

## Mycoses in Pediatric Patients

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Fungal pathogens are an increasingly recognized complication of organ transplantation, childhood malignancies, neonatal medicine, and pediatric surgery. Fortunately the antifungal armamentarium available to clinicians has increased in the last several years to include new formulations of amphotericin B, antifungal triazoles, and the echinocandins. Important advances have been achieved in understanding the safety, tolerability, and pharmacokinetics of these antifungal agents in pediatric patients. Studies are ongoing as to the optimal use of these antifungal agents in the settings of prophylaxis, empiric therapy, and treatment of proven invasive fungal infections. Although data continue to accumulate on adult patients who have invasive fungal disease, there remains a paucity of pediatric interventional data. This discrepancy forces pediatricians to extrapolate many recommendations for use of antifungal agents in children from the studies conducted in adult patients. This article provides a brief overview of some of the unique differences in invasive fungal infections in children compared with those of adults and then focuses on the key differences in antifungal pharmacology and use in children. The specific pathogens are covered in greater detail elsewhere in this issue.

A worldwide survey of *Candida* isolates separated the results based by age and demonstrated that, although infection with *C albicans* was nearly uniform among all age groups, infection with *C parapsilosis* was more common in younger patients, whereas *C glabrata* was more prevalent in older patients [1]. Fluconazole was found to be less active against *C glabrata* in the youngest age group ( $\leq 1$  year), whereas the species was more susceptible in the older cohorts. There were no highly resistant *C glabrata* isolates (minimum

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inhibitory concentration [MIC]  $\geq 64$   $\mu\text{g/mL}$ ) in that youngest age group, but 5% to 9% of the isolates in the older groups were highly resistant [1]. This observation may be related to the greater exposure of older children to fluconazole for prophylaxis or therapeutic intervention.

Candidemia seems to have a somewhat different clinical presentation in children versus adult patients. In one prospective study the incidence of septic shock was greater in children versus adults (20% versus 10.8%,  $P = .02$ ) with candidemia. Additionally, meningitis was found in 11.4% of infected children versus only 0.8% of infected adults ( $P = .001$ ) [2]. A subsequent study confirmed the earlier epidemiologic reports of an increased proportion of *C parapsilosis* and decreased prevalence of *C glabrata* compared with that of adult patients [3]. This study also found that candidemia persisted longer in children compared with adult patients, and with a greater median number of positive blood cultures in pediatric candidemic patients.

The risk factors for candidemia in neonatal patients are different from those of older children. Risk factors have been clearly associated with a myriad of clinical aspects, including gestational age, birthweight, and others [4]. Birthweight in particular is consistently noted to be significantly correlated with disease development. In one study, infants with a birthweight of 400 to 750 grams possessed an odds ratio of 3.22 for developing candidiasis by the third day of life, compared with those infants born at 751 to 1000 grams [5]. Numerous organ systems can be involved in neonatal candidiasis, including most significantly a 49% concordance with urinary involvement in candidemia as reviewed in a large meta-analysis [6]. In a recent study of 4579 infants born at less than 1000 grams, 7% developed candidemia. Approximately 10% developed *Candida* meningitis, and yet half of those patients who developed meningitis had negative blood cultures [5].

Invasive aspergillosis in children offers some clinical differences from adult patients also [7]. Earlier reports have suggested that the species distribution of *Aspergillus* isolates for pediatric and adult patients is different. A large National Institute of Allergy and Infectious Diseases Bacteriology and Mycoses Study Group study reviewed 256 isolates of *Aspergillus* species from patients who had invasive aspergillosis from 24 medical centers [8], and *A fumigatus* yielded 67% (171/256) of isolates, whereas *A flavus* was the second most common isolate at 16% (41/256). This parallels the species distribution in the large voriconazole randomized clinical trial [9], in which 77% (85/110) were *A fumigatus* and 6% (7/110) were *A flavus*. In two large pediatric studies from Toronto [10] and St. Jude [11], however, *A flavus* was the predominant pathogen. In Toronto, 65% (17/26) of isolates were *A flavus*, followed by 15% (4/26) *A fumigatus* as the second most common pediatric *Aspergillus* isolate. At St. Jude, 72% (28/39) isolates were *A flavus*, followed by 38% (15/39) *A fumigatus* isolates. These differences may reflect greater environmental distribution of *A flavus* in these institutions.

