

Antifungal agents for the treatment of systemic fungal infections in children

UD Allen; Canadian Paediatric Society, Infectious Diseases and Immunization Committee



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Traditionally, the mainstay of systemic antifungal therapy has been amphotericin B deoxycholate (conventional amphotericin B). Newer agents have been developed to fulfill special niches and to compete with conventional amphotericin B by virtue of having more favourable toxicity profiles. Some agents have displaced conventional amphotericin B for the treatment of specific fungal diseases. For example, voriconazole has emerged as the preferred treatment for invasive pulmonary aspergillosis. This notwithstanding, conventional amphotericin B remains a useful agent for the treatment of paediatric fungal infections. Knowledge of the characteristics of the newer agents is important, given the increasing numbers of patients who are being treated with these drugs. Efforts need to be directed at research aimed at generating paediatric data where these are lacking. The antifungal agents herein described are most often used as monotherapy regimens because there is no uniform consensus on the value of combination therapy, except for specific scenarios.

Key Words: Amphotericin B; Antifungal therapy; Echinocandins; Triazoles

Over the past 15 years, there has been a major increase in the number of available antifungal agents. The newer agents have been evaluated to a lesser degree in children compared with adults (1). The present overview offers a perspective on amphotericin B deoxycholate and the newer antifungal agents, as well as their roles in paediatric antifungal therapy.

AMPHOTERICIN B PRODUCTS

Preparations, dosing and toxicity profiles

Amphotericin B products are available as parenteral agents. Newer and more costly (lipid-based) formulations of amphotericin B are increasingly being used in clinical practice (2-7). The major toxicities associated with amphotericin B are nephrotoxicity and infusion-related events (fevers, chills and rigors) (8). The lipid-based products are less nephrotoxic, with comparable efficacy relative to conventional amphotericin B (amphotericin B deoxycholate). The dosing of these agents, indications and body fluid concentrations are shown in Table 1.

UD Allen; Société canadienne de pédiatrie, comité des maladies infectieuses et d'immunisation. Les antifongiques pour le traitement des infections fongiques systémiques chez les enfants

Le désoxycholate d'amphotéricine B (amphotéricine B classique) a toujours été la principale thérapie antifongique systémique. Les agents plus récents ont été mis au point pour occuper des créneaux spéciaux et pour faire concurrence à l'amphotéricine B classique grâce à des profils de toxicité plus favorables. Certains agents ont fait reculer l'amphotéricine B classique pour traiter des maladies fongiques précises. Par exemple, le voriconazole émerge comme traitement de choix contre l'aspergillose pulmonaire envahissante. Malgré tout, l'amphotéricine B classique demeure un agent utile pour traiter les infections fongiques en pédiatrie. Il faut connaître les caractéristiques des nouveaux agents étant donné le nombre croissant de patients traités à l'aide de ces médicaments. Il faut également orienter les efforts vers des recherches visant à obtenir des données pédiatriques dans les secteurs où on n'en possède pas. Les antifongiques décrits dans le présent commentaire sont surtout utilisés en monothérapie, parce qu'il n'existe pas de consensus uniforme sur la valeur d'une polythérapie, sauf dans des scénarios précis.

Clinical use in paediatrics: Amphotericin B is a broad-spectrum antifungal agent (Table 2). The variable agents (amphotericin B products) have comparable efficacy, although in some clinical settings, the lipid products might be advantageous because higher doses per unit body weight can be used while preserving renal function. The lipid-based products are usually recommended in patients who are refractory to or intolerant of amphotericin B deoxycholate (9). The lipid-based agents that are most readily available for clinical use are amphotericin B lipid complex and liposomal amphotericin B. A third lipid-based product, amphotericin B colloidal dispersion, is associated with more fever and chills compared with conventional amphotericin (10).

THE TRIAZOLES

Preparations, dosing and toxicity profiles

Fluconazole: Fluconazole is an oral and parenteral agent. It readily penetrates into tissues due to its low lipophilic nature and limited protein binding; it is approximately 90%

Correspondence: Canadian Paediatric Society, 2305 St Laurent Boulevard, Ottawa, Ontario K1G 4J8. Telephone 613-526-9397, fax 613-526-3332, websites www.cps.ca, www.caringforkids.cps.ca

TABLE 1
Antifungal agents for the treatment of systemic fungal infections in children

