Use of Antifungals Other Than Amphotericin B for Invasive Fungal Infections in Neonates and Children

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ABSTRACT

Antifungal therapy for neonates, children, and adolescents, especially in those with primary or secondary immunodeficiencies having invasive fungal infections, is possible today due to the advent of newer antifungals. Studies of antifungals in the pediatric age-group are limited to those for cutaneous fungal infections. Although there are a few studies on the pharmacokinetics and safety, these drugs are used off-label, and most dosage recommendations are extrapolated from the adult data. A review of the use of antifungals other than amphotericin B for treatment of invasive fungal infections in pediatrics is the focus of this article.

Keywords: Antifungal agents, Caspofungin, Children, Fluconazole, Itraconazole, Neonate.

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INTRODUCTION

The need for newer antifungals and the issues regarding the pharmacologic characteristics of antifungals in neonates and children were discussed in the article on amphotericin B in the last issue.[1]

Dosing Strategies

A number of dosing strategies have been tried of which probably the most accurate is that based on surface area of the child; assessment of surface area of newborn child is difficult and often not accurate. The various strategies used for the various antifungals discussed in this review are listed in Table 1.[2] Note that most dosages are calculated on a "mg kg^{-1}" basis, which carries a significant risk of underdosing in neonates and children if the reference dose is the adult dosage. In case of micafungin, the dose is bracketed for ranges of weights and/or ages that could result in erroneous dosing in the extremes of the given range.

Classification of Antifungals According to the Mechanism of Action

The antifungal drugs are classified into 3 groups: antifungal agents acting on plasmatic membranes (azoles, polyenes), drugs acting on synthesis of nucleic acids (5-flucytosine), or those acting on fungal cell walls (echinocandins).[3]

Antifungal Agents, Other Than Amphotericin B, Currently Available for Treating IFI in Neonates and Children

Antifungals for systemic use other than amphotericin B include fluconazole capsule, oral suspension and intravenous (IV), itraconazole as capsule and IV, oral cyclodextrin suspension and IV cyclodextrin (if these formulations are available), IV caspofungin, and IV micafungin. The specific indications for each of these antifungals are also detailed in Table 1.[2]

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Drug Monographs of Antifungals Other Than the Polyenes (Amphotericin B) with Reference to Use in IFI in Neonates and Children

Flucytosine [5FC, 5-flurocytosine]

Rapid development of resistance to flucytosine occurs when it is administered as a standalone drug in the treatment of ISI. Therefore, it is advisable that flucytosine be administered in combination with other antifungal agents. The main advantage of this drug is its property to achieve high levels in tissues (including CSF and urine) and thereby be useful adjuvants to first-line drugs in treating cryptococcal meningitis or candida infections in central nervous system and urinary tract,[4–6] even in neonates[7] although a study cast doubts on its effectiveness in treating HCME.[8]

The fact that flucytosine is poorly tolerated and causes severe gastrointestinal upset, in turn delaying early oral feeding in neonates, must be factored when deciding to use the drug in the newborn period. Concentration-dependent myelotoxicity— aplastic anemia, leukopenia, and thrombocytopenia—and hepatotoxicity are the most severe side effects of flucytosine, possibly avoidable with close monitoring to maintain 5-FC concentrations at <100 mg/L and reversible with drug discontinuation or reduction of dose in adults;[9] no data on this is thus far available in children.

Table 1: Antifungal agents, other than amphotericin B, currently available for treating IFI in neonates and children[2]

Drug	Formulation	Adult regimen	Neonatal regimen	Pediatric regimen	Indications
Fluconazole	Capsule, oral suspension and IV injection	Prophylaxis: 200 mg daily	Newborn (0–14 days) maximum dose 12 mg kg^{-1} every 72 h	Infants and children 6–12 mg kg^{-1} daily	• Mucosal candidiasis (oropharyngeal, esophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients.
		Treatment: 400–800 mg daily	Newborn (15–27 days) maximum dose 12 mg kg^{-1} every 48 h		• Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence.
			Consideration given to a loading dose 25 mg kg^{-1}		
Itraconazole	Capsule, oral cyclo-dextrin suspension and IV 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	• Very limited data - preferable to use other antifungals whenever possible
					• Oral and/or esophageal candidosis in HIV-positive or other immunocompromised patients.
					• As prophylaxis of deep fungal infections (in cases where indicated) that are expected to be susceptible to itraconazole, when standard therapy is considered inappropriate (prophylaxis against aspergellosis - little evidence)
Voriconazole	Capsule, oral suspension and IV cyclodextrin injection	Oral dosing: 400 mg twice daily for two doses, then 200 mg 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 hours)	• Only licensed for children >2 years.
		i.v. dosing: 6 mg kg^{-1} twice daily for two doses, then 4 mg kg^{-1} twice daily		i.v. dosing: 9 mg kg^{-1} twice daily for two doses, then 8 mg kg^{-1} twice daily	• Invasive aspergillosis.
					• Candidaemia in non-neutropenic patients.
					• Fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).
					• Serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.
Caspofungin	IV 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)*	• Invasive candidiasis