In two more recent studies, however, the pediatric epidemiology paralleled previous adult studies. In the pediatric voriconazole compassionate

release study, the species distribution was predominantly with patients infected with *A fumigatus* (26/42), followed by *A flavus* (6/42), and *A nidulans* (3/42) [12]. In a French pediatric study with amphotericin B lipid complex (ABLC) the most common isolates were *A fumigatus* (11/23), *A flavus* (6/23), *A niger* (1/23), and unspiciated *Aspergillus* spp (5/23) [13]. The differences in environmental exposure also parallel the differences in the site of infection, because the earlier studies with *A flavus* predominance cited a large percentage of cutaneous disease [10,11], whereas the later treatment studies contained mostly patients who had pulmonary aspergillosis [12,13].

The diagnostic features of invasive aspergillosis seem to also be different in children. In adult series of pulmonary aspergillosis, approximately 50% of cases show cavitation and 40% air crescent formation [14]. In one 10-year review of 27 consecutive pediatric patients (mean age, 5 years), there was central cavitation of small nodules in 25% of children and no evidence of air crescent formation within any area of consolidation [15]. In another pediatric report there was a 22% rate (6/27) of cavitation on chest radiography [16], and in a separate report there was a 43% rate (6/14) of cavitation on CT [17]. In these later two pediatric series, the mean ages were greater than the report of lower rates of cavitation and no air crescent formation, suggesting that there is a spectrum of radiologic disease presentation that is directly related to age. Perhaps cavitation and air crescent formation is more likely in the older child and adult than in the younger child.

Diagnosis of pediatric invasive aspergillosis with the enzyme immunoassay for galactomannan (GM) that is approved for use in adult patients is potentially difficult, because studies have shown repeated differences in pediatric and adult values. In one prospective study from Europe (1995–1998) of 450 adult allogeneic HSCT patients (3883 samples) and 347 children with hematologic malignancies (2376 samples), the false-positive rate in adult patients was 2.5% (10 of 406) and in children it was 10.1% (34 of 338) [18]. In another European study of 797 episodes, including 48 pediatric patients, the false-positive rate in the fever of unknown origin group was 0.9% in adults and 44.0% ( $P < .0001$ ) in children. Additionally, the specificity of the test was lower in children, at 47.6% compared with 98.2% ( $P < .0001$ ) in adult patients [19]. The causes of the false-positive results in these studies were not elucidated.

Galactomannan testing in children is associated with false-negative results in some specific pediatric patients, such as those who have chronic granulomatous disease (CGD). One report details a non-neutropenic 4-year-old child who had CGD and invasive aspergillosis diagnosed by lung biopsy who had persistent false-negative serum GM testing [20]. Another study evaluated patients who had CGD ( $n = 10$ ), Job syndrome ( $n = 6$ ), and invasive aspergillosis, and found GM antigenemia was detected in 4/15 cases of CGD and Job syndrome versus 24 of 30 cases of all other immunocompromised conditions ( $P = .0004$ ) [21].

## Antifungal options for pediatric and neonatal patients

There are several general reviews of antifungal pharmacology and spectrum of antifungal activity available [22–24]. One of the largest practical clinical issues facing those who care for children who have invasive fungal infections, however, is the lack of dedicated pediatric data. This problem is driven in part by the smaller number of patients available to perform complicated studies of pharmacology and dosing. During the past 15 years, however, there have been several studies dedicated to the systematic understanding of the safety, tolerability, and pharmacology of antifungal agents in pediatric patients. There are numerous precedents in medicine to suggest that dosing of antifungals would be different in children versus adults. Going beyond the concept of the correct dosage of antifungal is the obvious extension addressing efficacy in children, for which there are limited data. Here the authors' focus on some of the current thoughts on antifungal pharmacology and dosing in children.