Agent	Routes of administration/ relative costs*	Dosage/day	Most common indications for use [†]	Adverse events/ cautionary notes	Body fluid concentrations [‡]	
					CSF/serum/ comments	Other sites
Amphotericin B deoxycholate	IV: \$ (for 1 mg/kg/day)	0.25 mg/kg to 0.5 mg/kg initially, increased to 0.5 mg/kg to 1.5 mg/kg [§] Dosage for aspergillosis: 1.5 mg/kg	Invasive fungal infections caused by susceptible organisms as shown in Table 2 Empirical therapy of presumed fungal infections in febrile neutropenic patients	Infusion-related toxicity Nephrotoxicity, including hypokalemia Medication errors have occurred due to confusion between the lipid-based products and conventional amphotericin B. The dose of conventional amphotericin B should not exceed 1.5 mg/kg/day	3%	Newborn serum/ maternal serum = 50% Aqueous humor/ serum = 25%
Liposomal amphotericin B (AmBisome)	IV: \$\$\$ (for 3 mg/kg/day)	3 mg/kg to 5 mg/kg Dosage for aspergillosis: AmBisome 5 mg/kg to 10 mg/kg; likely up to 10 mg/kg	Invasive fungal infections, refractory or intolerance to conventional amphotericin B	Fewer infusion-related reactions and nephrotoxicity than amphotericin B deoxycholate	Higher levels may be achievable in brain tissue due to potential for greater per kg dosing	Concentrates in reticulo-endothelial system
Amphotericin B lipid complex (Abelcet)	IV: \$\$\$\$ (for 5 mg/kg/day)	5 mg/kg Dosage for aspergillosis: Abelcet 5 mg/kg to 10 mg/kg; likely up to 7.5 mg/kg	Invasive fungal infections; refractory or with intolerance to conventional amphotericin B	Less nephrotoxicity than amphotericin B deoxycholate	Higher levels may be achievable in brain tissue due to potential for greater per kg dosing	Concentrates in reticulo-endothelial system
Fluconazole	PO; IV PO: \$ (for 5 mg/kg/day) IV: \$ (for 5 mg/kg/day)	PO: 6 mg/kg once, then 3 mg/kg/day for oropharyngeal or esophageal candidiasis; 6 mg/kg/day to 12 mg/kg/day for invasive fungal infections; 6 mg/kg/day for suppressive therapy in HIV-infected children with cryptococcal meningitis IV: 3 mg/kg to 6 mg/kg, single dose; up to 12 mg/kg per day for serious infections	<i>Candida</i> infections (eg, intra-abdominal abscess, peritonitis, pleural space infection, candidemia, esophageal candidiasis, oropharyngeal candidiasis, <i>Candida</i> urinary tract infections, endophthalmitis) Cryptococcal infections Antifungal prophylaxis in HSCT patients and neonates	Rare, serious hepatotoxicity possible Cytochrome P450 isoenzyme drug interactions	50% to 94%	Newborn serum/ maternal serum = 85%
Itraconazole	PO; IV PO: \$ (for 5 mg/kg/day) IV: (Not marketed)	IV, PO: 5 mg/kg/day to 10 mg/kg/day divided into 2 doses	Invasive and noninvasive aspergillosis, oropharyngeal and esophageal candidiasis Blastomycosis Chronic pulmonary histoplasmosis Antifungal prophylaxis in HSCT and lung transplant patients	Elevated liver enzymes Gastrointestinal intolerance: abdominal pain, vomiting, diarrhea Cytochrome P450 isoenzyme drug interactions	<10%	Tissue and bronchial secretions levels higher than plasma Ocular levels low
Voriconazole	PO; IV PO: \$\$ (for 100 mg PO bid) IV: \$\$\$ (for 8 mg/kg/day)	PO: 8 mg/kg every 12 h for one day, then 7 mg/kg every 12 h IV: 6 mg/kg to 8 mg/kg every 12 h for one day, then 7 mg/kg every 12 h	Invasive aspergillosis Esophageal candidiasis Refractory infections due to <i>Scedosporium</i> , <i>Angiospermum</i> and <i>Fusarium</i> species	Main side effects are liver function abnormalities, skin rash, visual disturbances, CYP450 isoenzyme drug interactions	42% to 67%	Excellent tissue penetration; levels exceed trough plasma levels several fold

TABLE 1 – CONTINUED
Antifungal agents for the treatment of systemic fungal infections in children

