

## Antifungal Agents in Children

William J. Steinbach, MD<sup>a,b,\*</sup>

<sup>a</sup>*Department of Pediatrics, Division of Pediatric Infectious Diseases, Box 3499,  
Duke University Medical Center, Durham, NC 27710, USA*

<sup>b</sup>*Department of Molecular Genetics and Microbiology, Duke University Medical Center,  
Durham, NC 27710, USA*

Fungal pathogens are an increasingly recognized complication of organ transplantation and the ever more potent chemotherapeutic regimens for childhood malignancies. There has been a recent surge in the development of antifungals, including new formulations of older drugs and the discovery of a class of agents with a novel target. More recent studies have expanded knowledge on how to optimize the utility of these new agents. Because of the paucity of pediatric data, however, many recommendations for use of antifungals in children are derived from experience in adult patients.

This article provides a brief overview of the current state of systemic antifungal therapy. Currently licensed drugs, including amphotericin B and its lipid derivatives; 5-fluorocytosine; the azoles, including fluconazole, itraconazole, and voriconazole; and a representative of the new class of echinocandin agents, caspofungin, are discussed. Newer second-generation azoles (posaconazole and ravuconazole) and echinocandins (micafungin and anidulafungin) that are likely to be licensed in the United States in the next few years also are addressed. The

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\* Department of Pediatrics, Division of Pediatric Infectious Diseases, Box 3499, Duke University Medical Center, Durham, NC 27710.

*E-mail address:* [stein022@mc.duke.edu](mailto:stein022@mc.duke.edu)

Table 1  
Spectrum of activity of selected antifungal agents

Antifungal	Important clinical uses
Amphotericin B	<i>Blastomyces dermatitidis</i> , <i>Coccidioides immitis</i> , <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i> , <i>Paracoccidioides brasiliensis</i> , <i>Sporotrix schenckii</i> , most <i>Candida</i> species, <i>Aspergillus</i> , Zygomycetes (not: <i>Candida lusitanae</i> , <i>Scedosporium</i> , <i>Fusarium</i> , <i>Trichosporon</i> )
5-Fluorocytosine	Only in combination therapy for <i>Candida</i> , <i>C. neoformans</i> , dematiaceous molds
Fluconazole	Most <i>Candida</i> , <i>C. neoformans</i> , <i>B. dermatitidis</i> , <i>H. capsulatum</i> , <i>C. immitis</i> , <i>P. brasiliensis</i> (not: <i>Candida krusei</i> , <i>Candida glabrata</i> , <i>Aspergillus</i> )
Itraconazole	<i>Candida</i> , <i>Aspergillus</i> , <i>B. dermatitidis</i> , <i>H. capsulatum</i> , <i>C. immitis</i> , <i>P. brasiliensis</i>
Voriconazole	<i>Candida</i> , <i>Aspergillus</i> , <i>Fusarium</i> , <i>B. dermatitidis</i> , <i>H. capsulatum</i> , <i>C. immitis</i> , <i>Malassezia</i> species, <i>Scedosporium</i> , dematiaceous molds (not: Zygomycetes; caution: <i>C. glabrata</i> )
Caspofungin	<i>Candida</i> , <i>Aspergillus</i> (not: <i>C. neoformans</i> , <i>Fusarium</i> , Zygomycetes)

antifungal spectra of each agent are presented on Table 1, and recommended dosages are summarized on Table 2.

## Polyenes: amphotericin B

### *Mechanism of action*

The oldest antifungal class is the polyene macrolides, amphotericin B and nystatin. Since its initial approval for use in 1958, amphotericin B deoxycholate remains the “gold standard” for the therapy of many invasive fungal infections and the comparative agent for all newer antifungal agents. Amphotericin B binds to ergosterol, the major sterol found in fungal cytoplasmic membranes, creating transmembrane channels resulting in an increased permeability to monovalent cations. Fungicidal activity is believed to be caused by leakage of essential nutrients from the fungal cell.