### *Polyenes*

#### *Amphotericin B*

Despite the availability of conventional amphotericin B deoxycholate for more than half a century, there are no studies comparing different dosages for the treatment of documented infections. Although opinions abound to this day, the optimal therapeutic dosage for this nephrotoxic agent for treatment of invasive fungal infections is not established. Although a higher dosage is likely to be more nephrotoxic, this does not necessarily translate into improved efficacy. Because of greater nephronal reserve, pediatric patients tend to tolerate the glomerular toxicity better than do adults; however, tubular toxicity reflected by hypokalemia in pediatric patients may be severe. The available pharmacokinetic data in pediatric patients suggest that the dosages of amphotericin B deoxycholate confer similar exposure to those of adults and do not require adjustment in children.

A multicenter maximum-tolerated dose study of liposomal amphotericin B (L-AmB) in adult patients using dosages from 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, infusion-related toxicity, or improvement in efficacy [25]. A recent randomized clinical trial comparing L-AmB at a standard dose of 3 mg/kg/d versus a higher dose of 10 mg/kg/d in adults failed to show any improvement in efficacy and only yielded more nephrotoxicity with the higher dose [26]. A pharmacokinetic study of L-AmB conducted in 39 children observed no dose-related trends in adverse events and a maximally-tolerated dose of 10 mg/kg/d (Gilead Sciences, data on file), similar to adult data. A 56-center prospective study evaluated the safety and efficacy of L-AmB administered to 260 adults, 242 children (<15 years), and 43 infants younger than

2 months of age [27]. In general, the infants and children tolerated the largest doses of L-AmB administered for the longest period of time (median, 16 days) [27], dispelling historical notions that children were unable to tolerate such a potentially toxic antifungal agent.

There are no large randomized controlled studies comparing amphotericin B deoxycholate and a lipid formulation of amphotericin B for treatment of documented invasive mycoses [28–32]. The few randomized studies, although informative, are limited by a heterogeneous patient population and small sample size (large beta error). Although mortality was slightly lower in patients treated with L-AmB compared with AmB in one study with a small number of patients [33], another study showed no difference in response in treatment of documented invasive aspergillosis with amphotericin B colloidal dispersion versus deoxycholate amphotericin B [34]; amphotericin B deoxycholate was, however, more nephrotoxic. Although amphotericin B-induced nephrotoxicity is associated with excess mortality in adults, its impact in pediatric patients is not well defined. A study of 56 infants who had 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-AB ( $n = 6$ ), or amphotericin B colloidal dispersion ( $n = 16$ ) [35]. The decision to prescribe a lipid formulation of amphotericin B therefore should be based on the potential of reducing nephrotoxicity or infusion-related toxicity rather than anticipated therapeutic benefit.

Among six children with hepatosplenic candidiasis (HSC) who received 2.5 mg/kg of ABLC for 6 weeks for a total dosage of 105 mg/kg, the mean serum creatinine ( $0.85 \pm 0.12$  mg/dL at baseline) was stable at the end of therapy at  $0.85 \pm 0.18$  mg/dL and at 1-month follow-up at  $0.72 \pm 0.12$  mg/dL [36]. Plasma pharmacokinetics suggested steady state was achieved by day 7 of therapy. The five evaluable patients responded to ABLC with complete or partial resolution of physical findings and of lesions of HSC. During the course of ABLC infusions and follow-up, there was no progression of HSC, breakthrough fungemia, or post-therapy recurrence. Hepatic lesions continued to resolve after the completion of administration of ABLC.

A more recent study of the pharmacokinetics of ABLC in neonates who had invasive candidiasis demonstrated that this compound has a similar pharmacokinetic profile to that of adults [37]. ABLC also was active in treatment of candidemia in these infants.

In non-comparative 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% (38/54) of patients, including 56% (14/25) of those who had aspergillosis and 81% (22/27) of those who had candidiasis [38]. A retrospective study of 46 children treated with ABLC reported an overall response rate of 83% (38/46), including 78% (18/23) against aspergillosis and 89% (17/19) against candidiasis [13].

There are few published data on the use of lipid formulations of amphotericin B in neonates. One study that included 40 preterm neonates (mean birthweight, 1090 g; mean gestational age, 28.4 weeks) noted that L-AmB was associated with clinical resolution in more than 70% of patients who had candidiasis [39]; other uncontrolled studies have confirmed the high response rates. For example, in three other studies, 83% to 100% of neonates who had candidiasis cleared their infections [40].