Agent	Routes of administration/ relative costs*	Dosage/day	Most common indications for use†	Adverse events/ cautionary notes	Body fluid concentrations‡	
					CSF/serum/ comments	Other sites
Posaconazole	PO: \$\$\$\$	200 mg 4 times daily (age ≥13 years)	Aspergillosis, fusariosis and zygomycosis in patients intolerant/refractory to other agents	Gastrointestinal symptoms, headache, elevated liver enzymes, cytochrome P450 3A4 enzyme drug interactions	CSF penetration low, but activity demonstrated against CNS infections	Tissue penetration excellent
Ravuconazole	PO; IV Cost to be determined	Not established	Under evaluation	Limited data	Low levels in CSF in animal model; brain tissue levels higher than in CSF	Concentration in liver greatest, followed by lungs, then kidneys, then brain
Caspofungin	IV: \$\$\$ (for 50 mg/m ² /day)	70 mg/m ² loading, then 50 mg/m ² once daily	<i>Candida</i> infections (eg, intra-abdominal abscess, peritonitis, pleural space infection, candidemia, esophageal candidiasis) Invasive aspergillosis in patients refractory/intolerant to other therapy Empirical therapy in febrile neutropenic patients	Liver function abnormalities, fever, headache, rash, gastrointestinal symptoms, anemia	Low levels in CSF	In murine model, tissue levels higher than serum levels in liver and kidney; lower in heart and brain; similar in lung and spleen
Micafungin	IV: \$\$\$\$	4 mg/kg to 12 mg/kg once daily (higher doses for children <8 years of age)	Similar to caspofungin prophylaxis of <i>Candida</i> infections in HSCT patients	Liver function abnormalities, nausea, vomiting	Low to undetectable	Low levels in aqueous humor
Anidulafungin	IV Cost to be determined	0.75 mg/kg to 1.5 mg/kg	Being evaluated for esophageal candidiasis	Phlebitis/thrombophlebitis, fever, headache, nausea, vomiting, rash	CSF levels not therapeutic	–
Flucytosine	PO (no longer marketed in Canada)	50 mg/kg to 150 mg/kg in 4 doses	Combination therapy with amphotericin B for <i>Candida</i> and cryptococcal infections	Gastrointestinal intolerance and bone marrow suppression	60% to 100%	Penetrates well into aqueous humor, joints, bronchial secretions, peritoneal fluid, brain, bile, bone

*These costs are for illustrative purposes to show relative costs and are based on the treatment of a 20 kg child for five days at The Hospital for Sick Children, Toronto, Ontario (modified from the 2009/2010 Drug Handbook and Formulary, The Hospital for Sick Children). Costs may vary across provinces. Doses may also vary depending on the nature of the illness. The costs reflect drug costs only; †This is not meant to be an all inclusive list; it includes licensed indications plus key scenarios in which the drugs have been identified as acceptable therapy; ‡Data are lacking regarding tissue levels for several antifungal agents. Available data are summarized in different formats based on how they were generated; §A prospective surveillance study suggested little or no benefit when a titrated dosing regimen is used (39). \$ <\$200; \$\$ \$200 to \$500; \$\$\$ \$500 to \$750; \$\$\$\$ \$750 to \$1200; bid Twice a day; CNS Central nervous system; CSF Cerebrospinal fluid; HSCT Hematopoietic stem cell transplant; IV Intravenous; PO Oral

bioavailable. Concentrations in urine are several fold greater than in blood (10- to 20-fold greater) (11,12). Rare, but serious, hepatotoxicity may be associated with fluconazole. Drug interactions are possible because fluconazole is an inducer of cytochrome P450 isoenzymes.

Clinical use in paediatrics: Fluconazole, the azole that is most widely used in paediatrics, is often used in the treatment of *Candida* and cryptococcal infections. It is more active against *Candida albicans* compared with other candidial strains (eg, *Candida parapsilosis*, *Candida glabrata*, *Candida krusei* and

Candida tropicalis). It has no activity against *Aspergillus* species or other moulds. As a prophylactic agent, fluconazole is used in allogeneic hematopoietic stem cell transplant recipients (13). Data are emerging on its role as a prophylactic agent in neonates at high risk of invasive candidiasis (14,15).

Itraconazole: Itraconazole is available for oral and parenteral administration (16). Pharmacokinetic studies (17) of itraconazole oral solution have demonstrated that children younger than five years of age tend to have lower plasma concentrations than older children or adults. Gastrointestinal