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Drug	Formulation	Adult regimen	Neonatal regimen	Pediatric regimen	Indications
				*Increased to 70 mg m^{-2} daily if clinical response inadequate.	• Invasive aspergillosis 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 forpresumed fungal infections (*Candida* or *Aspergillus)* in febrile neutropenia.
Micafungin	IV injection	Treatment of invasive candidi-asis: 100 mg daily, increased to 200 mg daily if clinical response inadequate	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 in children <16 years, including neonates. • Prophylaxis of *Candida* infection in patients undergoing allogeneic hematopoietic stem cell transplantation or patients who are expected to have neutropenia for 10 or more days.
		Treatment of esophageal candidiasis: 150 mg daily Prophylaxis of *Candida* infec-tion in patients undergoing allo-geneic hemato-poietic stem cell transplantation or patients who are expected to have neutropenia for 10 or more days.		Invasive candidiasis 2 mg kg^{-1} daily** Esophageal candidi-asis 3 mg kg^{-1} daily	
				Prophylaxis: 50 mg day^{-1} **Increased to 4 mg kg^{-1} daily if clinical response inadequate	
Flucytosine	IV or oral		50 mg/kg every 12 hours	Child: Usual dose 50 mg/kg every 6 hours usually for not more than 7 days, alterna-tively 25–37.5 mg/kg every 6 hours usually for not more than 7 days, lower dose may be sufficient for sensi-tive organisms	Systemic yeast and fungal infec-tions	Adjunct to amphotericin in severe systemic candidiasis and in other severe or long-standing infections
			50 mg/kg every 12 hours.	25 mg/kg every 6 hours for 2 weeks	Cryptococcal meningitis (adjunct to amphotericin)

*Note comment in indications column
**The studies on higher doses in children are lacking

Triazoles

This category of drugs enabled the treating pediatrician the much needed oral therapy in their armamentarium to manage ISI; drugs of choice till then were the parenteral polyenes and echinocandins. Since *Candida albicans* is the predominant fungal pathogen encountered in the neonate, fluconazole, which affords

excellent candida cover, has become the triazole most extensively used in neonatology.[10] The drug has been extensively studied and recommended for prophylaxis against invasive fungal infection in preterm infants in neonatal intensive care units (NICUs).[11] Fluconazole penetrates the central nervous system (including CSF) and the urine and may therefore be useful for treatment of infections at these sites.[12–14]

Fluconazole is also used orally or IV for prevention of fungal infections in immunocompromised patients, including children with acute leukemia, myelodysplastic syndromes, and those undergoing allogeneic hematopoietic stem cell transplant (allo-HSCT). Neonate up to 14 days and after 14 days up to 28 days may be given 3–12 mg/kg every 72 hours and 3–12 mg/kg every 48 hours, respectively, the dose being adjusted according to extent and duration of neutropenia. For children, commence the treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count is in desirable range at a dose of 3–12 mg/kg daily (max. per dose 400 mg), dose given according to extent and duration of neutropenia. But since high doses, resulting in adverse reactions, are required in these conditions, and since it does not cover some strains of Candida like *C. krusei* and *C. glabrata*, newer fluconazole drugs are being considered.[15]

Fluconazole is also used for the prevention of relapse of cryptococcal meningitis in HIV-infected patients after completion of primary therapy at 6 mg/kg (max 600 mg) orally or IV.

