

Expert Opinion

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Clinical pharmacology of antifungal agents in pediatric patients

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Invasive fungal infections have emerged as important causes of morbidity and mortality in profoundly immunocompromised children including cancer, transplant and intensive care unit patients. Present treatment strategies for these infections are limited by toxicity, drug interactions and expense. In order to overcome these limitations, new antifungal compounds are being developed, which may improve the therapeutic armamentarium for prevention and treatment of invasive mycoses in high-risk children. This article summarizes the clinical pharmacology of established and newly developed antifungal agents, including new triazoles and echinocandins in pediatric age groups.

Keywords: amphotericin, anidulafungin, antifungal agent, caspofungin, children, fluconazole, flucytosine, itraconazole, micafungin, mycoses, pharmacology, posaconazole, voriconazole

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1. Introduction

Invasive fungal infections are important causes of morbidity and mortality in immunocompromised children. These infections remain difficult to diagnose and outcome depends critically on the prompt initiation of appropriate antifungal chemotherapy, expert supportive care and restoration of host defenses.

The last two decades have seen a dramatic increase in both number and overall relevance of invasive fungal infections in the hospital. At the same time, however, improved microbiologic and imaging techniques and an increased awareness among physicians have shifted the diagnosis of fungal infections from the autopsy theatre to the bedside. Major advances have been made in the definition of fungal diseases, the algorithms of antifungal interventions, the design and implementation of clinical trials and the development of standardized *in vitro* susceptibility testing. Most importantly, however, a number of new antifungal agents have entered the clinical arena and have made antifungal therapy safer, more effective, but also more complicated.

This article reviews the clinical pharmacology of established and new antifungal agents in pediatric patients and their use for treatment and prevention of invasive fungal infections in this setting. General principles of developmental pharmacology will not be addressed in this discussion.

2. Pediatric pharmacology of established antifungal agents

2.1 Amphotericin B deoxycholate

For many years, amphotericin B deoxycholate (DAMB) has been the standard agent for systemic antifungal therapy. Amphotericin B primarily acts by binding to ergosterol in the fungal cell membrane, leading to pore formation and ultimately,

cell death [1]. Amphotericin B possesses a broad spectrum of antifungal activity that includes most fungi pathogenic in humans. However, some of the emerging pathogens such as *Aspergillus terreus*, *Trichosporon asahii*, *Scedosporium prolificans* and certain *Fusarium* spp. may be microbiologically and clinically resistant [2].

After intravenous administration of the deoxycholate formulation, amphotericin B rapidly dissociates from its vehicle and becomes highly protein bound before distributing predominantly into the liver, spleen, bone marrow, kidney, lung and other sites [3]. Elimination from the body is slow; only small quantities are excreted into urine and bile [4,5]. Due to the heterogeneity in underlying disease conditions and differences in the modes of administration, the reported pharmacokinetics of DAMB in pediatric patients are characterized by a high variability among individual patients [6–8]. Infants and children appear to clear the drug more rapidly than adults, as indicated by a significant negative correlation between patient age and clearance of DAMB [7,8]. Whether or not this enhanced clearance from the bloodstream has implications for dosing is unknown as systematic studies correlating pharmacokinetic parameters with measures of outcome or toxicity have not been performed thus far.

Infusion-related reactions and nephrotoxicity are major problems associated with the use of DAMB and often limit successful therapy. Infusion-related reactions (fever, rigors, chills, myalgias, arthralgias, nausea, vomiting and headaches) are thought to be mediated by the release of cytokines from monocytes in response to the drug [11] and can be noted in $\leq 73\%$ of patients prospectively monitored at the bedside [12]. In a more recent prospective study in pediatric cancer patients, fever and/or rigors associated with the infusion of DAMB were observed in 19 out of 78 treatment courses (24%) [13]. Interestingly, however, these characteristic adverse effects of DAMB are only rarely observed in the neonatal setting [14]. Infusion-related reactions may be blunted by slowing the infusion rate, but often require acetaminophen, hydrocortisone (0.5 – 1.0 mg/kg) or meperidine (0.2 – 0.5 mg/kg) premedication [15]. Less common are hypotension, hypertension, flushing and vestibular disturbances; bronchospasm and true anaphylaxis are all rare [16]. Cardiac arrhythmias and cardiac arrest due to acute potassium release may occur with rapid infusion (< 60 min), in particular if there is pre-existing hyperkalemia and/or renal impairment [17,18].

The hallmarks of amphotericin B-associated nephrotoxicity are azotemia, wasting of potassium and magnesium, whereas tubular acidosis and impaired urinary concentration ability are rarely of clinical significance [16,19]. As assessed prospectively in a large clinical trial in the setting of empirical therapy in persistently granulocytopenic patients, relevant electrolyte wasting occurs in $\sim 12\%$ and increases in the serum creatinine by $> 100\%$ in 34% of patients [12]. Azotemia can be exacerbated by concomitant nephrotoxic

agents, in particular by ciclosporin and tacrolimus, but also by aminoglycosides and glycopeptides [20]. Although some data suggest a somewhat lower rate of azotemia in children as compared with adults [21], this has not been a consistent observation [20]. Of note, DAMB-associated azotemia has been reported in only 2% of pediatric cancer patients receiving the drug at 1 mg/kg/day for comparatively short periods as empirical antifungal therapy [10]; in premature neonates, in a more contemporary series containing safety data of DAMB (0.5 – 1.0 mg/kg), the incidence of azotemia ranged from 0 to 15% [14,22–24], indicating that DAMB is much better tolerated as reported early during its use [25]. The renal toxicity associated with DAMB-therapy may lead to renal failure and dialysis; however, azotemia most often stabilizes on therapy and is usually reversible after discontinuation of the drug [26]. Avoiding concomitant nephrotoxic agents, and using appropriate hydration and normal saline loading (10 – 15 ml NaCl/kg/day) [27–29] may lessen the likelihood and severity of azotemia.

With the advent of new antifungal agents and following the completion of pivotal clinical Phase III trials, few indications are left for antifungal treatment of opportunistic mycoses with conventional deoxycholate amphotericin B. These include candidemia and acute disseminated candidiasis, particular in neonates, and induction therapy for cryptococcal meningitis. The recommended daily dosage in these settings ranges from 0.7 to 1.0 mg/kg/day administered over 2 – 4 h as tolerated. Treatment should be started at the full target dosage with careful bedside monitoring during the first hour of infusion [26]. Although better tolerated, continuous infusion over 24 h is not recommended due to the complete lack of efficacy data [30].

2.2 Lipid formulations of amphotericin B

During the last decade, three novel formulations of amphotericin B have become available for clinical use: amphotericin B colloidal dispersion (ABCD, AmphocilTM or AmphotecTM), amphotericin B lipid complex (ABLC or AbelcetTM) and a small unilamellar vesicle liposomal formulation (LAMB, AmBisomeTM). In comparison to DAMB, the lipid formulations share a reduced nephrotoxicity, which allows for the safe delivery of higher dosages of amphotericin B [31].

Each of the lipid formulations possesses distinct physicochemical and pharmacokinetic properties (Table 1). However, all three preferentially distribute to the reticulo-endothelial system (RES) and functionally spare the kidney. Although the micellar dispersion of ABCD behaves very similarly as compared to DAMB, the unilamellar liposomal preparation is only slowly taken up by the RES and achieves strikingly high peak plasma concentrations and AUC values. In contrast, the large ribbon-like aggregates of ABLC are rapidly taken up by the RES, resulting in lower peak plasma and AUC values [31,32]. Whether and how the distinct physicochemical and pharmacokinetic features of

Table 1. Physicochemical properties and multiple-dose pharmacokinetic parameters of the four licensed amphotericin B formulations.

	DAMB	ABCD	ABLC	LAMB
Lipids (molar ratio)	Deoxycholate	Cholesteryl sulfate	DMPC/DMPG (7:3)	HPC/CHOL/DSPG (2:1:0.8)
% Molar weight AmB	34%	50%	50%	10%
Lipid configuration	Micelles	Micelles membrane-like		SUVs
Diameter (μm)	0.05	0.12 – 0.14	1.6 – 11	0.08
Dosage (mg AmB/kg)	1	5	5	5
C _{max} (μg/ml)	2.9	3.1	1.7	58
AUC _{0-∞} (μg/ml·h)	36	43	14	713
VD _{ss} (l/kg)	1.1	4.3	131	0.22
CL (l/h/kg)	0.028	0.117	0.476	0.017

Data represent mean values, stem from adult patients and were obtained after different rates of infusion. Modified from Groll *et al.* (1998) [16].

AmB: Amphotericin B; AUC_{0-∞}: Area under the concentration versus time curve from time zero to infinity; CHOL: Cholesterol; CL: Plasma clearance;

DAMB: Amphotericin B deoxycholate; DMPC: Dimiristoyl phosphatidylcholine; DMPG: Dimiristoyl phosphatidylglycerol; DSPG: Distearoyl phosphatidylglycerol;

HPC: Hydrogenated phosphatidylcholine; LAMB: Liposomal amphotericin B; SUV: Small unilamellar vesicles; VD_{ss}: Apparent volume of distribution at steady-state.

each formulation translate into different pharmacodynamic properties *in vivo* is largely unknown.

Safety and antifungal efficacy of ABCD, ABLC, and LAMB have been demonstrated in an array of Phase II and III clinical trials in immunocompromised patients. The overall response rates in these trials ranged from 53 to 84% in patients with invasive candidiasis and from 34 to 59%, respectively, in patients with presumed or documented invasive aspergillosis [31-34]. A few randomized, controlled trials have been completed in which one of the new formulations has been compared with DAMB [12,20,35]. These studies have consistently shown at least equivalent therapeutic efficacy, but reduced nephrotoxicity of the lipid formulations [33].

A considerable number of pediatric patients have been treated with either ABCD, ABLC or LAMB within the above mentioned protocols, but separately published pediatric data remain limited.