### *Pharmacology and toxicities*

The fungicidal activity of amphotericin B is concentration-dependent, increasing directly with the amount of drug attained at the site of infection. Amphotericin B also has a prolonged postantifungal effect. That is, antifungal activity persists even after the concentration of drug declines to less than the amount needed to kill the fungus. These pharmacodynamic characteristics suggest that a single daily dose of amphotericin B would be effective [1]. Although there is a relationship between total dose administered and tissue concentrations [2], there is no conclusive clinical evidence that doses greater than 1 mg/kg/d

Table 2  
Preferred pediatric dosing of approved systemic antifungal agents

Drug class	Antifungal drug	Preferred adult dosing	Preferred pediatric dosing	Pediatric dosing comments
Polyene	Amphotericin B deoxycholate (Fungizone)	1–1.5 mg/kg/d	1–1.5 mg/kg/d	Children generally can tolerate higher doses than adults
	Amphotericin B lipid complex (Abelcet)	5 mg/kg/d*	5 mg/kg/d	
	Amphotericin B colloidal dispersion (Amphocil; Amphotec)	5 mg/kg/d*	5 mg/kg/d	
	Liposomal amphotericin B (AmBisome)	5 mg/kg/d*	5 mg/kg/d	
Pyrimidine analogue	5-Fluorocytosine (Ancobon)	150 mg/kg/d divided q6h	150 mg/kg/d divided q6h	Use caution with large oral volume for neonates
Triazole	Fluconazole (Diflucan)	100–800 mg/d; 3–6 mg/kg/d	6–12 mg/kg/d	Dose higher in children due to shorter half-life; neonates require further special dosing
	Itraconazole (Sporanox)	200–400 mg/d	2.5–5 mg/kg/dose bid	Dosing BID preferred in children
	Voriconazole (Vfend)	Load: 6 mg/kg/dose bid × 1 d Maintenance: 3–4 mg/kg/dose bid	Load: 6 mg/kg/dose bid × 1 d Maintenance: 4–8 mg/kg/dose BID <sup>†</sup>	Linear pharmacokinetics in children; exact pediatric dose not yet determined, but believed to be greater than adult dosing
Echinocandin	Caspofungin (Cancidas)	Load: 70 mg qd × 1 d Maintenance: 50 mg qd	Load: 70 mg/m <sup>2</sup> QD × 1 d Maintenance: 50 mg/m <sup>2</sup> qd	Dosing for hepatic insufficiency in children is 35 mg/m <sup>2</sup> qd, similar to the adult decrease to 35 mg qd

\* Abelcet is officially recommended at 5 mg/kg/d; Amphocil, at 3–5 mg/kg/d; and AmBisome, at 1–5 mg/kg/d. Most clinical data have been obtained with the use of these preparations at 5 mg/kg/d, and most clinicians use and prefer this higher dosing.

<sup>†</sup> Suggested dosing by the author; exact pediatric dosing for voriconazole not yet determined.

of amphotericin B deoxycholate are necessary for successful therapy [3,4]. Cerebrospinal fluid (CSF) concentrations are only 2% to 4% of serum concentrations [5], so this agent is a poor choice as monotherapy for the treatment of meningitis.

In addition to fungal ergosterol, amphotericin B binds to cholesterol in human cell membranes, likely accounting for its toxicity [6]. Lipid formulations of amphotericin B generally are better tolerated than the conventional deoxycholate preparation, perhaps because the lipid stabilizes the drug in a self-associated state so that it cannot interact with the cholesterol of human cellular membranes [7,8]. The reduced nephrotoxicity of lipid formulations also may result from their preferential binding to serum high-density lipoproteins. High-density lipoprotein-bound amphotericin B seems to be released to the kidney more slowly, or to a lesser degree, than conventional amphotericin B that is bound to low-density lipoproteins [9].

Three lipid-associated formulations of amphotericin B offer the advantage of an increased daily dose of the parent drug, better delivery to the primary reticuloendothelial organs (lungs, liver, spleen) [10,11], and reduced toxicity. The US Food and Drug Administration (FDA) approved amphotericin B lipid complex (ABLC, Abelcet) in December 1995, amphotericin B colloidal dispersion (ABCD, Amphocil, Amphotec) in December 1996, and liposomal amphotericin B (L-amphotericin B, AmBisome) in August 1997 [12]. It is postulated that activated monocytes/macrophages take up drug-laden lipid formulations and transport them to the site of infection, where phospholipases release free drug [12,13]. A multicenter maximum tolerated dose study of L-amphotericin B using doses of 7.5 to 15 mg/kg/d found a nonlinear plasma pharmacokinetic profile with a maximal concentration at 10 mg/kg/d and no demonstrable dose-limiting nephrotoxicity or infusion-related toxicity [14].

Amphotericin B nephrotoxicity is generally less severe in infants and children than in adults, likely resulting from the more rapid clearance of the drug in children. Reduced nephrotoxicity with a lipid formulation has been reported in adults and has been observed in children [15,16] and neonates [17]. A pharmacokinetic study of L-amphotericin B conducted in 39 children ranging in age from 1 to 17 years observed no dose-related trends in adverse events and a maximally tolerated dose of 10 mg/kg/d (Gilead Sciences, data on file). These results are similar to the results in studies conducted in adults [14]. A 56-center prospective study evaluated the safety and efficacy of L-amphotericin B administered to 260 adults, 242 children (<15 years old), and 43 infants (<2 months old) [18]. In general, the infants and children tolerated the largest doses of L-amphotericin B administered for the longest time (median 16 days) [18].