TABLE 2
Spectrum of activity of more commonly used systemic antifungal agents

Selected fungal species	Antifungal agents*				
	Amphotericin B products	Fluconazole	Voriconazole	Posaconazole	Echinocandins
<i>Aspergillus fumigatus</i>	++	–	+++	+++	++
<i>Aspergillus terreus</i>	–	–	+++	+++	++
<i>Aspergillus flavus</i>	++	–	+++	+++	++
<i>Candida albicans</i>	+++	+++	+++	+++	+++
<i>Candida glabrata</i>	++	+/-	+	+	+++
<i>Candida lusitanae</i>	+/-	+	++	++	++
<i>Candida tropicalis</i>	+++	+++	+++	+++	+++
<i>Candida krusei</i>	++	–	++	++	+++
<i>Candida parapsilosis</i>	+++	+++	+++	+++	++
<i>Candida guilliermondii</i>	++	+++	+++	+++	++
<i>Cryptococcus neoformans</i>	+++	+++	+++	+++	–
<i>Fusarium</i> species	++	–	++	++	–
	(applies to lipid products)				
<i>Scedosporium apiospermum</i>	+/-	–	+++	+++	+/-
<i>Scedosporium prolificans</i>	+/-	–	+/-	+/-	–
Zygomycetes (eg, <i>Absidia</i> , <i>Mucor</i> , <i>Rhizopus</i>)	+++	–	–	+++	–
	(applies to lipid products)				
Dematiaceous moulds [†]	+	+/-	+++	+++	+
Dimorphic fungi [‡]	+++	+	++	++	–
		+++ <i>Coccidioides</i> +/- <i>Sporothrix</i>	– <i>Sporothrix</i>	+ <i>Sporothrix</i>	

The above is based on *in vitro* activity, which does not always predict outcomes in clinical practice. *Flucytosine: Use only in combination therapy for *Candida*, *Cryptococcus neoformans* and selected dematiaceous moulds; [†]Dematiaceous moulds: *Alternaria*, *Bipolaris*, *Curvularia*, *Exophiala*; [‡]Dimorphic fungi: *Blastomyces dermatitidis*, *Coccidioides immitis/posadasii*, *Histoplasma capsulatum*, *Sporothrix schenckii*. *Itraconazole* is a first-line therapy for dimorphic fungi. Adapted from reference 40

intolerance, related to the osmotic properties of the cyclodextrin carrier, appears to be the dose-limiting toxicity of the itraconazole oral solution (18). Common adverse events include abdominal pain, vomiting, diarrhea and elevated liver enzymes. Given that itraconazole inhibits the cytochrome P450 3A4 enzyme, drug interactions are common.

Clinical use in paediatrics: Itraconazole may be advantageous for prophylaxis in situations in which prevention of *Candida* and *Aspergillus* infections are desirable (eg, hematopoietic stem cell transplant recipients) (19). It is often used for prophylaxis in lung transplant recipients who are colonized by *Aspergillus* (20). The drug is also used selectively in severe *Aspergillus* infections or as step-down therapy.

Voriconazole: Voriconazole is available as an oral or parenteral formulation. The intravenous formulation should be avoided in patients experiencing moderate or severe renal failure because of the potential toxic effects of the accumulation of the solvent vehicle. Voriconazole plasma levels are very variable among individuals. Children have a higher capacity for elimination of voriconazole compared with adults (21). The paediatric dose that is equivalent in drug exposure to the usual adult maintenance dose of 4 mg/kg, twice a day (bid), remains to be determined. Current recommendations suggest that the paediatric dose of voriconazole should be 8 mg/kg bid for one day, then 7 mg/kg bid for the treatment of invasive aspergillosis (22).

Adverse events include skin rash, visual abnormalities, (photophobia and blurred vision) photosensitivity reactions and elevated hepatic transaminase or serum bilirubin levels (23). All are generally reversible.

Clinical use in paediatrics: The main role for voriconazole is in the treatment of invasive aspergillosis, where it has emerged as the preferred treatment of invasive pulmonary aspergillosis in older children and adults (24,25). It may also be used to treat systemic *Candida* infections, although in clinical practice, fluconazole would be considered first.

Posaconazole: This drug is currently available as an oral agent. It is a second-generation triazole that is structurally similar to itraconazole (6,26). It is a broad-spectrum agent with activity against *Candida* species, *Aspergillus* species and zygomycetes, among other fungal organisms (Table 2).

Clinical use in paediatrics: Paediatric experience is limited (26). Currently, in clinical practice, this agent is being used as salvage therapy in situations in which first-line antifungal agents have failed or are contraindicated due to toxicity. Infections that have been treated include invasive aspergillosis and zygomycetes infection. It is also used for prophylaxis among allogeneic hematopoietic stem cell transplant recipients and selected high-risk cancer patients.

Ravuconazole: Ravuconazole is available as oral and intravenous formulations. Structurally similar to fluconazole and voriconazole, it has a half-life of approximately 100 h (6,27), which would make it ideal for step-down therapy and treatment in ambulatory care settings (28). It has activity against *Candida* species, *Aspergillus* species, *Cryptococcus neoformans*, *Histoplasma capsulatum* and *Coccidioides immitis* (Table 2). The safety profile appears to be similar to fluconazole.