2.2.1 Amphotericin B colloidal dispersion

Population-based multiple-dose pharmacokinetic studies with ABCD in bone marrow transplant patients with systemic fungal infections included the compartmental analysis of five children < 13 years of age who received the compound at 7.0 and 7.5 mg/kg/day. Estimated pharmacokinetic parameters in these children were not significantly different from those obtained in a dose-matched cohort of adult patients [36]. A total of 49 children with febrile neutropenia were treated in a prospective, randomized trial comparing ABCD with DAMB; an additional 70 children with presumed or proven fungal infection were treated on five different open-label Phase II trials of ABCD. In the randomized trial, there was significantly less renal toxicity in the children receiving ABCD than in those receiving amphotericin B (12.0 versus 52.4%; $p = 0.003$); other adverse symptoms were not

significantly different. In the additional open-label studies, although 80% of patients receiving ABCD reported some adverse symptom, the majority of these were infusion related and nephrotoxicity was reported in only 12%; there were no other unexpected severe toxicities [37].

2.2.2 Amphotericin B lipid complex

The pharmacokinetics of ABLC have been studied in pediatric cancer patients who received the compound at 2.5 mg/kg over 6 weeks for hepatosplenic candidiasis; ABLC was effective and well tolerated, and no pharmacokinetic differences were observed as compared to those in adults [38].

Safety and antifungal efficacy of ABLC were studied in 111 treatment episodes in pediatric patients aged 21 days – 16 years refractory of or intolerant to conventional antifungal agents through an open-label, emergency use protocol. ABLC was administered at a mean daily dosage of 4.85 mg/kg (ranging from 1.1 to 9.5 mg/kg/day) for a mean duration of 38.9 days (ranging from 1 to 198 days). The mean serum creatinine for the entire study population did not significantly change between baseline (1.23 ± 0.11 mg/dl) and cessation of ABLC therapy (1.32 ± 0.12 mg/dl) during 6 weeks. No significant differences were observed between baseline and end-of-therapy levels of serum potassium, magnesium, hepatic transaminases, alkaline phosphatase and hemoglobin. However, there was an increase in the mean total bilirubin (3.66 ± 0.73 – 5.13 ± 1.09 mg/dl) at the end of therapy ($p = 0.054$). In seven patients (6%), ABLC therapy was discontinued because of one or more adverse effects. Among 54 cases fulfilling criteria for evaluation of antifungal efficacy, a complete or partial therapeutic response was obtained in 38 patients (70%) after ABLC therapy [39]. The safety and efficacy of ABLC was also assessed in 548 children and adolescents who were enrolled in the

Collaborative Exchange of Antifungal Research registry of the manufacturer between 1996 and 2000. Most patients were either intolerant of or refractory to conventional antifungal therapy. Response data were evaluable for 255 of the 285 patients with documented single or multiple pathogens. A complete (cured) or partial (improved) response was achieved in 54.9% of patients. There was no significant difference between the rates of new hemodialysis versus baseline hemodialysis. Elevations in serum creatinine of $> 1.5 \times$ baseline and $> 2.5 \times$ baseline values were seen in 24.8 and 8.8% of all patients, respectively. The overall response rate and safety profile in pediatric patients were consistent with earlier reported findings of smaller trials [40].

A population pharmacokinetic study in 28 mostly immature neonates with invasive *Candida* infections has demonstrated that the disposition of ABLC in neonates is similar to that observed in other age groups: weight was the only factor that influenced clearance. Based on the results of this study and a cure rate of $> 80\%$, a dosage of 2.5 – 5.0 mg/kg is recommended for treatment of neonatal candidiasis [41].

2.2.3 Liposomal amphotericin B

The pharmacokinetics of LAMB in pediatric patients beyond the neonatal period have been investigated in a formal Phase II dose-escalation trial investigating dosages of 2.5, 5.0 and 7.5 mg/kg in immunocompromised patients, as well as by using a population-based approach. The results of these studies indicate that the disposition of LAMB in pediatric patients is not fundamentally different from that in adults and that weight is a covariate that determines clearance and volume of distribution [42,43]. Many pediatric patients have been enrolled on clinical trials with LAMB, but were not separately evaluated [12,44]. A total of 204 children (mean age, 7 years) with neutropenia and fever of unknown origin were randomized in an open-label, multicenter trial to receive either DAMB 1 mg/kg/day ($n = 63$), LAMB 1 mg/kg/day ($n = 70$) or LAMB 3 mg/kg/day ($n = 71$) for empirical antifungal therapy [21]. A total of 29% of patients treated with LAMB 1, 39% of patients treated with LAMB 3 and 54% of patients treated with DAMB experienced adverse effects ($p = 0.01$); nephrotoxicity, defined as a $\geq 100\%$ increase in serum creatinine from baseline, was noted in 8, 11 and 21%, respectively (not significant). Hypokalemia (< 2.5 mmol/l) occurred in 10, 11 and 26% of patients ($p = 0.02$), increases in serum transaminase levels (≥ 110 U/l) in 17, 23 and 17% and increases in serum bilirubin (≥ 35 μ mol/l) in 11, 12 and 10% of patients, respectively. Efficacy assessment by intent-to-treat analysis indicated successful therapy in 51% of children treated with DAMB and 64 and 63% in children treated with LAMB at either 1 or 3 mg/kg/day ($p = 0.22$). LAMB at either 1 or 3 mg/kg/day was significantly safer and at least equivalent to DAMB with regard to resolution of fever of unknown origin [21]. LAMB was well tolerated and effective in small cohorts of immunocompromised children requiring

antifungal therapy for proven or suspected infections, including patients with bone marrow transplant for primary immunodeficiencies [45] and cancer patients [46–48]. A Phase IV analysis of 141 courses of LAMB administered for a mean of 17 days at a mean maximum dosage of 2.5 mg/kg for various indications to pediatric cancer/hematopoietic stem cell transplantation (HSCT) patients revealed a low rate of adverse events (4%) necessitating discontinuation. Although mean glutamate-oxalate transaminase, glutamate-pyruvate transaminase, alkaline phosphatase and bilirubin values were slightly higher at end of treatment ($p < 0.01$), bilirubin and creatinin values were not different from baseline. LAMB had acceptable safety and tolerance and displayed efficacy in prevention and treatment of invasive fungal infections [49].

LAMB (2.5 – 7 mg/kg/day) was evaluated prospectively in 24 very low birth weight infants (mean birth weight 847 ± 244 g, mean gestational age 26 weeks) with systemic candidiasis. A total of 13 infants failed previous antifungal therapy with amphotericin B (with or without 5-flucytosine). *Candida* spp. were isolated from the blood in all 25 episodes and from skin abscesses and urine in four infants each, respectively. The mean duration of therapy was 21 days; the cumulative LAMB dose was 94 mg/kg. Fungal eradication was achieved in 92% of the episodes; 20 (83%) infants were considered clinically cured at the end of treatment. No major adverse effects were recorded; one infant developed increased bilirubin and hepatic transaminases levels during therapy. Four (17%) infants died; in two of them (8%) the cause of death was directly attributed to systemic candidiasis [50]. In a second study undertaken by the same investigators, high-dose LAMB 5 – 7 mg/kg/day was evaluated prospectively in 41 episodes of systemic candidiasis occurring in 37 neonates (36 of the 37 were premature infants with very low birth weights) *Candida* spp. were isolated from blood in all patients and from urine, skin abscesses and peritoneal fluid in 6, 5 and 1 neonates, respectively. A total of 28, 5 and 8 infants received 7, 6 – 6.5 and 5 mg/kg/day, respectively. Median duration of therapy was 18 days; median cumulative dose was 94 mg/kg. Fungal eradication was achieved in 39 out of 41 (95%) episodes; one patient died due to systemic candidiasis on day 12 of therapy. High-dose LAMB was effective and safe in the treatment of neonatal candidiasis. Fungal eradication was more rapid in patients treated early with high doses and in patients who received high-dose LAMB as first-line therapy [50].

Taken together, the lipid formulations of amphotericin B have less renal toxicity as defined by development of azotemia than conventional amphotericin B. Distal tubular toxicity may also be somewhat reduced. Infusion-related side effects of fever, chills and rigor appear to be substantially less frequent with LAMB only, whereas the infusion-related reactions of ABCD and ABLC appear to be similar to those of DAMB. Several individual cases of substernal chest discomfort, respiratory distress and of sharp flank pain have been noted during infusion of LAMB [51,52].

Similarly, in comparative studies in mostly adult individuals, hypoxic episodes associated with fever and chills were more frequent in ABCD-recipients than in DAMB recipients [20,53]. Mild increases in serum bilirubin and alkaline phosphatase have been registered with all three formulations and mild increases in serum transaminases with LAMB. However, no case of fatal liver disease has occurred. Pharmacokinetic and safety data from children so far indicate no fundamental differences in these parameters as compared to those obtained in the adult population.

The lipid formulations of amphotericin B are presently licensed for the treatment of patients with invasive mycoses refractory of or intolerant to DAMB and limited to LAMB for empirical therapy of persistently neutropenic patients. Evidence-based, but not licensed indications for first-line therapy exist for LAMB for treatment of invasive aspergillosis [54], invasive candidiasis [55] and zygomycosis (all formulations) [56]. The recommended therapeutic dosages are 3–5 mg/kg/day for LAMB and 5 mg/kg for ABCD and ABLC, respectively [56]; the therapeutic dosage for treatment of zygomycosis should not be < 5 mg/kg/day. Similar to conventional amphotericin B (DAMB), treatment should be started with the full calculated dosage at the infusion rate recommended by the manufacturer.

2.3 Antifungal triazoles

The antifungal triazoles have become an important component of the antifungal armamentarium. They are associated with overall less toxicity than DAMB, possess a suitable spectrum of activity and have demonstrated clinical efficacy under many circumstances. The triazoles function by inhibiting the CYP450-dependent conversion of lanosterol to ergosterol, which leads to altered membrane properties and inhibition of cell growth and replication. Whereas fluconazole and itraconazole have now been available for more than a decade, new triazoles such as voriconazole and posaconazole have entered the clinical arena only recently [16,57].