#### *Clinical experience and pediatric data*

The optimal duration of amphotericin B therapy is unknown, but likely depends on underlying disease, extent of fungal infection, resolution of neutropenia, degree of immunosuppression, and graft function after transplan-

tation. No specific total dose of amphotericin B currently is recommended; rather, a standard approach is to initiate therapy with 1 mg/kg/d, reducing the dose if toxicity develops [19]. No data indicate that any of the amphotericin B lipid formulations are more effective than conventional amphotericin B [10,12,20–22]. A study of 56 infants with candidiasis, including 52 preterm infants, showed no differences in mortality or time to resolution of candidemia between neonates receiving conventional amphotericin B ( $n=34$ ), L-amphotericin B ( $n=6$ ), or ABCD ( $n=16$ ) [23]. The decision to prescribe a lipid formulation of amphotericin B should be based on the potential of reducing nephrotoxicity or infusion-related toxicity rather than anticipated therapeutic benefit.

In noncomparative studies, ABLC has been found to be an effective antifungal agent in children. In an open-label pediatric trial, complete or partial therapeutic response was observed in 70% (38 of 54) of patients, including 56% (14 of 25) of patients with aspergillosis and 81% (22 of 27) of patients with candidiasis [16]. A retrospective study of 46 children treated with ABLC reported an overall response rate of 83% (38 of 46), including 78% (18 of 23) against aspergillosis and 89% (17 of 19) against candidiasis [24].

Few published data exist on the use of lipid formulations of amphotericin B in neonates. One study that included 40 preterm neonates (mean birth weight 1090 g, mean gestational age 28.4 weeks) noted that L-amphotericin B was associated with clinical resolution in greater than 70% of patients with candidiasis [25]; other uncontrolled studies have confirmed the high response rates. In three other studies, 21 of 21, 35 of 37, and 20 of 24 neonates with candidiasis cleared their infections [26–28].

## **Pyrimidine analogues: 5-Fluorocytosine**

### *Mechanism of action*

5-Fluorocytosine (5-FC, Ancoban) is a fluorinated analogue of cytosine that has antimycotic activity resulting from the rapid conversion of 5-FC into 5-fluorouracil (5-FU) within susceptible fungal cells [29,30]. 5-FU inhibits fungal protein synthesis after incorporation into fungal RNA in place of uridylic acid or through inhibition of thymidylate synthetase, inhibiting fungal DNA synthesis [30]. 5-FC has little inherent antimold activity [31], and most reports detail clinical failure with monotherapy against yeast infections [32]. Antifungal resistance develops quickly to 5-FC monotherapy, so the drug should be used only in combination with other agents. 5-FC is thought to enhance the antifungal activity of amphotericin B, especially in anatomic sites where amphotericin B penetration is poor, such as CSF, heart valves, and the vitreal body [3]. One explanation for the synergism detected with amphotericin B plus 5-FC is that the membrane-permeabilizing effects of low concentrations of amphotericin B facilitate penetration of 5-FC to the cell interior [33].

### *Pharmacology and toxicities*

5-FC is well absorbed after oral administration [30]. 5-FC distributes widely, attaining therapeutic concentrations in most body sites, such as the CSF, vitreous and peritoneal fluids, and inflamed joints, because it is small and highly water soluble and not bound by serum proteins to a great extent [30]. It is often technically difficult to treat neonates with 5-FC because of the large volume necessitated by using the oral formulation and the lack of an intravenous formulation available in the United States.

5-FC toxicity seems to be due to its conversion to 5-FU, with reports of 5-FU concentrations being in the range found after chemotherapeutic doses [34]. 5-FC may exacerbate myelosuppression in patients with neutropenia, and trough serum concentrations of 100 µg/mL or greater are associated with bone marrow aplasia. 5-FC serum concentrations should be monitored, and levels should be maintained at approximately 40 to 80 µg/mL. In a review of a multicenter trial of 194 patients who received amphotericin B plus 5-FC for cryptococcal meningitis, hematologic toxicity appeared in the first 2 weeks of therapy in 56% of patients and in the first 4 weeks of therapy in 87% [35].