Fluconazole has no inherent activity against *Aspergillus* spp (very occasional pathogen in newborn) and the extended spectrum triazoles with anti-*Aspergillus* activity—itraconazole, voriconazole, and posaconazole—are used in that setting.[16] These extended spectrum triazoles are used extensively in children. While the overall rates of triazole resistance remain low, there are increasing reports of resistance to fluconazole in the neonates[17] and concerns emerging regarding the possibility of *Aspergillus* spp. resistance to the extended spectrum triazoles.[18,19]

Itraconazole is not generally used in the NICU. There are only limited pharmacokinetic data for itraconazole administered to children aged >6 months. Its use is mainly for superficial keratinizing fungal infection and not for ISI.

Itraconazole, voriconazole, and posaconazole showed comparable efficacy as antifungal prophylaxis in pediatric patients after allogeneic HSCT.[20]

Voriconazole and posaconazole are effective in treating infections by fluconazole-resistant *Candida spp*. and molds, *Aspergillus* spp., and *Fusarium* spp.[15,18,19,21] Unlike voriconazole, posaconazole has activity against the Mucorales order and is used for the treatment of mucormycosis and disseminated zygomycosis.[22,23] Voriconazole is also approved for use as salvage therapy for *Scedosporium apiospermum* osteoarticular infections in children following injury.[24] Voriconazole and posaconazole therapeutic drug monitoring (TDM) can be utilized to improve patient outcomes and, in the case of voriconazole, to limit toxicity.

Voriconazole is a well-tolerated drug. The most frequently occurring adverse drug reactions (ADRs) are visual disturbances (23–35%) demonstrated as color vision change, blurred vision, scotoma, and photophobia. These reactions appear at the time of administration and return to normal after about 30 minutes. ADRs that occur more often during treatment with voriconazole than posaconazole are sinusitis, hypoglycemia, hypokalemia, depression, hallucinations, anxiety, headache and dizziness, peripheral edema, thrombophlebitis, hypotension, acute respiratory distress syndrome, pulmonary edema, jaundice, backache, acute renal failure, and hematuria.[25] In general, posaconazole has a very good safety and tolerability profile.[26] In clinical trials, posaconazole was also particularly well tolerated. The main side effects experienced by the participants were gastrointestinal distress (nausea, vomiting, and diarrhea), neutropenia, and elevated liver enzymes.

Echinocandins

This group includes caspofungin, micafungin, and anidulafungin.

Candida albicans and *C. glabrata* are sensitive to echinocandins. Of late, resistance among the latter is being reported.[27] These strains of *C. glabrata* are frequently triazole resistant and are difficult to treat. Resistance to echinocandins is due to mutations resulting in substitutions of amino acids in the Fks1 subunit of 1,3-β-D-glucan synthase which render them inactive.[28] *Candida parapsilosis*, in which Fks1p harbors an intrinsic amino acid change at position 660 of the hot spot 1 region, is less sensitive to echinocandins.[29]

The recommendation for use in neonates is not clear. They seem safe in the newborn, but more data on its pharmacokinetics and dosing are required before regularizing its use in this age-group. The echinocandin most studied in the neonate is micafungin for the treatment of invasive candidiasis;[30] a higher dose is recommended for HCME[31] as shown in Table 1. However, the predominance of *C. parapsilosis* in the nursery[32] needs to be factored when using echinocandins in neonatal fungal infections.

There being very little difference in-between these three echinocandins, they may be used interchangeably in older children. There is limited evidence for use of anidulafungin in neonates.[33]

In children, some experts have started recommending this group of antifungals as firstline for ISI caused by *Candida* species and as salvage therapy for invasive aspergillosis.[34] But their use as a single agent in the treatment of invasive pulmonary aspergillosis in the immunocompromised is uncertain.[35]

Caspofungin is approved for empiric therapy of febrile neutropenia, and micafungin is licensed for antifungal prophylaxis in stem cell transplantation.[36]

SUMMARY

Invasive fungal infections are serious, difficult to diagnose, difficult to confirm bacteriologically, life-threatening conditions throughout childhood, especially in the neonate and the immunocompromised child. They present complex therapeutic dilemmas, which antifungal to choose in a given setting. If the diagnosis is missed, ISI could result in death. Death or severe long-term sequelae occurs even with the best of care and the selection of the most appropriate antifungal. Although some recommendations have been made regarding the spectrum, pharmacokinetics, and dosing of antifungals in neonates and children, many more well-designed studies are required to elucidate data on dosing strategies, drug resistance, mono- or combination antifungal therapy.

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