2.3.1 Fluconazole

The availability of fluconazole has been a major advance in antifungal therapy. Its spectrum of activity includes *Candida* spp., *Cryptococcus neoformans*, *T. asahii* and endemic dimorphic fungi, but not *Aspergillus* spp. and the other opportunistic molds. *C. krusei* and, to a lesser extent, *C. glabrata* are considered intrinsically resistant to fluconazole *in vitro* [58].

Available as oral and parenteral formulations, fluconazole possesses almost ideal pharmacokinetic properties. Independent of food or intragastric pH, oral bioavailability is > 90%. Due to its free solubility in water, protein binding is low and penetration into cerebrospinal fluid (CSF) and tissues is excellent; most of the drug is excreted in an unchanged form into the urine [16]. The plasma pharmacokinetics of fluconazole in pediatric age groups exhibit changes in the volume of distribution and clearance that are characteristic for a water

soluble drug with minor hepatic metabolism and predominantly renal elimination. Except for premature neonates, where clearance is decreased, pediatric patients tend to have an increased normalized plasma clearance and a shorter half-life in comparison with adults [59–64] (Table 2). As a consequence, dosages at the higher end of the recommended dosage range are necessary for the treatment of invasive mycoses in children. Because exposure over time appears to be the pharmacodynamic parameter that is most predictive of antifungal activity [65,66], fractionating the daily dose is not required in infants and children despite the shorter half-life in these age groups.

In adults, dosages of ≤ 1200 mg/kg/day have been safely administered over prolonged periods of time [68]. In pediatric patients of all age groups, at dosages of ≤ 12 mg/kg/day, fluconazole is generally well tolerated [69]. The most common reported side effects in pediatric patients include gastrointestinal disturbances (8%), increases in hepatic transaminases (5%) and skin reactions (1%); toxicity-related discontinuation of therapy with fluconazole occurs in $\sim 3\%$ of patients [68]. Severe side effects, including relevant hepatotoxicity and exfoliative skin reactions have been reported anecdotically in association with fluconazole therapy [16]. Fluconazole undergoes minimal CYP450 metabolism, but inhibits CYP3A4 and several other isoforms and interacts with enzymes involved in glucuronidation, thereby leading to numerous drug–drug interactions. However, due to a lesser affinity for human CYP450 3A, the number and frequency of relevant drug–drug interactions are lower than those of ketokonazole or itraconazole [16,69,70].

Several controlled studies including both neutropenic and non-neutropenic adult patients have demonstrated that intravenous fluconazole 400–800 mg/day is as effective as DAMB 0.5–1.0 mg/kg/day against candidemia and other forms of documented or suspected invasive candidiasis, and that it is better tolerated [71–74]. Apart from oropharyngeal and esophageal candidiasis [75–78], fluconazole can be used for invasive *Candida* infections caused by susceptible organisms in patients who are in a stable condition and who have not received prior azole therapy [79]. This also applies to the neonatal setting: in six published series including ≥ 10 patients with proven invasive *Candida* infections, treatment with fluconazole at a daily dosage of 5–6 mg/kg was successful in 83–97% and crude mortality ranged from 10 to 33%; none of the 125 patients discontinued fluconazole due to toxicity [80–85]. The recommended dosage range for pediatric patients of all age groups is 6–12 mg/kg/day; in view of the faster clearance rate, however, 12 mg/kg/day may be the most appropriate dosage for treatment of life-threatening infections in infants and children. Because of an initially decreased clearance in preterm neonates of < 1500 g, the authors advocate every other day dosing with 6–12 mg/kg during the first week of life in this specific setting.

Further potential indications for fluconazole include consolidation therapy for chronic disseminated candidiasis [86,87]

Table 2. Pharmacokinetic parameters of fluconazole in pediatric patients.

Age group	VD _{ss} (l/kg)	CL (l/h/kg)	T _{1/2} β (h)
Preterm < 1500 g, day 1	1.18	0.010	88
Day 6	1.84	0.019	67
Day 12	2.25	0.031	55
Term neonates	1.43	0.036	28
Infants > 1 – 6 months	1.02	0.037	19
Children, 5 – 15 years	0.84	0.031	18
Adult volunteers	0.65	0.015	30

Data represent mean values and are compiled from six studies [59-64].

CL: Total plasma clearance; VD_{ss}: Apparent volume of distribution at steady-state.

and cryptococcal meningitis [88,89]. High-dose fluconazole has been used for infections by the yeast *T. asahii* in non-neutropenic hosts; because of the potential for breakthrough infections by other opportunistic fungi, voriconazole may be a better option in persistently neutropenic patients [12]. Fluconazole has become the drug of choice for treatment of coccidioidal meningitis [90,91] and has proven effectiveness in non-meningeal coccidioidal infections [91]. However, fluconazole appears comparatively less active than itraconazole in the treatment of other endemic mycoses such as paracoccidioidomycosis, blastomycosis, histoplasmosis and sporotrichosis [92-97].

Fluconazole is also active in preventing mucosal candidiasis in patients with HIV infection or cancer [98-100] and has proven efficacy in preventing invasive *Candida* infections in patients undergoing HSCT [101,102]. Fluconazole has been shown to reduce *Candida* infections in low birth-weight infants [103-108]. Thus, fluconazole prophylaxis is a valid option for centers with a high frequency (> 10%) of invasive *Candida* infections in premature infants of < 1000 g birth weight or in the setting of a nosocomial outbreak by a fluconazole-susceptible *Candida* species.

2.3.2 Itraconazole

Itraconazole has antifungal activity comparable to fluconazole, but also possesses useful activity against *Aspergillus* spp. and certain dematiaceous moulds [16,33]. In contrast to fluconazole, however, itraconazole is water-insoluble, highly protein-bound and undergoes extensive metabolism in the liver. Absorption from the capsule form is dependent on a low intragastric pH, compromised in the fasting state and, thus, often erratic [16,69]. The hydroxypropyl-β-cyclodextrin solution of itraconazole improves oral bioavailability [109,110] and, in conjunction with the intravenous formulation [111-113], has enhanced the clinical use of itraconazole.

Itraconazole is usually well tolerated with a similar pattern and an approximately identical frequency of adverse effects as fluconazole [69]. However, both propensity

and extent of drug-drug interactions through interference with mammalian CYP4500-dependent drug metabolism appear greater [13,33].

The safety and pharmacokinetics of cyclodextrin itraconazole solution in immunocompromised pediatric patients have been studied in two Phase II clinical trials [114,115]. The solution was well tolerated and safe in 26 infants and children with cancer (n = 20) or liver transplantation who received the compound at 5 mg/kg/day for documented mucosal candidiasis or as antifungal prophylaxis for 2 weeks [114]. Treatment with cyclodextrin itraconazole achieved potentially therapeutic concentrations of itraconazole in plasma; these levels, however, were substantially lower than those reported in adult cancer patients [116]. In a cohort of 26 HIV-infected children and adolescents, cyclodextrin itraconazole was safe and effective for treatment of oropharyngeal candidiasis at dosages of 2.5 mg/day or 2.5 mg b.i.d. given for > 14 days. Both dosage regimens resulted in higher peak plasma concentrations and AUC 0 – 24 h values than reported in the above referenced study in pediatric cancer patients. Based on safety and efficacy, a dosage of 2.5 mg/kg b.i.d. was recommended for the treatment of oropharyngeal candidiasis in pediatric patients ≥ 5 years of age [115]. Vomiting (12%), abnormal liver function tests (5%) and abdominal pain (3%) were the most common adverse effects considered definitely or possibly related to cyclodextrin itraconazole solution in an open study in 103 neutropenic pediatric patients who received the drug at 5 mg/kg/day for antifungal prophylaxis; 18% of patients withdrew from the study because of adverse events [117]. Pharmacokinetics and safety of the intravenous formulation in pediatric patients have not been reported yet; similarly, only anecdotal reports have been published on the use of itraconazole in the neonatal setting.

Itraconazole is a useful agent for dermatophytic infections and pityriasis versicolor [118,119]. It is effective in the treatment of oropharyngeal and esophageal candidiasis including adult and pediatric patients who have developed resistance to fluconazole [33,114,115,120]. The clinical efficacy of itraconazole in candidemia and deeply invasive *Candida* infections has not been systematically evaluated. However, itraconazole is used for long-term treatment of cryptococcal meningitis in patients with HIV infection [88,89].

Itraconazole is approved as a second-line agent for treatment of invasive *Aspergillus* infections. Two separate uncontrolled studies, that have investigated oral itraconazole for treatment of proven or probable invasive aspergillosis, suggest a response rate comparable to that reported for amphotericin B deoxycholate [121,122]. Experience with the intravenous formulation for this indication is limited [113]. Itraconazole may also be indicated for treatment of invasive infections by dematiaceous moulds [123], but it has no clinically documented activity against zygomycosis and fusariosis.

Itraconazole is the present treatment of choice for all types of sporotrichosis [124] and non-life-threatening, non-meningeal

paracoccidioidomycosis, blastomycosis and histoplasmosis in non-immunocompromised patients [125-128]. It also has established efficacy in both induction and maintenance therapy of mild-to-moderate, non-meningeal histoplasmosis in HIV-infected patients [129,130]. The activity of itraconazole against non-meningeal and meningeal coccidioidomycosis appears somewhat inferior to that of fluconazole [131-131]. It should be emphasized, however, that amphotericin B is the treatment of choice for most immunocompromised patient and those with life-threatening infections by the endemic fungi [16,33].