### *Clinical experience and pediatric data*

A pivotal trial showed that the combination of amphotericin B plus 5-FC was more effective than amphotericin B alone in the treatment of cryptococcal meningitis [36]. A subsequent multicenter study of 194 patients with cryptococcal meningitis concluded that 4 weeks of amphotericin B plus 5-FC was adequate for immunocompetent patients without neurologic complications, such as hydrocephalus. In immunocompromised patients, 6 weeks of combination therapy resulted in fewer relapses [37]. Amphotericin B combined with 5-FC currently is recommended as initial therapy for cryptococcal meningitis [38]. These two agents also are suggested for use in patients with candidal meningitis [39].

Data regarding the use of 5-FC in children are limited. One review of 17 cases of candidal meningitis that included 11 patients younger than 12 months old noted improvement in 15 patients treated with amphotericin B and 5-FC [40].

## **Azoles**

### *Mechanism of action*

The azole antifungals are heterocyclic synthetic compounds that inhibit the fungal lanosterol 14 $\alpha$ -demethylase, which catalyzes a late step in ergosterol biosynthesis. The drugs block demethylation of the C-14 of lanosterol, leading to substitution of methylated sterols in the fungal cell membrane and depletion of ergosterol. The result is an accumulation of precursors leading to abnormalities in

fungal membrane permeability, membrane-bound enzyme activity, and a lack of coordination of chitin synthesis [41,42].

### *Fluconazole*

#### *Pharmacology and toxicities*

Fluconazole (Diflucan) is a triazole that was approved by the FDA for treatment of cryptococcosis and *Candida* infections in 1990. Fluconazole's activity is concentration-independent; it does not increase when the maximal fungistatic concentration is attained [43]. Fluconazole is available as either an oral or an intravenous form, and oral fluconazole is approximately 90% bio-available. Unchanged drug is cleared predominantly by the kidneys; metabolism accounts for only a minor proportion of fluconazole clearance [44]. Drug concentrations in CSF and vitreous humor are approximately 80% of the concentrations found in blood [45]. Fluconazole passes into tissues and fluids rapidly, probably as a result of its relatively low lipophilicity and limited binding to plasma proteins. Concentrations of fluconazole are 10-fold to 20-fold higher in the urine than in the blood, and it is particularly appropriate for the therapy of fungal urinary tract infections.

The pharmacokinetics of fluconazole differ between adults and children. A review of five separate fluconazole pharmacokinetic studies that included 101 infants and children ranging in age from 2 weeks to 16 years [44] showed that fluconazole clearance is more rapid in children than adults. The mean plasma half-life was approximately 20 hours in children compared with 30 hours in adults. To achieve comparable drug exposure, the daily fluconazole dose needs to be approximately doubled for children older than 3 months to 6 to 12 mg/kg/d.

The volume of distribution of fluconazole is greater and more variable in neonates than in infants and children. There is also a slow elimination of fluconazole, however, with a mean half-life of 88.6 hours at birth, decreasing to approximately 55 hours by 2 weeks of age. Neonates should be treated with a higher dose of fluconazole to compensate for their increased volume of distribution, but the frequency of dosing needs to be decreased because of their slow elimination. Specifically, during the first 2 weeks of life, fluconazole should be dosed every 72 hours; this dosing interval can be reduced to 48 hours during the next 2 weeks of life [44]. The pharmacologic consequence of such a long half-life is that patients require at least 8 days to reach steady state [46].

Side effects of fluconazole are uncommon. In one study of 24 immunocompromised children, elevated transaminases were observed in only 2 children [47]. Another review of 562 children confirmed that pediatric results mirror the excellent safety profile seen in adults. The most common side effects were gastrointestinal upset (vomiting, diarrhea, nausea) (7.7%) or skin rash (1.2%) [48].

#### *Clinical experience and pediatric data*

In one clinical trial of 206 nonneutropenic adult patients with invasive candidiasis, the rate of successful therapy with 0.5 to 0.6 mg/kg/d of ampho-

tericin B (79%) was similar to that with 400 mg/d of fluconazole (70%) [49]. Another multicenter trial of 219 mostly nonneutropenic adult patients with invasive candidiasis found that patients treated with a combination of fluconazole and amphotericin B ( $n = 112$ ) showed no difference in the 30-day time to failure compared with patients treated with fluconazole alone ( $n = 107$ ) [50]. Although a secondary analysis suggested that combination therapy was superior in efficacy to fluconazole alone, the difference in favorable outcome was small (69% versus 56%). A definitive conclusion regarding the benefit of this combination therapy to treat candidiasis is unproven.

