–2 mg kg^{-1} daily have been used in conjunction with other antifungal agents for a small number of neonates with candidaemia [90]. A relatively small pharmacokinetic study concluded that dosing should be administered on the basis of surface area (despite the problems with this measure of size in neonates and infants) and suggested an appropriate regimen is 25 mg m^{-2} daily [93]. Importantly, however, the dosage of caspofungin that is required to treat HCME is not known from either clinical studies or preclinical models. Furthermore, the pharmacokinetic data and analyses do not enable confident predictions about the relationship

between dosage and systemic drug exposure to be established.

There is both preclinical and clinical evidence to support the use of micafungin in neonates. There is ongoing debate regarding the optimal regimen. The efficacy of micafungin 0.5–1 mg kg^{-1} has been described in a small case series [94]. The original neonatal pharmacokinetic study characterized the serum concentrations in premature infants receiving dosages of 0.75–3 mg kg^{-1} daily [95]. This study demonstrated that the pharmacokinetics are linear, but that younger infants have higher weight-based clearances and therefore lower systemic drug exposures than children and adults. An *in vivo*-to-human bridging study suggests that dosage escalation may be required to ensure near maximal antifungal therapy in the central nervous system [96]. Based on this pre-clinical study, as well as a series of sequential clinical pharmacokinetic studies and population pharmacokinetic models examining regimens of 7, 10 and 15 mg kg^{-1} [97–99], a phase III clinical trial is currently comparing micafungin 10 mg kg^{-1} daily with amphotericin B deoxycholate.

The evidence supporting the use of anidulafungin in neonates is currently somewhat limited. Anidulafungin 1.5 mg kg^{-1} day^{-1} results in exposures for infants and neonates that appear comparable with older children receiving the same weight-adjusted dosage [100, 101] and adults receiving 100 mg day^{-1} [102]. A PK–PD bridging study suggests that a higher dosage may be required to treat HCME (e.g. 9 mg kg^{-1} load, followed by 4.5 mg kg^{-1} daily) [103]. The safety of this higher dosage has not yet been determined.

Echinocandins for children The use of echinocandins in children with invasive fungal infections is largely predicated on efficacy studies performed in adults (e.g. [84, 104–106]), with only a single sub-study that has compared micafungin with liposomal amphotericin B in children [107]. For adult patients, the echinocandins are first line agents for the treatment of candidaemia and invasive candidiasis [31]. All three licensed agents have activity against *Aspergillus* spp. in laboratory animal models of invasive pulmonary aspergillosis [108–110], although their use for the treatment of invasive aspergillosis (as single agents) remains somewhat uncertain, especially for profoundly immunocompromised hosts [111, 112]. Caspofungin and micafungin have been used for salvage therapy for patients with invasive aspergillosis who are refractory or intolerant of other antifungal agents [111, 113]. The echinocandins can be used for patients with profound and prolonged neutropenia, with fever that is refractory to broad-spectrum antibacterial agents (caspofungin is currently the only agent with a licence for this indication) [114, 115]. Both preclinical and retrospective clinical studies suggest the echinocandins may also have a role in combination with triazoles for treatment of patients with invasive aspergillosis (see for example [116, 117]). However, the final results of a randomized clinical study comparing anidulafungin and voriconazole *vs*. voriconazole alone are pending.

Caspofungin is extensively used in children. The pharmacokinetics of caspofungin in age-stratified cohorts (2–11 and 12–17 years) suggest that dosages of 1 mg kg^{-1} daily result in drug exposures that are significantly lower than observed in adults receiving a standard 50 mg daily [3]. In contrast, surface area-adjusted dosing (70 mg m^{-2} loading dose followed by 50 mg m^{-2} maintenance, with the option to increase the maintenance to 70 mg m^{-2} day^{-1} if clinically indicated) results in drug exposures across a range of ages that are clinically effective and comparable with adults [3, 118].

Similarly, the pharmacokinetics of micafungin are well characterized in children aged 2–17 years [7, 119]. A population pharmacokinetic model provides an estimate of dosing across a range of weights that are required to achieve comparable AUCs with adults [7]. The current licensed regimen for invasive candidiasis is 2 mg kg^{-1} with the option to increase to 4 mg kg^{-1} for children < 40 kg. A different regimen is suggested for prophylaxis and treatment of oesophageal candidiasis (see Table 1).