Amphotericin B nephrotoxicity is generally less severe in infants and children than in adults, likely because of the greater nephronal reserve in children. Reports of reduced nephrotoxicity with a lipid formulation in adults also have been observed in children [38,41] and neonates [42].

### *Triazoles*

#### *Fluconazole*

The pharmacokinetics of fluconazole differ between adults and children. In an early study of the safety, tolerance, and pharmacokinetics of fluconazole in children who had neoplastic diseases, the plasma half-life was found to be approximately one half that of adults, indicating the need for a higher dosage of fluconazole in pediatric patients [43]. A subsequent review of five separate fluconazole pharmacokinetic studies that included 101 infants and children ranging in age from 2 weeks to 16 years [44] demonstrated that fluconazole clearance is more rapid in children than in 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 dosage therefore needs to be approximately doubled for children older than 3 months of age to 6 to 12 mg/kg/day.

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 therefore 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 [45].

Side effects of fluconazole are uncommon. Among 26 pediatric oncology patients receiving fluconazole, there was no nausea or vomiting related to fluconazole, whereas three patients had an asymptomatic increase in hepatic aminotransferase values after 4 to 6 doses (one patient at 2 mg/kg/d and two patients at 8 mg/kg/day), which returned to normal within 2 weeks after discontinuation of the drug [43]. In another study of 24 immunocompromised children, elevated transaminases were observed in only two cases [46].

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 (7.7%) (vomiting, diarrhea, nausea) or a skin rash (1.2%) [47].

Clinical and mycologic response was observed in 97% of 40 neonates and infants who had candidiasis treated with fluconazole. These children had been either nonresponsive or intolerant to standard antifungal therapy [48]. In another report, 80% of 40 neonates who had invasive candidiasis were successfully treated 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) [49]. Finally, a prospective randomized study that compared fluconazole to amphotericin B in 24 infants who had candidemia noted a survival benefit among those treated with fluconazole (67%) compared with those who received amphotericin B (55%) [50].

Fluconazole also has been evaluated for neonatal antifungal prophylaxis. A prospective, placebo-controlled, randomized, double-blind evaluation of prophylactic fluconazole has been conducted in 100 low birthweight (<1000 g) infants. Six weeks of fluconazole therapy resulted in a statistically significant reduction in the frequency of fungal colonization (22% versus 60%;  $P = .002$ ) and a decrease in the development of invasive fungal infection (0% versus 20%) [51]. The risk for developing a fungal infection in the fluconazole-prophylaxis infants was 0.20 (95% CI, 0.04–0.36,  $P = .008$ ), but overall mortality was unaffected. A subsequent study evaluated only twice-weekly prophylaxis and found that fluconazole at the lower total dose led to lower colonization and disease compared with placebo and no emergence of fluconazole resistance [52]. Whether fluconazole should be used in prophylaxis in low-birthweight infants in a given institution depends on the frequency of invasive candidiasis in the NICU.

### *Itraconazole*

In a study of 26 pediatric oncology patients (ages 6 months to 12 years), itraconazole oral solution produced a maximum concentration lower than in adults, whereas other pharmacokinetic properties such as half-life are similar to that of adults [53]. In this study, itraconazole at 5 mg/kg once daily resulted in plasma concentrations substantially lower than that historically reported in adults, especially in the children less than 2 years old [53]. The reason for this difference may have been related to the effects of chemotherapy on mucosal integrity and bioavailability. Another study of children aged 1.7 to 14.3 years showed that a split dosing of 2.5 mg/kg twice daily yielded peak and trough plasma concentrations similar to adults, but there was less exposure in the children younger than 5 years old [54].

The safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole (CD-ITRA) oral suspension also were investigated in an open sequential dose-escalation study in 26 HIV-infected children and adolescents (5–18 years of age; mean CD4+ count, 128/ $\mu$ L) with oropharyngeal

candidiasis (OPC) [55]. Patients received either 2.5 mg/kg daily or 2.5 mg/kg twice daily of CD-ITRA for a total of 15 days. Apart from mild to moderate gastrointestinal disturbances in three patients (11.5%), CD-ITRA was well tolerated; however, two patients (7.6%) discontinued treatment prematurely because of study-drug-related adverse events. A significantly higher percentage ( $P < .05$ ) of patients in the 2.5 mg/kg twice-daily cohort achieved a complete clinical and mycologic response at end of therapy, indicating dose-dependent antifungal efficacy. Pharmacodynamic modeling revealed significant correlations between plasma concentrations and antifungal efficacy. Based on this documented safety and efficacy, a dosage of 2.5 mg/kg twice daily was recommended for treatment of OPC in pediatric patients older than 5 years of age [55].