Clinical and mycologic response was observed in 97% of 40 neonates and infants treated with fluconazole. These children had been nonresponsive or intolerant to standard antifungal therapy [51]. In another report, 80% of 40 neonates with invasive candidiasis were treated successfully with 6 mg/kg/d of fluconazole. Although three of these patients relapsed, they ultimately were cured with an increased dose of fluconazole (10 mg/kg/d) [52]. Finally, a prospective randomized study that compared fluconazole with amphotericin B in 24 infants with candidemia noted a survival benefit among infants treated with fluconazole (67%) compared with infants who received amphotericin B (55%) [53].

Fluconazole also has been evaluated for antifungal prophylaxis. Randomized, placebo-controlled clinical trials have shown that the prophylactic use of fluconazole after allogeneic bone marrow transplantation results in lower rates of candidal infection and graft-versus-host disease [54]. Studies conducted in adult stem cell transplant recipients observed that 200 mg/d of prophylactic fluconazole is as effective as 400 mg/d [55,56]. One concern with this patient population continues to be the lack of anti-*Aspergillus* activity with fluconazole. A prospective, placebo-controlled, randomized, double-blind evaluation of prophylactic fluconazole has been conducted in 100 low-birth-weight (<1000 g) infants. Six weeks of fluconazole therapy resulted in a statistically significant reduction in the incidence of fungal colonization (22% versus 60%) and a decrease in the development of invasive fungal infection (0% versus 20%) [57].

### *Itraconazole*

Itraconazole (Sporanox) is fungicidal and has been available for clinical use since 1990 [58]. Limitations of itraconazole include lack of a parenteral formulation, erratic oral absorption in high-risk patients, and frequent drug interactions.

### *Pharmacology and toxicities*

Itraconazole has a high volume of distribution and accumulates in tissues [42]. It is not reliably absorbed from the gastrointestinal tract and has high protein binding [1].  $H_2$  receptor antagonists may result in decreased drug absorption, whereas acidic beverages, such as colas or cranberry juice, may enhance absorption [59]. Administration of the capsular formulation with food increases absorption, but the oral suspension is better absorbed on an empty stomach [5].



Elimination of itraconazole is primarily hepatic; there is no need for dosage adjustment in the presence of renal function impairment [42].

Serum concentrations of itraconazole are much lower in children than in adults after administration of the oral solution. This is especially true in children younger than 5 years old [60–62]. Children usually need twice-daily dosing, whereas once-daily dosing is appropriate for adults.

Itraconazole is well tolerated. Nausea and vomiting occur in about 10% of subjects, and elevated transaminases occur in 5% [63]. Rare cases of cardiomyopathy have been reported in adults, but no cases have been described in children. Itraconazole is a potent inhibitor of the cytochrome CYP3A4 enzyme and can result in important drug interactions. Prior or concurrent use of rifampin, phenytoin, carbamazepime, and phenobarbital should be avoided, and concomitant use with cyclophosphamide should be discouraged [64]. Any drug handled by this cytochrome pathway with normally low bioavailability, extensive first-pass metabolism, or a narrow therapeutic window may be especially vulnerable [65].

#### *Clinical experience and pediatric data*

Itraconazole is currently more appealing as a prophylactic rather than a therapeutic agent. It may be superior to fluconazole for this purpose. In one large randomized, controlled trial conducted in 445 patients with hematologic malignancy, itraconazole oral solution prevented more fungal infections than fluconazole suspension. Specifically, six proven fungal infections, including four fatal cases, occurred in the fluconazole recipients compared with one nonfatal case of candidiasis in the itraconazole recipients [66]. Additionally, although there were no cases of invasive aspergillosis in the patients receiving itraconazole, four cases of aspergillosis were diagnosed among patients receiving fluconazole. Itraconazole and fluconazole prophylaxis had similar prophylactic efficacy in a trial conducted in liver transplant recipients [67]. Itraconazole also has been shown to be an effective prophylactic agent in patients infected with HIV. A double-blind, placebo-controlled trial conducted in 63 patients with HIV infection in Thailand showed a reduction in fungal infections from 16.7% in the placebo recipients to 1.6% in patients taking itraconazole [68].

There are no pivotal studies of itraconazole prophylaxis in children, and the few children enrolled in the larger prophylaxis studies were not analyzed separately. A phase I study in 26 HIV-infected children showed the cyclodextrin itraconazole solution was well tolerated and efficacious against oropharyngeal candidiasis, including responses in all patients with fluconazole-resistant isolates [62].

#### *Voriconazole*

Voriconazole (Vfend) is a second-generation triazole and a synthetic derivative of fluconazole. Voriconazole combines the broad spectrum of anti-

fungal activity of itraconazole with the increased bioavailability of fluconazole. It is fungicidal against *Aspergillus* and fungistatic against *Candida* species [58, 69–71].