Prophylactic itraconazole may reduce the incidence of proven or suspected invasive fungal infections in patients with hematologic malignancies [134] and following HSCT [135,136]. Efficacy in the prevention of invasive aspergillosis is supported by a large meta-analysis [137], but not by a randomized, comparative trial. Finally, itraconazole was at least as effective as conventional amphotericin B and was superior with respect to its safety profile when investigated as empirical antifungal therapy in persistently neutropenic cancer patients [112].

The recommended starting dosage range for oral itraconazole in pediatric patients beyond the neonatal period is 5 mg/kg/day in two divided doses of the oral suspension. Achievement of adequate plasma levels is important and drug monitoring is strongly recommended in patients with serious disease. The recommended target level is $> 0.5 \mu\text{g/ml}$ of the parent itraconazole before the next dose, as measured by high performance liquid chromatography [56]. Data on the use of intravenous itraconazole in pediatric patients are lacking; the dosage regimen used in the published adult studies is 200 mg b.i.d. for 2 days, followed by 200 mg/day for a maximum of 12 days [112,113].

2.4 5-Fluorocytosine

5-Fluorocytosine (5-FC) is a fungus-specific synthetic base analog that acts by causing RNA-misreading and inhibition of DNA-synthesis. Its antifungal activity *in vitro* is essentially limited to yeasts and certain dematiaceous fungi [138].

In the US, 5-FC is available only as an oral formulation; in several European countries, 5-FC is also marketed as an intravenous solution. The low molecular-weight, water soluble compound is readily absorbed from the gastrointestinal tract. 5-FC has negligible protein binding and distributes well into all tissues and body fluids, including the CSF. In humans, $< 1\%$ of a given dose of 5-FC is believed to undergo hepatic metabolism; $\sim 90\%$ is excreted into the urine in an unchanged form by glomerular filtration with an elimination half-life from plasma of 3 – 6 h in patients with normal renal function [16]. In neonates, an extreme interindividual variability in clearance and distribution volume has been reported [9]; separate pharmacokinetic data for infants and children are lacking.

Due to the propensity of susceptible organisms to develop resistance *in vitro* [139], 5-FC is not administered as a single agent. An established indication is its use in

combination with DAMB for induction therapy of cryptococcal meningitis [88,140]. The combination with DAMB may also be recommended for the treatment of *Candida* infections involving deep tissues, in particular for *Candida* meningitis, severe infections by certain non-albicans *Candida* species such as *Candida glabrata*, and for critically ill patients [15]. 5-FC in combination with fluconazole may be used for cryptococcal meningitis, when treatment with DAMB or LAMB is not feasible or when an all-oral regimen is needed [141]. 5-FC has also shown clinical effectiveness against chromoblastomycosis.

The major potential toxicities of 5-FC are gastrointestinal intolerance and hematopoietic toxicity, which is possibly due to the conversion of 5-FC into fluorouracil by intestinal bacteria [16]. Close monitoring of plasma levels and adjustment of the dosage is recommended, in particular when there is evidence for impaired renal function; peak plasma levels between 40 and 60 $\mu\text{g/ml}$ correlate with antifungal activity, but are seldom associated with marrow toxicity [138]. A starting dosage for both adults and children of 100 mg/kg daily divided into 3 or 4 doses is presently recommended.

3. New agents for treatment and prevention and their pediatric development

3.1 New antifungal triazoles

The structures of the new triazoles and, for comparison, those of fluconazole and itraconazole are listed in Figure 1.

3.1.1 Voriconazole

Voriconazole is a recently approved synthetic antifungal triazole with activity against a wide spectrum of clinically important yeasts and molds, including *Candida* spp., *C. neoformans*, *Aspergillus* and other hyaline moulds, dematiaceous moulds as well as dimorphic moulds, both *in vitro* as well as in animal models. A notable exemption are the zygomycetes, against which voriconazole is intrinsically inactive. Similar to itraconazole, voriconazole is generally considered fungistatic against *Candida*, but fungicidal against *Aspergillus* spp. [33,142].

Voriconazole is available in oral and intravenous formulations; oral bioavailability exceeds 90% in the fasted state (Table 3). In adults, the compound has non-linear pharmacokinetics. Plasma protein binding is 58% and the mean volume of distribution accounts for 2 l/kg. Tissue and CSF levels exceed those of trough plasma levels severalfold. The plasma half-life is 6 h, with elimination primarily occurring by oxidative hepatic metabolism to at least eight metabolites that are eliminated in the urine; $< 2\%$ of a dose of voriconazole is excreted unchanged in urine. The major isoenzyme involved in voriconazole metabolism is CYP2C19, but CYP2C9 and CYP3A4 also contribute. There is a wide between-subject variability in the disposition of voriconazole that is related to genetic CYP2C19 polymorphisms [33,143].

Clinical pharmacology of antifungal agents in pediatric patients

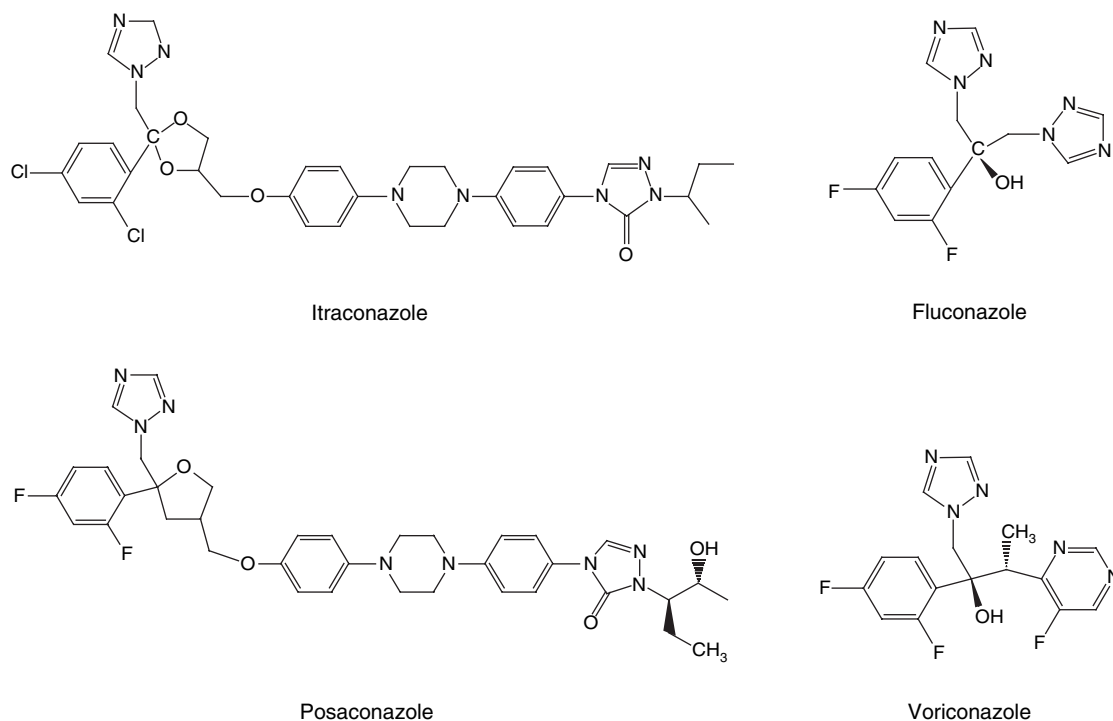


Figure 1. Chemical structures of voriconazole and posaconazole in comparison with fluconazole and itraconazole. Whereas voriconazole is structurally related to fluconazole, posaconazole is structurally related to itraconazole.

Table 3. Principal pharmacokinetic properties of the new antifungal triazoles, voriconazole and posaconazole.

	Voriconazole	Posaconazole
Formulation	p.o./i.v.	p.o
Dose-linearity	No	No
Oral bioavailability (%)	> 90	> 50
Protein binding (%)	58	> 95
Volume of distribution (l/kg)	2	> 5
Elimination half-life (h)	6	25
Substrate/inhibitor of CYP450	3A4, 2C9, 2C19	(3A4)*
Elimination by means of		
- feces (%/% metabolites)	< 20/?	77/-
- urine (%/% metabolites)	80/78	14/14

Data derived from references [143,158,159].

i.v.: Intravenously; p.o.: Orally.

*Inhibitor only.

Voriconazole has an acceptable safety profile. The accrued clinical data indicate that side effects include four distinct clinical categories: Transient liver enzyme abnormalities (10 – 20%), skin reactions (< 10%), hallucinations or confusion (< 10%) and transient, dose-related visual disturbances (altered or enhanced perception of light, blurred vision; 25 – 45%) [33]. However, drug-related adverse effects requiring the discontinuation of voriconazole were infrequent in comparative clinical trials (2 – 13%) [144–146]. Voriconazole is both substrate and inhibitor of CYP2C19, CYP2C9 and

CYP3A4 and, therefore, a number of clinically relevant and potentially hazardous drug–drug interactions need to be considered [33].

Voriconazole has demonstrated excellent clinical efficacy in Phase II and III clinical trials in patients with oropharyngeal candidiasis and esophageal candidiasis [144,147]. In salvage studies of invasive aspergillosis and other mycoses, responses were observed in 41 – 55% of patients [148,149]. A multi-national, randomized Phase III clinical trial of voriconazole and conventional amphotericin B followed by other licensed

antifungal therapy for primary therapy of invasive aspergillosis revealed superior antifungal efficacy and improved survival of voriconazole-treated patients at week 12 [145]. A randomized comparative study of voriconazole versus conventional amphotericin B followed by fluconazole for treatment of candidemia in non-neutropenic patients showed similar response rates at end of treatment and similar survival at 3 months [150]. In a large, international collaborative study of voriconazole versus liposomal amphotericin B for empirical therapy, voriconazole did not meet the prespecified statistical end point for non-inferiority in a composite end point, but was associated with significantly fewer breakthrough invasive fungal infections, particularly those due to invasive aspergillosis [151]. Finally, several reports also suggest the potential usefulness of voriconazole for treatment of infections by unusual hyaline and dematiaceous fungi [149], and for treatment of cerebral mold infections [152].