A double-blind trial of 63 patients who had HIV infection in Thailand with itraconazole versus placebo showed development of systemic fungal infection decreased from 16.7% of patients given placebo versus 1.6% taking itraconazole, with only one infection with *Penicillium marneffeii* in the itraconazole treatment arm [56].

### *Voriconazole*

A multicenter study of the safety, tolerability, and plasma pharmacokinetics of the parenteral formulation of voriconazole in immunocompromised pediatric patients (2–11 years of age) demonstrated that children require higher dosages of voriconazole than adults to attain similar serum concentrations over time, because the drug exhibits nonlinear pharmacokinetics in adults, but exhibits linearity in children at the dosages between 3 and 4 mg/kg/dose [57]. Body weight was more influential than age in accounting for the observed variability in voriconazole pharmacokinetics. As observed in adults, elimination capacity correlated with CYP2C19 genotype. This study concluded that pediatric patients have a higher elimination capacity per kilogram of body weight of voriconazole than do adult healthy volunteers and that dosages of 4 mg/kg may be necessary to achieve exposures consistent with those in adults following 3 mg/kg, whereas dosages  $\geq 5$  mg/kg would be necessary to exposures comparable to that of 4 mg/kg in adults.

A subsequent pharmacokinetic study was performed to evaluate dosages of 4 to 8 mg/kg [58]. Although there was a large inter-patient variation in the individual pharmacokinetic parameters, the population-based pharmacokinetic model of these data support a dosage of 7 mg/kg in pediatric patients to approach an exposure achieved by 4 mg/kg in adults.

The largest pediatric report of voriconazole is an open-label, compassionate-use evaluation of the drug in 58 children who had proven or probable invasive fungal infection refractory to or intolerant of conventional antifungal therapy [12]. Voriconazole was administered as a loading dose of 6 mg/kg every 12 hours on the first day of therapy, followed by 4 mg/kg every 12 hours on subsequent days. When possible, the conversion to oral therapy

was made with a dose of 100 or 200 mg twice a day for patients weighing less than 40 kg and greater than or equal to 40 kg, respectively. Almost three quarters of the patients had invasive aspergillosis. The most common treatment-related adverse reactions were transaminase or bilirubin elevation in 13.8% of patients, rash in 13.8%, abnormal vision (photophobia or blurred vision) in 5.1%, and photosensitivity reactions in 5.1% of patients. Only three patients discontinued voriconazole because of toxicity. Complete or partial response was observed in 43% of children who had aspergillosis, 50% with candidemia and 63% with scedosporiosis.

Voriconazole has not been formally tested in neonates. Because of reports of visual adverse events in adults and pediatric patients, there is concern over the unknown interactions with the developing retina and there are no planned clinical trials in this age group.

### *Posaconazole*

Posaconazole has dose-proportional pharmacokinetics up to 800 mg/d, with bioavailability greatest when administered in divided doses, and has a large apparent volume of distribution with slow elimination, suggesting an extensive distribution into tissues [59]. Although approved in the European Union, posaconazole is currently only used as a compassionate release agent in the United States as an oral formulation, but an intravenous pro-drug is also under development.

One retrospective study analyzed the pharmacokinetic profile of posaconazole for 12 pediatric patients (<18 years old) with resistant or refractory invasive fungal infections. These patients received a maintenance dose of 800 mg/d of posaconazole oral suspension given in two or three divided daily doses, compared with adult patients (18–64 years old) who received a maintenance dose of 800 mg/d and who were used as a comparison. The overall success rate and adverse event profile were similar for pediatric and adult patients [60]. Although only preliminary data, these results suggest that posaconazole pharmacokinetics are similar in adults and the children examined in this study.