### *Pharmacology and toxicities*

Voriconazole metabolism is nonlinear in adults with an approximately threefold increase in the area under the concentration-time curve after a 33% increase in dosage. In contrast, elimination of voriconazole seems to be linear in children after doses of 3 mg/kg and 4 mg/kg every 12 hours [72].

Children require higher doses of voriconazole than adults to attain similar serum concentrations over time. Based on limited pharmacokinetic analyses, it seems that a pediatric dosage of 11 mg/kg administered every 12 hours is approximately bioequivalent to an adult dosage of 4 mg/kg given every 12 hours [72]. The correct pediatric dosage is unknown, but seems to be much higher than the dosage for adult patients. Using voriconazole at recommended doses for adults may lead to clinical failures in children.

After nearly complete oral absorption, voriconazole is extensively metabolized by the liver. As a result of a point mutation in the gene encoding CYP2C19, some people are poor metabolizers, and some are extensive metabolizers [73]. About 5% to 7% of whites and 20% of non-Indian Asians have a deficiency in expressing this enzyme. As a result, voriconazole levels are fourfold greater in these subjects than in homozygous subjects who metabolize the drug more extensively [74,75].

Voriconazole's main side effects include reversible dose-dependent visual disturbances (increased brightness, blurred vision) [76] in one third of treated patients, elevated hepatic transaminases with increasing doses [77,78], and occasional skin reactions likely secondary to photosensitization [41,69,79]. Drug interactions also can be problematic. Concomitant use with sirolimus is contraindicated because concentrations of the immunosuppressant can be increased 2-fold to 10-fold [80,81].

### *Clinical experience and pediatric data*

Voriconazole is statistically superior to amphotericin B deoxycholate in the therapy of aspergillosis. In a prospective clinical trial of 392 patients with invasive aspergillosis, more than 50% of patients initially treated with voriconazole compared with only about 30% of patients treated with amphotericin B had complete or partial responses. Improved survival also was observed among patients initially treated with voriconazole [82]. Similar positive experience with voriconazole was noted in an open-label multicenter study of 116 patients with invasive aspergillosis treated with voriconazole as either primary (60 patients) or salvage (56 patients) therapy [83]. These data have led clinicians to conclude that voriconazole is the preferred agent for treatment of invasive aspergillosis.

Voriconazole also is effective in the treatment of *Candida* infections. In a multicenter evaluation of the therapy of esophageal candidiasis in 391 immunocompromised patients, voriconazole was successful in 98.3%, and fluconazole was successful in 95.1% [84]. In another study of 422 patients with invasive candidiasis, approximately 40% of patients were treated successfully with voriconazole. This success rate was virtually identical to that of amphotericin B therapy, followed by oral fluconazole [85]. Voriconazole also has been evaluated in the management of febrile neutropenic patients. In one large study of more than 800 episodes of fever and neutropenia, voriconazole was slightly inferior to L-amphotericin B. Voriconazole was effective in 26% of 415 subjects, and L-amphotericin B was effective in 30% of 422 subjects. There were more breakthrough infections in the L-amphotericin B recipients, however, including 13 cases of invasive aspergillosis versus 4 cases in the voriconazole recipients [86].

The largest pediatric report of voriconazole is an open-label, compassionate-use evaluation of the drug in 58 children with proven or probable invasive fungal infection refractory to or intolerant of conventional antifungal therapy [87]. Almost three quarters of the patients had aspergillosis. After a mean of 3 months of therapy, 45% of the children had a complete or partial response. Only 7% of the subjects could not tolerate the drug. Stratifying outcome by pathogen revealed a complete or partial response of 43% against aspergillosis, 50% against candidemia, and 63% against scedosporiosis.

#### *Experimental azoles: posaconazole and ravuconazole*

Posaconazole is a second-generation triazole that is closely related to itraconazole. It is fungicidal in vitro against *Aspergillus* and has a half-life of at least 18 to 24 hours in humans [41,88]. Presently, only an oral formulation of posaconazole is available. Posaconazole was found to be effective and well tolerated in a multicenter study in patients refractory to other antifungal agents [89]. Experience with posaconazole in children is limited. In an open-label study, two of seven patients with chronic granulomatous disease and invasive fungal infection were younger than 18 years old [90]. Six patients had a complete response. Similarly, two patients were younger than 18 years old in another open-label study of 23 patients with zygomycosis. The overall success rate of therapy in this study was 70% [91]. Posaconazole is likely to play a role in antifungal management as an excellent oral agent, but detailed pediatric studies have yet to be performed.