There are fewer data for anidulafungin. One potential difference with the other echinocandins relates to the unique mechanism of clearance, whereby the parent compound undergoes spontaneous non-enzymatic hydrolysis in the blood [11]. Thus, clearance may not be affected by weight to the same extent as other compounds. In older children, the administration of a fixed weight-based regimen to neutropenic children (aged 2–17 years) results in similar AUCs across a wide range of weights [101]. A dosage of 0.75 and 1.5 mg kg^{-1} day^{-1} results in drug exposures that are comparable with adults receiving 50 and 100 mg day^{-1}, respectively [101, 102]. Further studies are required to determine the safety and efficacy of anidulafungin for children.

Research challenges and future opportunities

Practical challenges

Invasive fungal infections represent the worst of all worlds for paediatric therapeutic needs. Fungal infections are common enough that they represent a significant health burden for children, but they are infrequent enough that a well-powered efficacy study for treatment remains challenging. These obstacles are further compounded by the fact that consent rates in neonatal studies are typically low and many patients with confirmed infection have already received antifungal therapy. This has prompted the development of research networks in several countries (e.g. Medicines for Children Research Network in the UK). Recently, more pragmatic enrolment strategies have been employed, including enrolment of children receiving

antifungals in accordance with local standards of care, and the inclusion of those receiving empirical antifungal therapy. These methods increase the number of potential eligible infants and have already been successfully used to study a number of antifungal agents [8, 99, 101].

The frequency of sampling is a critically important issue for infants and children. Multiple blood draws in critically-ill infants may be difficult to justify. The overall goal is to describe the pharmacokinetics as precisely as possible with the fewest samples. The collection of information-poor data may lead to biased parameter estimates, which may lead to poor predictions for candidate antifungal regimens. Statistical methods such as D-optimal design theory can be used to identify the most informative sampling times throughout the dosing interval (see for example [99]). Use of dried blood spots and ultra-low sample volumes (e.g. <50 µl) are further ways that will lead to an improved understanding of pharmacokinetics for neonates and children [120].

Regulatory issues

Children present unique challenges for the conduct of high quality clinical trials. The FDA and the EMA have attempted to facilitate paediatric clinical trials to meet the urgent need for high quality studies specifically addressing the many clinical questions in paediatric populations.

There are three large programmes in the United States: (i) The Pediatric Research Equity Act that enables phase I and II trials of newly developed anti-infective agents, and are usually planned at the time of phase III testing in adults, (ii) The Best Pharmaceuticals for Children Act Program, administered by the National Institute of Child Health and Human Development facilitates phase II pharmacokinetic–pharmacodynamic and safety trials for off-patent agents and (iii) The Pediatric Exclusivity Program, which often results in larger phase II and phase III trials and are usually planned post-licensure during the latter half of the patent life of the compound.

The European Union, via the EMA, now mandates that at the end of phase I testing of new compounds, a Paediatric Investigational Plan (PIP) is designed and is a prerequisite for the approval of new agents. These studies are variable in size and scope and typically reflect adult indications. These programmes have been a significant step forward for paediatric therapeutics. They have provided substantial pharmacokinetic, safety and efficacy data for many compounds [121].

Conclusions

Invasive fungal infections are devastating infective syndromes that still result in death or serious long term morbidity in neonates and children. We know that dependence on extrapolation from studies in adults leaves a gaping deficiency in the knowledge necessary to inform clinical practice, and poorly designed trials and/or pedestrian pharmacokinetic modelling squanders the relatively limited opportunities to improve the treatment for this vulnerable patient population. Much progress has been in the way that new antifungal agents are being investigated in paediatric populations, with more precise dosing strategies based on an understanding of pharmacokinetics. However, for many antifungal agents, data that support optimal dosing and target drug ranges specifically in neonates and children are lacking. The challenge, therefore, is to ensure funding bodies, physicians and pharmacologists can work together to ensure focussed and efficient studies are appropriately designed and executed in order to improve clinical outcomes.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: JML; no support from any organization for the submitted work; MCW has received grant support from NIH and acted as a consultant for Pfizer Inc.; DKB has received grant support from Astra Zeneca, NIH, UCB Pharma, and acted as a consultant for Cubist Pharmaceuticals, Johnson and Johnson, Merck, Pfizer and The Medicines Co; PBS has received grant support from NIH, CV Therapeutics and acted as a consultant to Astellas, Johnson and Johnson, and Pfizer; WWH has received grant support from MRC, NIHR, EU FP7, NC3Rs, Astellas, Pfizer and Gilead, has given talks and acted as a consultant for Pfizer, Astellas, F2G, Vectura and Gilead.

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