Experience with posaconazole in children is limited. A recent open-label study of eight patients who had chronic granulomatous disease and invasive mold infection treated with posaconazole salvage therapy included seven pediatric patients. All patients had received itraconazole prophylaxis and had prior antifungal therapy with voriconazole, caspofungin, or a lipid formulation of amphotericin B [61]. There was a complete response with posaconazole in 7 of 8 patients, including 6 of 7 pediatric patients. Two other pediatric patients were enrolled in another open-label study of 23 patients who had zygomycosis. The overall success rate of therapy in this second study was 70% [62], but there were no pediatric-specific outcomes reported. Posaconazole may have an important role in antifungal management in the future; however, further studies of the pharmacokinetics, safety, and efficacy in pediatric patients have yet to be performed.

## *Echinocandins*

### *Caspofungin*

Caspofungin was evaluated in a pharmacokinetic study conducted in 39 children between the ages of 2 and 17 years. Data were analyzed on the basis of weight (1 mg/kg/d) and body surface area (50 or 70 mg/m<sup>2</sup>/day) [63]. When compared with plasma concentrations attained in adults treated with 50 mg/day, the weight-based approach resulted in suboptimal plasma concentrations, whereas the 50 mg/m<sup>2</sup>/day dose yielded similar plasma concentrations in children. Caspofungin's half-life is approximately one third less in children than in adults. Additionally, pediatric patient concentrations descend more rapidly compared with adults. The nuances in children continue, however, because body surface area dosing is consistent across pediatric ages; yet, there are statistically significant decreases in end-of-infusion concentrations of caspofungin with increasing age. Based on this initial study, subsequent dosing in children has been proposed to include a loading dose of 70 mg/m<sup>2</sup> followed by daily maintenance dosing of 50 mg/m<sup>2</sup>.

A multicenter retrospective survey in Germany analyzed 53 immunocompromised pediatric patients considered to require caspofungin therapy [64] for refractory infection (n = 35), intolerance of standard agents (n = 7), or as the best perceived therapeutic option (n = 11). In 13 evaluable patients who had proven infection, complete responses (4 of 13), partial responses (6 of 13), or stabilization (2 of 13) were observed. This was compared with 11 evaluable patients who had probable infection, in whom complete responses (3 of 11), partial responses (1 of 11), or stabilization (3 of 11) were observed. Most patients (11 of 13) on empiric therapy completed without breakthrough fungal infection. Overall survival was 72% at end of therapy and 64% (44 evaluable patients) at 3 months post-end of therapy [64].

Several pediatric clinical studies using caspofungin are currently in progress. These include a multicenter, open-label comparative study evaluating the safety, tolerability, and efficacy of caspofungin in children who have documented *Candida* or *Aspergillus* infections and a pharmacokinetic and safety study in children between the ages of 3 and 24 months who have new-onset fever and neutropenia. Although there are good pharmacokinetic data to show the importance of an increased dose of caspofungin in a child versus an adult patient, the data on efficacy and the range of usefulness of the drug in children who have invasive fungal infections are largely limited to case reports and case series data. It is hoped these ongoing phase IV studies will allow greater insight into pediatric uses of caspofungin.

There have been limited reports of caspofungin use in neonates who have invasive candidiasis. The first case series of caspofungin for rescue therapy in treatment of refractory invasive candidiasis in neonates was reported by Odio and colleagues [65]. The population consisted of one term and nine premature neonates who had invasive candidiasis caused by *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida glabrata*.

Despite initial therapy with amphotericin B deoxycholate, blood cultures remained positive in all patients for 13 to 49 days. Invasive candidiasis progressed to meningitis and enlarging renal *Candida* bezoars in the kidney of one patient and an enlarging atrial vegetation in another infant. A caspofungin dosage of 1 mg/kg/d for 2 days followed by 2 mg/kg/d resulted in all positive blood cultures clearing between 3 and 7 days. The atrial vegetation and the renal *Candida* bezoars also resolved without attributable clinical adverse events. In the largest report, caspofungin was added to amphotericin B, fluconazole, or 5-fluorocytosine for 13 infants who had a median birth-weight of 800 grams whose candidemia persisted despite conventional antifungal therapy. After addition of caspofungin, blood sterilization occurred in a mean of 3 days [66].