Voriconazole is approved for treatment of invasive aspergillosis, fusariosis and scedosporiosis, and for primary treatment of invasive candidiasis in non-neutropenic patients. The recommended intravenous dosages for patients ≥ 12 years of age are 6 mg/kg b.i.d. on day 1, followed by 4 mg/kg b.i.d.. The oral dosages in adults are 400 mg b.i.d. on day 1 (< 40 kg; 200 mg b.i.d.), followed by 200 mg b.i.d. (< 40 kg; 100 mg b.i.d.). In patients with renal insufficiency, no dosage adjustment is needed for the oral formulation; because of the renal clearance of the intravenous carrier, patients with a creatinine clearance of < 50 ml/min should receive voriconazole by the oral route. In patients with mild-to-moderate hepatic function abnormalities, half of the daily maintenance dosage is recommended after the initial loading dose. Recommendations for severe liver failure are lacking [142].

Pediatric patients 1 to 11 years of age have a higher capacity for elimination of voriconazole per kilogram of body weight than adult healthy volunteers, resulting in a lower, potentially non-therapeutic exposure at similar dosages [153] (Table 4). An intraindividual dosage escalation study exploring pharmacokinetics and safety of higher dosage regimens of voriconazole in this patient population has been completed; based on the population-based analysis of the data set of that study, an intravenous dosage of 7 mg/kg b.i.d. and an oral dosage of 200 mg b.i.d. (oral suspension) without loading dosages is presently recommended for children 1 to 11 years of age [154]. Voriconazole has been administered safely and with success to a number of children < 12 years of age without a therapeutic alternative. Of 58 immunocompromised children with proven or probable invasive fungal infection refractory to or intolerant of conventional antiungal therapy, 26 patients (45%) had a complete or partial response and 4 patients (7%) were discontinued because of intolerance. A total of 23 patients had voriconazole-related adverse events, most commonly elevation in hepatic transaminases or bilirubin ($n = 8$), skin rash ($n = 8$), abnormal vision ($n = 3$) and photosensitivity

reactions ($n = 3$) [151]. The safety and tolerance of voriconazole were further analyzed in a retrospective cohort study of 37 immunocompromised children and adolescents requiring therapy for various indications. Voriconazole was administered intravenously and/or orally at dosages ranging from 2 to 8 mg/kg b.i.d. for a mean duration of 174 days (range: 5 – 998 days). Grade I or II adverse events were observed in 19 patients (51%); the most frequent events included transient increases in hepatic transaminases (19) and transient visual disturbances (5). Four patients (10%) experienced grade III/IV adverse events and three (8%) were permanently discontinued. Although not a primary end point of the analysis, voriconazole showed promising efficacy as a preventive and therapeutic modality [155].

3.1.2 Posaconazole

Posaconazole is a novel lipophilic antifungal triazole with potent and broad spectrum activity against opportunistic, endemic and dermatophytic fungi *in vitro*. This activity extends to organisms that are often refractory to existing triazoles, amphotericin B or echinocandins such as *C. glabrata*, *C. krusei*, *A. terreus* and *Fusarium* spp. Importantly, posaconazole also possesses activity against zygomycetes both *in vitro* and *in vivo*, distinguishing it from all available azoles [156,157].

Posaconazole is available as oral suspension only and achieves optimal exposure when administered in 2 – 4 divided doses given with food or a nutritional supplement. The compound has a large volume of distribution in the order of 5 l/kg and a prolonged elimination half-life of ~ 20 h. Posaconazole is not metabolized through the CYP450 enzyme system, but primarily excreted in an unchanged form in the feces. It is inhibitory against CYP3A4, but has no effects on 1A2, 2C8, 2C9, 2D6 and 2E1 isoenzymes and, therefore, a limited spectrum of drug–drug interactions can be expected (Table 3) [158,159].

Posaconazole appears to be well tolerated in a manner comparable to fluconazole. The overall safety of posaconazole has been assessed in > 400 patients with invasive fungal infections from two open-label clinical trials [160]. Treatment-related adverse events occurred in 38% of patients (164/428); the most common were nausea (8%), vomiting (6%), headache (5%), abdominal pain (4%) and diarrhea (4%). Treatment-related abnormal liver function test results were observed in $\leq 3\%$ of patients. Serious adverse events considered possibly or probably related to posaconazole occurred in 35 (8%) patients. The drug–drug interaction potential of posaconazole has been investigated in seven open-label, crossover drug interaction studies. As with other azoles, caution is advised when posaconazole is coadministered with CYP3A4 substrates (increased levels of coadministered drugs) and unspecific enzyme inducers (decreased levels of posaconazole) [156].

Apart from two Phase II clinical trials for first- [161] and second-line [162] therapy of HIV-associated oropharyngeal

Table 4. Simulated plasma concentrations of voriconazole following multiple doses of 3 and 4 mg/kg in pediatric versus adult patients.

Parameter	Value			
	Pediatric patients 2 – 11 years of age		Adult patients	
	3 mg/kg	4 mg/kg	3 mg/kg	4 mg/kg
AUC _{tau} (ng*h/ml)	10,670	14,227	13,855	38,605
C _{average} (ng/ml)	889	1186	1155	3217

Data are reported as medians following 6 mg/kg every 12 h on day 1 and maintenance dose 3.

Although in pediatric patients, an increase in dosage by a factor of 1.3 leads to a proportional increase in the C_{average} and in the mean area under the AUC_{tau}, adult patients display a 2.8-fold, hyperproportional increase in exposure, indicating non-linear disposition. As a consequence, pediatric patients dosed at 4 mg/kg do not achieve the same exposure as adults dosed at 4 mg/kg, the dosage that has led to the approval of voriconazole for first-line treatment of invasive aspergillosis. Modified from Walsh *et al.* [153].

AUC_{tau}: Area under the concentration-time curve of the dosing interval; C_{average}: Mean average plasma concentration.

and esophageal candidiasis, preliminary results have been presented for the pivotal Phase II salvage study in patients with possible, probable and proven invasive fungal infections refractory to or intolerant of standard therapies [163] and a Phase III randomized clinical trial comparing posaconazole with fluconazole for treatment of oropharyngeal candidiasis [164]. Posaconazole has demonstrated strong antifungal efficacy in Phase II and III clinical trials in immunocompromised patients with oropharyngeal and esophageal candidiasis. Posaconazole also showed promising efficacy as salvage therapy in a large Phase II study including 330 patients with invasive fungal infections intolerant of or refractory to standard therapies and a contemporaneous external control of 279 patients [163]. Most patients (86%) were refractory to previous therapy. Successful outcomes at the end of treatment in the posaconazole and in the contemporaneous external control cohorts were 42 versus 26% in aspergillosis (107 versus 86 points), 39 versus 50% in fusariosis (18 versus 4 points), 56 versus 50% in zygomycosis (11 versus 8 points), 69 versus 43% (16 versus 7 points) in coccidioidomycosis, 52 versus 53% in candidiasis (23 versus 30 points), 48 versus 58% in cryptococcosis (31 versus 64 points), 81 versus 0% in chromoblastomycosis (11 versus 2 points) and 64 versus 60% in other invasive fungal infections (30 versus 20 points), respectively. A retrospective analysis of the compassionate-use program of the manufacturer including 91 patients with proven or probable zygomycosis refractory or intolerant to prior antifungal therapy revealed a 60% success rate (complete and partial responses) at 12 weeks after initiation of therapy, supporting the usefulness of posaconazole for second-line or consolidation therapy of zygomycosis [165]. Preventative, randomized Phase III studies in high risk patients with HSCT and graft-versus-host disease [166] and acute leukemias [167] have been completed. In the first study, patients received either posaconazole 200 mg t.i.d. or fluconazole 400 mg/day, respectively, with the start of immunosuppression for a total of 16 weeks. Treatment with posaconazole led to a decreased

incidence of invasive fungal infections at 16 weeks (5 versus 9%, $p = 0.07$), with a statistically significant decrease in invasive *Aspergillus* infections (2 versus 7%, $p = 0.006$). After 7 days post end-of-treatment, fewer patients had invasive fungal disease (2 versus 8%, $p = 0.004$) and fewer patients had invasive aspergillosis (1 versus 6%, $p = 0.001$). There were no differences in overall mortality at 12 weeks and no differences in the rate of drug discontinuations due to adverse events between the two study arms. In the second study, patients received posaconazole 200 mg t.i.d. and either fluconazole 400 mg/day or itraconazole 200 mg b.i.d., respectively. Treatment was started with each cycle following a drop of the absolute neutrophil count to $\leq 500 \mu\text{l}$ for up to 12 weeks. Significantly less patients enrolled in the posaconazole arm developed an invasive fungal infection at day 7 post end-of-treatment as compared with the comparator arm (2 versus 8%, $p < 0.01$); most importantly, treatment with posaconazole resulted in a significant decrease in the rate of invasive aspergillosis (1 versus 7%, $p < 0.001$). At day 100 post randomization, the rate of invasive fungal infections was 5 and 11% ($p < 0.01$) and patients treated with posaconazole had a significantly improved survival probability ($p = 0.035$). These two landmark studies demonstrate the preventative efficacy of posaconazole in particular against invasive *Aspergillus* infections in high-risk patients and a survival benefit in patients with acute myeloblastic leukemia/myelodysplastic syndrome undergoing remission-induction chemotherapy.

