Antifungal agents for the treatment of systemic fungal infections in children

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Abstract
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. 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. The major toxicities associated with amphotericin B are nephrotoxicity and infusion-related events (fevers, chills and rigors). 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.

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. 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.

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% 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 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 is 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 pediatric 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 pediatric 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 \[26\]\[27\]. 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 \[28\]. 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 \[29\]\[30\], which would make it ideal for step-down therapy and treatment in ambulatory care settings \[29\]. 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 \[31\]. It is a broad-spectrum agent with in vitro activity against most yeasts and moulds including fluconazole-resistant Can-
dida strains, *Aspergillus* species and to a limited degree, zygomycetes

**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.

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

**Micafungin:** Linear pharmacokinetics occur over the dose range of 0.5 mg/kg/day to 4.0 mg/kg/day. 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.

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

**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.

**Clinical use in paediatrics:** Paediatric experience is limited.

### Antemetabolites – 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. 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.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Routes of administration/ relative costs*</th>
<th>Dosage/day</th>
<th>Most common indications for use†</th>
<th>Adverse events/ cautionary notes</th>
<th>Body fluid concentrations‡</th>
<th>Other sites</th>
</tr>
</thead>
</table>
| 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§ | Invasive fungal infections caused by susceptible organisms as shown in Table 2 | Infusion-related toxicity  | 3%                                         | Newborn serum/ maternal serum = 50%  
                               |                                            | Dosage for aspergillosis: 1.5 mg/kg     | Empirical therapy of presumed fungal infections in febrile neutropenic patients | Nephrotoxicity, including hypokalemia | Aqueous humor/ serum = 25%  |
| Liposomal amphotericin B (AmBisome) | IV: $$$ (for 3 mg/kg/day)                | 3 mg/kg to 5 mg/kg | Invasive fungal infections, refractory or intolerance to conventional amphotericin B | Fewer infusion-related reactions and nephrotoxicity than amphotericin B deoxycholate | Higher levels may be achievable in brain tissue due to potential for greater per kg dosing | Concentrates in reticulo-endothelial system |
| Amphotericin B lipid complex (Abelcet) | IV: $$$$ (for 5 mg/kg/day)             | 5 mg/kg | Invasive fungal infections; refractory or with intolerance to conventional amphotericin B | Less nephrotoxicity than amphotericin B deoxycholate | Higher levels may be achievable in brain tissue due to potential for greater per kg dosing | Concentrates in reticulo-endothelial system |
| Fluconazole                   | PO: IV                                   | PO: 6 mg/kg once, then 3 mg/kg/day for oropharyngeal or esophageal candidiasis; 6 mg/kg/day to 12 mg/kg/day for invasive fung- | Candida infections (eg, intra-abdominal abscess, peritonitis, pleural space infection, candidemia, esophageal candidiasis, oropharyngeal candidiasis, Candida urinary tract infec- | Rare, serious hepatotoxicity possible  
                               |                                            | torrent | | | | | Cytochrome P450 isoenzyme drug interactions | 50% to 94%  
<pre><code>                           |                                            |                                                   | | | | | Newborn serum/ maternal serum = 85%  |
</code></pre>
<table>
<thead>
<tr>
<th>Antifungal</th>
<th>PO; IV</th>
<th>PO: $ (for 5 mg/kg/day)</th>
<th>IV: (Not marketed)</th>
<th>IV, PO: 5 mg/kg/day to 10 mg/kg/day divided into 2 doses</th>
<th>Invasive and noninvasive aspergillosis, oropharyngeal and esophageal candidiasis</th>
<th>Elevated liver enzymes</th>
<th>&lt;10%</th>
<th>Tissue and bronchial secretions levels higher than plasma Ocular levels low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>PO; IV</td>
<td>PO: $ (for 100 mg PO bid) IV: $$$ (for 8 mg/kg/day)</td>
<td>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</td>