Ravuconazole is structurally similar to fluconazole and voriconazole. It is fungicidal [92,93], has 47% to 74% bioavailability with linear pharmacokinetics [41], and has a long half-life of approximately 100 hours [94]. Of 76 patients with esophageal candidiasis, 76% were cured with 7 days of therapy with ravuconazole. The drug's safety profile was similar to that of fluconazole [95]. Ravuconazole's long half-life could lead to potentially intermittent dosing. No pediatric data are available.

## Echinocandins

### *Mechanism of action*

For years, development of new systemic antifungals focused on chemically modifying existing classes. More recently, an entirely new class of antifungals, the echinocandins, has been discovered. These agents interfere with cell wall biosynthesis by noncompetitive inhibition of 1,3- $\beta$ -D-glucan synthase, an enzyme present in fungi but absent in mammalian cells [41,88]. This 1,3- $\beta$ -glucan, an essential cell wall polysaccharide, forms a fibril of three helically entwined linear polysaccharides and provides structural integrity to the fungal cell wall [96,97]. Echinocandins are fungicidal against *Candida* but fungistatic against *Aspergillus* [98]. These agents are not metabolized through the cytochrome enzyme system, but through a presumed O-methyltransferase, lessening some of the drug interactions and side effects seen with the azoles.

### *Caspofungin*

#### *Pharmacology and toxicities*

Caspofungin (Cancidas) is a fungicidal semisynthetic derivative of the natural product pneumocandin B<sub>0</sub>. It has linear pharmacokinetics [99], is excreted primarily by the liver, has a beta-phase half-life of 9 to 10 hours [100], and is well tolerated [101–104]. It is not metabolized by the cytochrome isoenzyme system [105], and at present there is no known maximal tolerated dose and no toxicity-defined maximal length of therapy. Elevations of caspofungin plasma concentrations are observed in patients with mild hepatic insufficiency, and a dose reduction in adults from 50 mg to 35 mg daily after the standard 70-mg loading dose is recommended in this setting [77].

A pharmacokinetic study conducted in children evaluated 39 patients between ages 2 and 17 years. Data were analyzed on the basis of weight (1 mg/kg/d) and body surface area (50 mg/m<sup>2</sup>/d or 70 mg/m<sup>2</sup>/d) [106]. Compared with plasma concentrations attained in adults treated with 50 mg/d, the weight-based approach resulted in suboptimal plasma concentrations, whereas the 50 mg/m<sup>2</sup>/d dose yielded similar plasma concentrations in the children. Caspofungin's half-life is approximately one third less in children than in adults.

Because 1,3- $\beta$ -glucan is a selective target present only in fungal cell walls and not in mammalian cells, caspofungin has few adverse effects [96]. The drug has no apparent myelotoxicity or nephrotoxicity [107]. Plasma concentrations of tacrolimus are reduced by about 20% when coadministered with caspofungin, but tacrolimus does not alter the pharmacokinetics of caspofungin [108]. Cyclosporine increases the concentration of caspofungin by about 35%, but plasma concentrations of cyclosporine are not altered by coadministration of caspofungin [109]. A retrospective analysis of the compassionate use of caspofungin in 25 children, most of whom also received other antifungals, noted that only 3 (12%) had a possible drug-related adverse event [110].

*Clinical experience and pediatric data*

In the pivotal clinical study that led to FDA approval, 56 adults with acute invasive aspergillosis received caspofungin as “salvage” therapy after failing primary therapy for more than 1 week or developing significant nephrotoxicity. More than 40% of the patients had a favorable response to therapy [111]. Additional patients have been enrolled in this trial, and to date, 45% (37 of 83) have had a complete or partial response, including 50% (32 of 64) with pulmonary aspergillosis and 23% (3 of 13) with disseminated infection [112]. Caspofungin has not been studied for use in primary therapy against invasive aspergillosis.

A study comparing caspofungin and amphotericin B in 224 adults with invasive candidiasis has been conducted. Response to caspofungin ( $n = 104$ ; 73.4%) was slightly better than response to amphotericin B ( $n = 115$ ; 61.7%) [113]. Caspofungin was as effective as amphotericin B against all the major species of *Candida*. Mortality was similar in both groups, and the proportion of patients with drug-related adverse events was substantially higher in the amphotericin B group. More recently, caspofungin ( $n = 556$ ) was compared with L-amphotericin B ( $n = 539$ ) in febrile neutropenic patients, and overall success was virtually identical (approximately 33%) [114].