Posaconazole has been approved in the EU for treatment of aspergillosis, fusariosis, chromoblastomycosis and coccidioidomycosis refractory to or intolerant of standard therapies; in addition, posaconazole is approved for prophylaxis in high-risk patients with acute myeloid leukemia/myelodysplastic syndrome, HSCT and graft-versus-host disease in both the EU and the US. The recommended daily dosage for salvage treatment is 400 mg b.i.d. given with food; for patients not tolerating solid food, a dosage of 200 mg/day is recommended, preferentially together

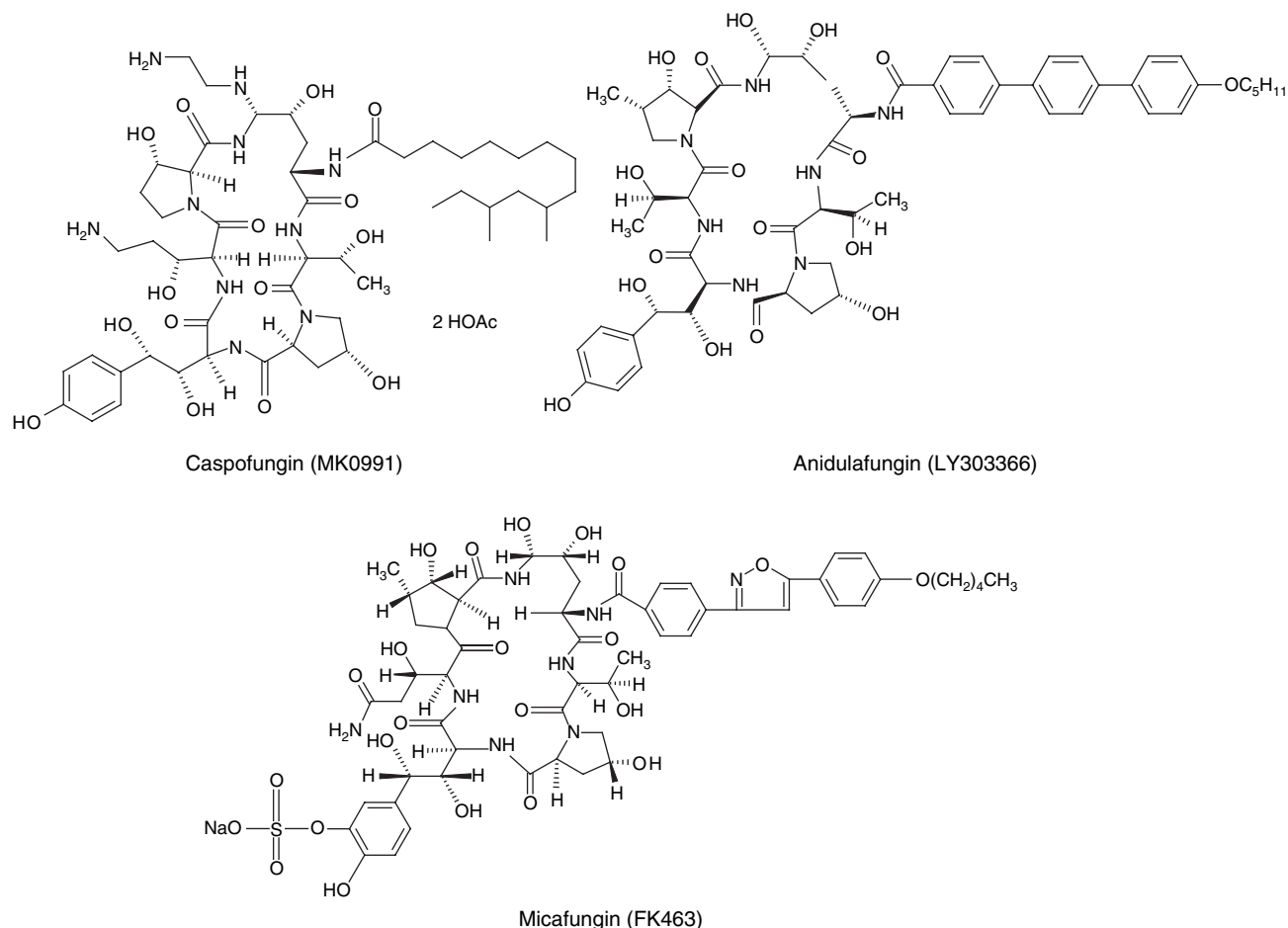


Figure 2. Chemical structures of caspofungin, anidulafungin and micafungin. The echinocandins are amphoteric cyclic lipopeptides with a hexapeptide core that is linked to a variably configured lipid side chain.

with a nutritional supplement. The dosage for prophylaxis is 200 mg t.i.d. Present data indicate no need for dosage adjustments based on differences in age, gender, race, renal or hepatic function [156]. The pharmacokinetics of posaconazole in pediatric patients (< 18 years of age) have not been studied yet. Very limited data obtained in 12 pediatric subjects ≥ 8 years of age appear to indicate no fundamental differences in trough plasma concentrations as compared to adults [168]. Salvage treatment with posaconazole resulted in successful outcomes in 5 out of 11 pediatric subjects (8 – 17 years of age), which appears similar to the outcome in the adult population [169].

3.2 Echinocandin lipopeptides

The echinocandins are a distinct class of semisynthetic amphiphilic lipopeptides that are composed of a cyclic hexapeptide core linked to a variably configured lipid side chain, which act by inhibiting the synthesis of 1,3- β -D-glucan. This homopolysaccharide is a major component of the cell wall of many pathogenic fungi and absent in mammalian cells. It provides osmotic stability and is

important for cell growth and division. The first compound of this class undergoing preclinical evaluation was cilofungin, a semisynthetic echinocandin B derivative with activity limited to *Candida* spp. However, clinical development was abandoned in the early stages due to toxicity concerns associated with the intravenous polyethylene glycol formulation vehicle [16]. Over the last decade, a second generation of semisynthetic echinocandins with extended antifungal spectrum against *Candida* and *Aspergillus* spp., a very favorable safety profile and pharmacokinetic characteristics have been developed: anidulafungin (EraxisTM), caspofungin (CancidasTM) and micafungin (MycamineTM) (Figure 2; Table 5). The data accumulated, thus far, indicate that these agents are not fundamentally different with respect to spectrum, pharmacokinetics, safety and antifungal efficacy.

3.2.1 Caspofungin

Caspofungin has been the first licensed compound of the echinocandin class of antifungal agents. *In vitro*, caspofungin has broad spectrum antifungal activity against *Candida* and *Aspergillus* spp. without cross-resistance to existing agents.

Table 5. Principal pharmacokinetic properties of the echinocandin lipopeptides caspofungin, anidulafungin and micafungin.

	Caspofungin	Anidulafungin	Micafungin
Formulation	i.v.	i.v.	i.v.
Dose-linearity	Yes	Yes	Yes
Oral bioavailability (%)	N/A	N/A	N/A
Protein binding (%)	97	84	99
Volume of distribution (l/kg)	N/A	0.7 – 0.9	0.24
Elimination half-life (h)	8 – 10	24	15
Substrate/inhibitor of CYP450	N/A	N/A	N/A
Routes of elimination	Degradation/metabolization, urine > feces	Degradation only, feces	Metabolization, feces > urine

Data derived from references [170,171,189-191,199,202].

N/A: Not applicable; i.v.: Intravenous.

The compound exerts prolonged postantifungal effects and fungicidal activity against *Candida* species and causes severe damage to *A. fumigatus* at the sites of hyphal growth. Animal models have demonstrated efficacy against disseminated candidiasis and disseminated and pulmonary aspergillosis, both in normal and in immunocompromised animals [170].

Caspofungin is only available for intravenous administration. The compound exhibits dose-proportional plasma pharmacokinetics with a beta half-life of ~ 15 h that allows for once daily dosing. It is highly (> 95%) protein bound and distributes into all major organ sites including the brain; however, concentrations in uninfected CSF are low. Caspofungin is metabolized by the liver following degradation and is slowly excreted into urine and feces; only small fractions (< 2%) of a dose are excreted into urine in an unchanged form [170,171]. At the present dosage, caspofungin is generally well tolerated and only a small fraction of patients enrolled on the various clinical trials (< 5%) discontinued therapy due to drug-related adverse events. The most frequently reported adverse effects include increased liver transaminases, gastrointestinal upset and headaches [172]. Because of transient elevations of hepatic transaminases in single-dose interaction studies in healthy volunteers [170], the concomitant use of ciclosporin is not recommended; clinical experience, however, indicates that both drugs can be given concomitantly under careful monitoring [173-175]. Caspofungin has no significant potential for drug interactions mediated by the CYP450 enzyme system. It can reduce the AUC of tacrolimus by ~ 20%, but has no effect on ciclosporin levels. Unspecific inducers of drug clearance and/or mixed inducer/inhibitors, namely efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone and carbamazepine may reduce caspofungin concentrations [170].

The clinical efficacy of caspofungin against *Candida* spp. has been demonstrated first in Phase II and III studies in immunocompromised patients with esophageal candidiasis [176-178]. A multi-center, randomized, double-blind

Phase III clinical trial investigated the efficacy of caspofungin for primary treatment of invasive *Candida* infections in 224 mostly non-neutropenic patients with amphotericin B deoxycholate (DAMB; 0.6 – 1.0 mg/kg) as the comparator agent. Among patients receiving at least one dose of study drug, 73% of patients in the caspofungin cohort and 61.7% of patients in the DAMB cohort had a therapeutic success at the end of intravenous therapy. Among patients who received five or more doses, the response rates were 80.7 and 64.9%, respectively. There was no difference in relapse or survival, but caspofungin was better tolerated [179]. A multi-center Phase II salvage trial of caspofungin has been completed in 83 patients with definite or probable invasive aspergillosis refractory or intolerant to standard therapies. As determined by an independent expert panel, a complete or partial response was observed in 45% of patients receiving at least one dose of caspofungin; in patients receiving the drug for > 7 days, the response rate was 56% [180]. Finally, in a large, randomized, double-blind clinical trial including 1095 patients, caspofungin was as effective as liposomal amphotericin B for empirical antifungal therapy in persistently febrile granulocytopenic patients, but better tolerated. The proportion of patients who survived at least 7 days after therapy was greater in the caspofungin group (92.6 versus 89.2%) [181].