Clinical use in paediatrics: Paediatric experience is lacking. **Isavuconazole:** Isavuconazole is a new triazole with oral and intravenous formulations. It is currently undergoing

phase III clinical trials in adults (29). It is a broad-spectrum agent with in vitro activity against most yeasts and moulds including fluconazole-resistant *Candida* strains, *Aspergillus* species and to a limited degree, zygomycetes (30).

Clinical use in paediatrics: Paediatric experience is lacking.

THE ECHINOCANDINS

Mechanism of action

These agents are glucan synthesis inhibitors that specifically inhibit beta (1-3)-D-glucan synthesis, thereby compromising the integrity of the fungal cell wall. Beta (1-3)-D-glucan synthesis does not occur in human cells.

Preparations, dosing and toxicity profiles

All are available only as parenteral formulations. To date, serious toxicities described with these drugs are uncommon.

Caspofungin: Dosing based on body surface area appears to be a more appropriate approach to dosing than a body weight approach; with 50 mg/m²/day, the area under the curve following multiple doses is similar to adults receiving 50 mg/day. The area under the curve and trough plasma concentrations were consistent among children and adolescents two to 17 years of age. However, younger children tend to have increased clearance (and thus a shorter half-life) of caspofungin compared with older children or adults (27).

Clinical use in paediatrics: Caspofungin is the echinocandin that has been most widely used in clinical practice (31-33). The drug is effective in treating invasive candidiasis and aspergillosis. It has emerged as an effective agent in the treatment of invasive pulmonary aspergillosis (25). In some centres, it is widely used as empirical treatment in febrile neutropenic patients with impaired renal function (33).

Micafungin: Linear pharmacokinetics occur over the dose range of 0.5 mg/kg/day to 4.0 mg/kg/day (34). Among children two to eight years of age, clearance is greater than that of older patients. Among premature infants weighing more than 1000 g, single doses of micafungin, ranging up to 3.0 mg/kg, were well tolerated with the elimination of half-life (8 h) and total plasma clearance in these infants being dissimilar to that reported for older children and adults. The half-life among premature neonates weighing 500 g to 1000 g was 5.5 h (35).

Clinical use in paediatrics: Micafungin has been evaluated in several paediatric studies. The indications for the use of caspofungin apply (36). It is an effective agent for fungal prophylaxis in hematopoietic stem cell transplant recipients (37).

Anidulafungin: Limited paediatric data are available for this intravenous agent. It has the longest half-life of all echinocandins (approximately 18 h) and is administered once daily. Tissue concentrations are highest in the lung and liver, followed by the spleen and kidneys (38).

Clinical use in paediatrics: Paediatric experience is limited.

ANTIMETABOLITES – FLUCYTOSINE

Preparations, dosing and toxicity profiles

Flucytosine is available as an oral agent. Gastrointestinal intolerance and bone marrow suppression are common. Rash, hepatotoxicity, headache, confusion, hallucinations, sedation and euphoria may occur. When combined with amphotericin B, the renal impairment caused by amphotericin B may increase the flucytosine levels in the body and, thus, potentiate its toxicity.

Clinical use in paediatrics: There is a large body of clinical experience with flucytosine in paediatrics, although clinical trial data are limited (22,27). It is invariably used in combination with amphotericin B in the treatment of *Candida* or cryptococcal infections, notably involving the central nervous system.

COMBINATIONS OF ANTIFUNGAL AGENTS

There is no convincing evidence that combination antifungal therapy offers advantages over monotherapy with the exception of therapy for cryptococcal meningitis. However, many experts advise combination therapy for some conditions including central nervous system fungal infections; disease with incomplete response to initial therapy, notably where optimal dosing is compromised by toxicity; empirical therapy of severe disease presumed to be due to organisms that are known to have distinct fungal susceptibility profiles (ie, a different drug is needed for each likely pathogen); and initial therapy of selected cases of invasive pulmonary aspergillosis, particularly for diseases in close proximity to major mediastinal blood vessels.

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Principal author: Dr Upton D Allen, Toronto, Ontario

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate. All Canadian Paediatric Society position statements and practice points are reviewed, revised or retired as needed on a regular basis. Please consult the "Position Statements" section of the CPS website (www.cps.ca/english/publications/statementsindex.htm) for the most current version. This article also appears in the Winter 2010 issue of *The Canadian Journal of Infectious Diseases & Medical Microbiology*.