*Experimental echinocandins: micafungin and anidulafungin*

Micafungin is an echinocandin lipopeptide compound [41,115,116] with a half-life of approximately 12 hours. As with other echinocandins, it is fungicidal against *Candida* and fungistatic against *Aspergillus* [117]. The highest drug concentrations of this agent are detected in the lung, followed by the liver, spleen, and kidney. Micafungin was undetectable in the CSF, but low levels were detected in the brain tissue, choroidal layer, and vitreous humor, but not the aqueous humor of the eye [99].

Several pediatric studies of micafungin have been completed. A phase I single-dose, multicenter, open-label study evaluated three dosages (0.75 mg/kg/d, 1.5 mg/kg/d, and 3 mg/kg/d) in two infant weight groups (500–1000 g and >1000 g). The mean serum concentration of micafungin was lower in the smaller infants, the serum half-life was shorter, and clearance was more rapid. In the neonates weighing 500 to 1000 g, the half-life was 5.5 hours with a clearance of 97.3 mL/h/kg. In the neonates weighing more than 1000 g, the half-life increased to 8 hours, whereas clearance decreased to 55.9 mL/h/kg. These findings compare with the findings in children (age 2–8 years), where half-life was 12 hours, and clearance was slowest at 32.2 mL/h/kg [118].

A study of micafungin in combination with a second antifungal agent in pediatric and adult bone marrow transplant recipients with invasive aspergillosis revealed an overall complete or partial response of approximately 40% [119]. A study comparing prophylaxis in 882 stem cell transplant recipients found that micafungin was more effective in preventing yeast and mold infections (80%) than fluconazole (73.5%) [120]. Other studies have shown the efficacy of

miconazole in the primary therapy of esophageal candidiasis [121] and as rescue therapy in patients failing to respond to first-line antifungals [122].

Anidulafungin is a semisynthetic terphenyl-substituted antifungal derived from echinocandin B, a lipopeptide fungal product [123]. It has linear pharmacokinetics [88] with the longest half-life of all the echinocandins (approximately 18 hours) [101,124]. Its *in vitro* activity is similar to that of the other echinocandins [125]. Neither end-stage renal impairment nor dialysis substantially alters the pharmacokinetics of anidulafungin [126]. Tissue concentrations after multiple dosing were highest in lung and liver, followed by spleen and kidney, with measurable concentrations in the brain tissue. The pharmacokinetics showed approximately sixfold lower mean peak concentrations in plasma and twofold lower area under the concentration-time curve values compared with values with similar doses of caspofungin and miconazole. A study of 601 patients with esophageal candidiasis compared anidulafungin with oral fluconazole and found endoscopic similar success rates exceeding 95% [127]. A phase I/II dose escalation study of anidulafungin involving five centers that enrolled children age 2 to 17 years old with persistent neutropenia who were at risk for invasive fungal infection is now complete, but results have not yet been presented.

## Summary

Since the 1960s, there has been limited progress in the treatment of invasive fungal infections, and the field of pediatric antifungal therapy has been largely ignored. Although conventional amphotericin B was the drug of choice for many invasive fungal infections, its clinical utility was thwarted by nephrotoxicity and infusion-related toxicity. Lipid formulations have reduced the toxicity of amphotericin B, and these agents have a role in the management of several specific diseases, such as zygomycosis and others.

The preferred treatment for invasive aspergillosis has shifted to voriconazole, with present debates centering on the possible use of combination antifungal therapy. A reason for failure of therapy in children may be the use of an inadequate dose of voriconazole, originally based on data derived from adults. A knowledge of the differences in the pharmacokinetics of the drug in children and adults results in more optimal dosing. Although voriconazole is a tremendous mold-active agent, gaps in coverage, such as the emerging zygomycosis and non-*albicans Candida* species, are important to address. Presently, investigational posaconazole seems to have better activity against zygomycosis, but no parenteral formulation of this drug is available. Although the extended half-life of ravuconazole could play a role in prophylaxis or long-term intermittent therapy, the drug is not yet available.

The echinocandin class presents one of the best options for therapy of candidiasis, combining an excellent safety profile with an effective fungicidal agent. Although caspofungin likely has some role in salvage therapy for recalcitrant invasive aspergillosis, it may prove to be most valuable as an anti-

*Candida* drug or possibly as part of combination therapy for invasive aspergillosis. Micafungin and anidulafungin have begun to acquire initial pediatric dosing data, and these drugs may prove to be useful in children.

Few antifungal studies have been conducted in children. Although there have been many phase III antifungal clinical trials in adults, there has never been a large phase III antifungal clinical trial dedicated to pediatric patients. Consequently, most information for the pediatrician has been extrapolated from adult data. Through dedicated clinicians and collaboration, pediatric indications and dosing strategies eventually will be discovered that will benefit pediatric patients directly.

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