At present, caspofungin is licensed in the EU and the US in patients ≥ 18 years of age for second-line therapy of definite or probable invasive aspergillosis, for primary therapy in non-neutropenic patients with invasive *Candida* infections and for empirical antifungal therapy in granulocytopenic patients with persistent fever. The recommended dose regimen consists of a single 70-mg loading dose on day 1, followed by 50 mg daily thereafter, administered over 1 h. No dosage adjustment is required in patients with renal insufficiency. In patients with mild hepatic insufficiency (Child-Pugh category A), no adjustments are needed; in patients with moderate hepatic

Table 6. Single-dose caspofungin pharmacokinetics in pediatric versus adult patients.

Dosage	Children (2 – 11 years of age)		Adolescents (12 – 17 years of age)	Adults
	1 mg/kg	50 mg/m ²	50 mg/m ²	50 mg
AUC _{0–24 h} (ugxh/ml)	41.5	96.4	77.6	70.6
C1 (µg/ml)	6.59	13.9	7.67	7.67
C24 (µg/ml)	0.45	1.09	1.35	1.35
T _{1/2} β (h)	7.2	7.6	11.7	11.7
CL (ml/min/m ²)	8.57	7.78	6.07	6.07

Least square means are reported for AUC, C_{max} and C_{min}, and harmonic means for T_{1/2} β. Data were obtained in groups of 6 – 10.

Pediatric patients and compared with those obtained in 32 adult patients with mucosal candidiasis.

In comparison with adult values, a 1 mg/kg dosage does not achieve the target trough concentration of caspofungin of 1 µg/ml and leads to a lower exposure as measured by the AUC_{0–24 h}; the dosage regimen of 50 mg/m² leads to similar or slightly higher trough concentrations and similar or slightly higher exposure (AUC_{0–24 h}) and has been selected for the further development program in pediatric patients. Modified from Walsh *et al.* [183].

C1: Peak plasma concentration; C24: Plasma concentration at trough; CL: Plasma clearance; T_{1/2} β: β-half-life in plasma.

insufficiency (Child-Pugh category B), decreasing the maintenance dose to 35 mg/day is recommended after the loading dose of 70 mg. No recommendations exist for patients with severe hepatic insufficiency (Child-Pugh category C) [170].

In children and adolescents, the pharmacokinetics and safety of caspofungin were investigated using either a weight-based regimen (1 mg/kg of body weight/day) or a body surface area regimen (50 mg/m²/day). Compared with adult patients treated with 50 mg/day, the maintenance dosage of 1 mg/kg/day achieved suboptimal exposure, whereas a maintenance dosage of 50 mg/m²/day provided similar or slightly higher exposure relative to adults [182] (Table 6). As a consequence, a dosage of 50 mg/m²/day (day 1: 70 mg/m²/day; maximum daily dose: 70 mg) has been selected for the further pediatric program. Although not approved in this population, caspofungin appears to be well-tolerated in pediatric patients. In the above mentioned Phase I/II dose-finding study in 39 children and adolescents, none of the patients developed a serious drug-related adverse event or was discontinued for toxicity [182]. A similarly favorable safety profile has also been reported in immunocompromised pediatric patients who received the compound for various indications mostly in combination with other antifungal agents [175,183] and in neonates with refractory invasive candidiasis [184-186].

3.2.2 Anidulafungin

The clinical efficacy of anidulafungin against *Candida* spp. has been demonstrated in Phase II or III studies in immunocompromised patients with esophageal candidiasis and candidemia. Anidulafungin had equivalent efficacy to fluconazole in esophageal candidiasis in a randomized, double-blind, international, multicenter study with success documented in 242 out of 249 evaluable anidulafungin patients (97.2%) and 252 out of 255 fluconazole patients (98.8%). Adverse events leading to discontinuation were reported in 29 anidulafungin patients (10%) versus 23 fluconazole patients (8%) [187]. In a non-comparative,

dose-ranging study of 100 mg loading dose followed by 50 mg daily, 150 mg loading dose followed by 75 mg daily and 200 mg loading dose followed by 100 mg daily for candidemia, successful global responses were seen in 83 – 92% of patients at the end of therapy and in 72 – 86% of patients 2 weeks after the end of therapy [177]. Anidulafungin has also been investigated in patients with invasive candidiasis, including candidemia. In a dose-ranging study in 123 patients, success rates at end of treatment were 84, 90 and 89% in the 50-, 75- and 100-mg groups, respectively [187]. This study was followed by a randomized, double-blind Phase III study that compared anidulafungin 100 mg once daily versus fluconazole 400 mg once daily in a total of 245 mostly non-neutropenic patients [188]. The preliminary data indicate that more patients receiving anidulafungin had a clinical and microbiologic success at the end of intravenous therapy (75.6 versus 60.2%); similar superiority was found at the 2- and 6-week follow ups after the end of all therapy (64.6 versus 49.2% and 55.9 versus 44.1%, respectively). Survival at the end of therapy was higher in the anidulafungin group (74 versus 69%).

Anidulafungin is licensed in the US in patients ≥ 18 years of age for primary therapy in non-neutropenic patients with invasive *Candida* infections and for esophageal candidiasis. Regulatory approval in Europe is expected in 2007. The recommended dose regimen consists of 100 mg (day 1: 200 mg) for invasive candidiasis and 50 mg/day (day 1: 100 mg) for esophageal candidiasis, administered at a rate not exceeding 1.1 mg/min. No dosage adjustment is needed in subjects with mild, moderate and severe renal impairment or in those undergoing hemodialysis [189-191]. Mild-to-moderate hepatic impairment (Child-Pugh class A and B) does not cause clinically significant changes in the pharmacokinetics of anidulafungin. Dosage recommendations for subjects with severe hepatic impairment (Child-Pugh class C) are pending [189-191].

A pediatric Phase I/II multicenter study of the pharmacokinetics and safety of anidulafungin has been

Table 7. Single-dose anidulafungin pharmacokinetics in pediatric versus adult patients.

Dosage	Pediatric patients (2 – 17 years of age)		Adults	
	0.75 mg/kg	1.5 mg/kg	50 mg	100 mg
C _{max} (µg/ml)	4.02	6.09	2.51	3.82
AUC _{0–24 h} (ugxh/ml)	48.0	89.7	53.3	104.8
T _{1/2} β (h)	20.8	19.5	39.3*	42.3*
CL (l/h/kg)	0.0175	0.0191	N/A	N/A
VD _{ss} (l/kg)	0.45	0.49	0.72	0.78

Pharmacokinetic parameters are expressed as mean values. Data were obtained in groups of 6 pediatric patients with compromised immunity and neutropenia per age group and dosage level, and compared with those obtained in 26 adult healthy volunteers. Modified from Benjamin *et al.* (2006) [192] and Rajman *et al.* [202].

CL: Plasma clearance; N/A: Not available; VD_{ss}: Apparent volume of distribution at steady-state.

*T_{1/2} γ.

Table 8. Single-dose micafungin pharmacokinetics in pediatric versus adult patients.

Dosage	Pediatric patients (2 – 17 years of age)			Adults	
	1 mg/kg	2 mg/kg	4 mg	50 mg	100 mg
C _{max} (µg/ml)	10.8	15.3	30.3	3.6	7.1
AUC _{0–24 h} (ugxh/ml)	40.3	83.0	191.4	33.9	59.9
T _{1/2} β (h)	12.5	13.2	11.6	12.5	13.0
CL (l/h/kg)	0.021	0.020	0.017	0.017*	0.018*
VD _{ss} (l/kg)	0.33	0.31	0.28	0.31*	0.32*

Pharmacokinetic parameters are expressed as mean values. Data were obtained in groups of 7 – 15 pediatric patients with compromised immunity and neutropenia per age group and dosage level and compared with those obtained in cohorts of 8 – 9 adult patients with hematopoietic stem cell transplantation. Modified from Driscoll *et al.* (2005) [200] and Hiemenz *et al.* (2005) [203].

*Weight normalization calculated by assuming an average body weight of 70 kg.

CL: Plasma clearance; VD_{ss}: Apparent volume of distribution at steady-state.

completed in 19 granulocytopenic children with cancer. Patients were divided into two age cohorts (2 – 11 and 12 – 17 years) and were enrolled into sequential groups to receive 0.75 or 1.5 mg/kg/day [192] (Table 7). No drug-related serious adverse events were recorded. Pharmacokinetic parameters were similar across age groups and dosage cohorts and similar relative to adult subjects. Following single and multiple daily doses of 0.75 mg/kg and 1.5 mg/kg, plasma concentration data corresponded to those in adults following a daily 50 and 100 mg dose, respectively. Thus, in pediatric patients, anidulafungin can be dosed based on body weight [192].

3.2.3 Micafungin

Micafungin has been studied in open-label, dose-ranging studies of endoscopically proven esophageal candidiasis in HIV patients [193,194]. A double-blind comparative study investigating micafungin 50, 100 and 150 mg/day versus fluconazole 200 mg/day for HIV-associated esophageal candidiasis showed similar endoscopic cure rates and safety profiles for micafungin at doses of 100 and 150 mg/day to fluconazole [195]. A further randomized, double-blind

comparative trial in 523 patients ≥ 16 years with oesophageal candidiasis investigated micafungin 150 mg/day versus fluconazole 200 mg/day [196]. For the primary end point of endoscopic cure, treatment difference was -0.3% (micafungin 87.7%, fluconazole 88.0%). A large, Phase III, 1:1 randomized, double-blind, non-inferiority trial has been completed that compared micafungin 100 mg/day and liposomal amphotericin B 3 mg/kg/day for first-line therapy of invasive *Candida* infections in a total of 531 adult patients [55]. The overall success rate in both treatment arms was similar (89.6 versus 89.5%). There was no difference in survival. Predefined safety parameters showed micafungin to have advantages over liposomal amphotericin B in renal function. The safety and efficacy of micafungin in combination with other antifungal agents for treatment of refractory aspergillosis were investigated in a non-comparative multinational study in 85 patients with bone marrow transplantation. A complete or partial response was reported for 33 patients (39%) [197]. Micafungin (50 mg/day; 1 mg/kg for patients < 50 kg) versus fluconazole (400 mg/day; 8 mg/kg for patients < 50 kg) has been investigated for prophylaxis of invasive fungal infections

in 882 patients undergoing HSCT. Prophylaxis was given from the start of the conditioning regimen until 5 days following engraftment. The overall success rate was significantly higher for patients randomized to receive micafungin (80.0 versus 73.5%; $p = 0.03$). Drug-related adverse events were comparable [198].