<td>Invasive aspergillosis Esophageal candidiasis Refractory infections due to <em>Scedosporium, Angiospermum</em> and <em>Fusarium</em> species</td>
<td>Main side effects are liver function abnormalities, skin rash, visual disturbances, CYP450 isoenzyme drug interactions</td>
<td>42% to 67%</td>
<td>Excellent tissue penetration; levels exceed trough plasma levels several fold</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>PO; IV</td>
<td>PO: $$$</td>
<td>PO: 8 mg/kg every 12 h for one day, then 7 mg/kg every 12 h</td>
<td>Aspergillosis, fusariosis and zygomycosis in patients intolerant/refractory to other agents</td>
<td>Gastrointestinal symptoms, headache, elevated liver enzymes, cytochrome P450 3A4 enzyme drug interactions</td>
<td>Low levels in CSF in animal model; brain tissue levels higher than in CSF</td>
<td>Concentration in liver greatest, followed by lungs,</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>PO: $$$</td>
<td>200 mg 4 times daily (age ≥13 years)</td>
<td></td>
<td>CSF penetration low, but activity demonstrated against CNS infections</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ravuconazole</td>
<td>PO; IV</td>
<td>Not established</td>
<td></td>
<td>Under evaluation</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Drug</td>
<td>Route/ Formulation</td>
<td>Dose Details</td>
<td>Indications</td>
<td>Side Effects</td>
<td>CSF Levels</td>
<td>Tissue Levels</td>
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<td></td>
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<tr>
<td>Caspofungin</td>
<td>IV: $$$ (for 50 mg/m²/day) 70 mg/m² loading, then 50 mg/m² once daily</td>
<td>Candida infections (eg, intra-abdominal abscess, peritonitis, pleural space infection, candidemia, esophageal candidiasis) Invasive aspergillosis in patients refractory/intolerant to other therapy Empirical therapy in febrile neutropenic patients</td>
<td>Liver function abnormalities, fever, headache, rash, gastrointestinal symptoms, anemia</td>
<td>Low levels in CSF</td>
<td>Low to undetectable</td>
<td>In murine model, tissue levels higher than serum levels in liver and kidney; lower in heart and brain; similar in lung and spleen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>IV: $$$$$ 4 mg/kg to 12 mg/kg once daily (higher doses for children &lt;8 years of age)</td>
<td>Similar to caspofungin prophylaxis of Candida infections in HSCT patients</td>
<td>Liver function abnormalities, nausea, vomiting</td>
<td>Low to undetectable</td>
<td>Low levels in aqueous humor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>IV Cost to be determined 0.75 mg/kg to 1.5 mg/kg</td>
<td>Being evaluated for esophageal candidiasis</td>
<td>Phlebitis/thrombophlebitis, fever, headache, nausea, vomiting, rash</td>
<td>CSF levels not therapeutic</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucytosine</td>
<td>PO (no longer marketed in Canada) 50 mg/kg to 150 mg/kg in 4 doses</td>
<td>Combination therapy with amphotericin B for Candida and cryptococcal infections</td>
<td>Gastrointestinal intolerance and bone marrow suppression</td>
<td>60% to 100%</td>
<td>Penetrates well into aqueous humor, joints, bronchial secretions, peritoneal fluid, brain, bile, bone</td>
<td></td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Selected fungal species</th>
<th>Antifungal agents*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amphotericin B products</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>++</td>
</tr>
<tr>
<td>Aspergillus terreus</td>
<td>–</td>
</tr>
<tr>
<td>Aspergillus flavus</td>
<td>++</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>+++</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>++</td>
</tr>
<tr>
<td>Candida lusitaniae</td>
<td>+/-</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>+++</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>++</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>+++</td>
</tr>
<tr>
<td>Candida guilliermondii</td>
<td>++</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>+++</td>
</tr>
<tr>
<td>Fusarium species</td>
<td>++ (applies to lipid products)</td>
</tr>
<tr>
<td>Scedosporium apiospermum</td>
<td>+/-</td>
</tr>
<tr>
<td>Scedosporium prolificans</td>
<td>+/-</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>+++ (applies to lipid products)</td>
</tr>
<tr>
<td>(eg, Absidia, Mucor, Rhizopus)</td>
<td></td>
</tr>
<tr>
<td>Dematiaceous moulds†</td>
<td>+</td>
</tr>
<tr>
<td>Dimorphic fungi‡</td>
<td>+++</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

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: Blastomycetes dermatitidis, Coccidioides immitis-posadasii, Histoplasma capsulatum, Sporothrix schenckii. Itraconazole is a first-line therapy for dimorphic fungi. Adapted from reference [40].

### References


30. Guinea J, Pelaez T, Recio S, Torres-Narbona M, Bouza E. In-vitro antifungal activities of


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