### *Micafungin*

Several pediatric studies of micafungin have been completed. A phase I single-dose, multicenter, open-label neonatal 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, and the serum half-life was shorter and clearance more rapid. For instance, in the 500- to 1000-gram neonates, the half-life was 5.5 hours with a clearance of 97.3 mL/h/kg. In the neonates weighing more than 1000 grams, the half-life increased to 8 hours, whereas clearance decreased to 55.9 mL/h/kg. This compares with children (ages 2–8 years) in whom half-life extended to 12 hours and clearance was slowest at 32.2 mL/h/kg [67].

A phase I study in persistently febrile neutropenic pediatric patients (2–17 years old) found that doses up to 4 mg/kg/d were well tolerated with no side effects. A total of 78 children (mean age, 7.1 years) received at least one dose of micafungin with no signs of nephrotoxicity or hepatotoxicity. The micafungin pharmacokinetics were dose-proportional over the range tested and mean half-life values were constant on days 1 and 4 [68]. Dosing in children younger than age 8 years seems to yield a clearance 1.3 to 1.5 times greater of micafungin, resulting in the likely need for an increased dose in this age cohort. In general, the terminal half-life of micafungin does not change appreciably in pediatric versus adult patients, and the volume of distribution is only slightly higher in children [69]. Despite these early pharmacokinetic studies and the recent FDA approval, there is no accepted dosage for micafungin in pediatric patients.

A recent study of micafungin in combination with a second antifungal agent in pediatric and adult bone marrow transplant recipients who had invasive aspergillosis revealed an overall complete or partial response of 39.1% in adult patients and 37.5% in pediatric (n = 16) patients [70]. Other studies have demonstrated the efficacy of micafungin in the primary therapy of esophageal candidiasis [71], and as rescue therapy in those failing to respond to first-line antifungals [72]. In an open-label non-comparative study

of new or refractory candidemia that included 15.1% (18 of 119) pediatric patients, the overall complete or partial response was 85.1% (86 of 101) in adult patients but only 72.2% (13 of 18) in pediatric patients [73], possibly because of inadequate dosing in children.

A study comparing prophylaxis in 882 stem-cell transplant recipients found that micafungin (80%) was more effective in preventing yeast and mold infections than fluconazole (73.5%) [74]. This study included 84 patients younger than age 16 years and found the success in those patients was 69.2% (27 of 39) in the micafungin arm and 53.3% (24 of 45) in the fluconazole arm. These values are lower than the results for patients aged 16 to 64 years in whom micafungin was 81.1% effective and fluconazole was 75.7% effective.

These few clinical studies comparing micafungin in adult and pediatric patients suggest further investigation into the nuances of pediatric efficacy is warranted. At present there are no reports of micafungin in neonates, but a large phase III trial comparing micafungin versus amphotericin B deoxycholate for neonatal candidiasis is currently underway.

### *Anidulafungin*

A phase I/II dose escalation study of anidulafungin involving five centers enrolled children who had persistent neutropenia who were at risk for invasive fungal infection, and data were determined in 12 patients (0.75 mg/kg/d) and 7 patients (1.5 mg/kg/d) following the first and fifth dose of anidulafungin. No drug-related serious adverse events were observed; one patient had fever and one patient had rash/facial erythema that resolved with slowing the infusion rate. Anidulafungin in pediatric patients was well tolerated and can be dosed based on body weight. Pediatric patients receiving 0.75 mg/kg/d or 1.5 mg/kg/d have pharmacokinetics similar to adult patients receiving 50 or 100 mg/d, respectively [75]. This important fact separates anidulafungin from the pharmacokinetic values observed with caspofungin, which necessitated a higher dosing based on body surface area.

### **Summary**

For more than 40 years, there has been limited progress in the treatment of invasive fungal infections. There are now numerous nuances to choosing the appropriate antifungal agent. Important advances have been achieved in understanding the safety, tolerability, and pharmacokinetics of these agents. One of the most important aspects for successful management of pediatric invasive fungal infections is an understanding of the differences in the pharmacokinetics of the drug in children and adults to offer optimal dosing strategies. Unfortunately there have been few antifungal studies conducted in children. Consequently most information for the pediatrician has been extrapolated from adult data. The breadth of antifungal data in children is

expanding, however, with newer studies underway. Through the efforts of dedicated clinicians and collaboration, pediatric indications and dosing strategies will eventually be discovered that directly benefit pediatric patients.

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