Micafungin is licensed only in the US for prevention of *Candida* infections in patients undergoing HSCT and for treatment of esophageal candidiasis. Renal dysfunction (creatinine clearance < 30 ml/min) or dialysis does not alter the pharmacokinetics of micafungin. Subjects with moderate hepatic dysfunction exhibited no differences in weight-normalized clearance [199].

Micafungin has been studied in 70 children and adolescents in an open-label, sequential group, dose-escalation study of empirical therapy in febrile granulocytopenic children aged 2 – 17 years. In this study, micafungin was well tolerated at dosages ranging from 0.5 to 3.0 mg/kg/day; pharmacokinetics were linear and pharmacokinetic parameters were similar to those observed in adults [200] (Table 8). A Phase I, single-dose, multicenter, open-label, sequential-dose trial has investigated the safety and pharmacokinetics of micafungin (0.75 mg/kg, 1.5 mg/kg and 3.0 mg/kg) in 18 premature infants weighing > 1000 g. Micafungin pharmacokinetics in preterm infants appeared to be linear. However, premature infants > 1000 g on average displayed a shorter half-life and a more rapid rate of clearance compared with published data in older children and adults. All doses of micafungin were well tolerated and no serious drug-related adverse events were observed [201]. A multinational, non-comparative study investigated the activity of micafungin alone ($n = 2$) or in combination ($n = 56$) with other agents in 58 pediatric patients with proven or probable invasive aspergillosis. A total of 54 patients had failed prior therapy. The mean daily dose was 2.0 ± 1.2 mg/kg/day and the mean duration of dosing was 67 ± 85 days. Overall response was 26 out of 58 (45%) [202]. The efficacy and safety of micafungin was further investigated in the pediatric subpopulation of a large, randomized, double-blind, Phase III trial in patients with invasive candidiasis or candidemia. Patients were randomised to receive micafungin 2 mg/kg/day i.v. or liposomal amphotericin B 3 mg/kg/day for a minimum of 14 days. In the intent-to-treat analysis, 36 out of 52 patients randomized to receive micafungin (69.2%) and 40 out of 54 (74.1%) randomized to receive liposomal amphotericin B were successfully treated. The incidence of serious adverse events (3.8 versus 9.3%) and the rate of patients discontinuing therapy because of an adverse event (3.8 versus 16.7%) were lower in micafungin-treated patients [203]. Thus, a considerable number of pediatric patients have been included in clinical trials with micafungin without evidence for differences in safety and tolerance as compared with adults. A final pediatric dosage, however, has not been proposed.

4. Conclusions

Pediatric age groups display important differences in host biology, predisposing conditions, epidemiology and presentation of fungal infections relative to the adult population. Over the past decade, major advances have been made in the field of medical mycology. Most importantly, an array of new antifungal agents has entered the clinical arena. Although the final pediatric approval of several of these agents remains to be established, the pediatric development is moving forward at a steady pace.

Invasive fungal infections will remain important causes for morbidity and mortality in immunocompromised pediatric patients. The availability of alternative therapeutic options is an important advance; at the same time, however, antifungal therapy has become increasingly complex. In addition to information on prior antifungal therapies, microbiologic data, existing co-morbidities and comedications, a detailed knowledge of the available antifungal armamentarium and contemporary clinical trials is needed more than ever in the management of the individual patient.

5. Expert opinion

New antifungal agents are now available for pediatric populations, including lipid formulations of amphotericin B, second generation triazoles (voriconazole, posaconazole) and the new class of echinocandins (caspofungin, micafungin and anidulofungin). With the advent of these new agents, few indications are left for antifungal treatment of opportunistic mycoses with conventional deoxycholate amphotericin B, a drug notorious for serious side effects.

5.1 Lipid formulation amphotericin B

The lipid formulations of amphotericin B (ABCD, ABLC, LAMB) preferentially distribute to the RES and functionally spare the kidney. As a result, the lipid formulations of amphotericin B have less renal toxicity as defined by development of azotemia than conventional amphotericin B. Of the three lipid formulations, the unilamellar liposomal preparation achieves strikingly high peak plasma concentrations and AUC values due to its slow uptake by the RES. Studies have shown that the disposition of the lipid formulations in pediatric patient is not fundamentally different from that in adults. The lipid formulations of amphotericin B are presently licensed for the treatment of patients with invasive mycoses refractory or intolerant to DAMB and, limited to LAMB, for empirical therapy of persistently neutropenic patients. A considerable number of pediatric patients have been treated with either ABCD, ABLC or LAMB; however, individually published pediatric data remain limited.

5.2 Triazole antifungals

The plasma pharmacokinetics of fluconazole in pediatric age groups exhibit changes in the volume of distribution

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and clearance that are characteristic for a water soluble drug with minor hepatic metabolism and predominantly renal elimination. Except for premature neonates, in whom clearance is decreased, pediatric patients tend to have an increased normalized plasma clearance and a shorter half-life in comparison with adults. Consequently, fluconazole dosages at the higher end of the recommended dosage range are necessary for the treatment of invasive mycoses in children with 12 mg/kg/day being the most appropriate for lifethreatening infections.

Problems with gastrointestinal absorption, tolerance and drug–drug interactions through interference with mammalian CYP4500-dependent drug metabolism are pronounced in itraconazole, limiting its clinical usage. In addition, this compound has not been approved in patient populations < 18 years of age.

5.3 Newer triazole antifungals

Voriconazole is approved for the treatment of invasive aspergillosis, fusariosis and scedosporiosis, and for primary treatment of invasive candidiasis in non-neutropenic patients. The recommended intravenous dosages for patients ≥ 12 years of age are 6 mg/kg b.i.d. on day 1, followed by 4 mg/kg b.i.d. Pediatric patients 2 – 11 years of age have a higher capacity for elimination than adult healthy volunteers, resulting in a lower, potentially non-therapeutic exposure at similar dosages. Voriconazole showed promising efficacy as a preventive and therapeutic modality in some pediatric patients.

Posaconazole has been approved in the EU for treatment of aspergillosis, fusariosis, chromoblastomycosis and coccidioidomycosis refractory to or intolerant of standard therapies; in addition, posaconazole is approved for prophylaxis in high risk patients with acute myeloid leukemia/myelodysplastic syndrome, HSCT and graft-versus-host disease in both the EU and the US. The recommended daily dosage for salvage treatment is 400 mg b.i.d. given with food; for patients not tolerating solid food, a dosage of 200 mg/day is recommended, preferentially together with a nutritional supplement. The dosage for prophylaxis is 200 mg t.i.d. Present data indicate no need for dosage adjustments based on differences in age, gender, race, renal or hepatic function. The pharmacokinetics of posaconazole in pediatric patients (< 18 years of age) have not yet been studied. Very limited data obtained in 12 pediatric subjects ≥ 8 years of age appear to indicate no fundamental differences in trough plasma concentrations as compared with adults.

5.4 Echinocandin lipopeptides

The echinocandins are a distinct class of antifungal agents that act by inhibiting the synthesis of 1,3- β -D-glucan, which

is not present in mammalian cells. At present, caspofungin is licensed in the EU and the US in patients ≥ 18 years of age for second-line therapy of definite or probable invasive aspergillosis, for primary therapy in non-neutropenic patients with invasive *Candida* infections and for empirical antifungal therapy in granulocytopenic patients with persistent fever. A dosage of 50 mg/m²/day (day 1: 70 mg/m²/day; maximum daily dose: 70 mg) has been selected for the further pediatric program based on the available pharmacokinetics and safety of caspofungin in children and adolescents. Although not approved in this population, caspofungin appears to be well-tolerated in pediatric patients.

Anidulafungin is licensed in the US in patients ≥ 18 years of age for primary therapy in non-neutropenic patients with invasive *Candida* infections and for esophageal candidiasis. Regulatory approval in Europe is expected in 2007. The presently available data in pediatric patients show that pharmacokinetic parameters are similar across age groups and dosage cohorts and similar relative to adult subjects. Following single and multiple daily doses of 0.75 mg/kg and 1.5 mg/kg, plasma concentration data corresponded to those in adults following a daily 50 and 100 mg dose, respectively. Thus, in pediatric patients, anidulafungin can be dosed based on body weight.

Micafungin is licensed only in the US for prevention of *Candida* infections in patients undergoing HSCT and for treatment of esophageal candidiasis. A larger number of pediatric patients have been included up to now in clinical trials with micafungin and varying dosages and for varying indications without evidence for differences in safety and tolerance as compared to adults. A final pediatric dosage, however, has not been proposed.

Combination antifungal therapy is being discussed as a modality for severe fungal infections. For cryptococcal meningitis, the efficacy of combination therapy with amphotericin B plus 5-FC is well established. For invasive aspergillosis, no evidence exists as to whether or not the combination of a new triazole with an echinocandin improves outcome, although it is a common practice in several cancer centers in the US. *In vitro* and animal data provide a rationale for this approach, but ultimate evidence for superior efficacy will have to be established by well designed, comparative clinical trials.

Disclosures

AH Groll has served as a consultant to Astellas, Cephalon, Essex Pharma, Gilead Sciences, Merck, Sharp & Dohme, Pfizer, Schering-Plough Research Institute and has served as clinical investigator for Atellas, Essex Pharma, Merck, Sharp & Dohme and Pfizer. TJ Walsh has cooperative research and development agreements with Astellas and Vicuron.

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