REVIEW ARTICLE

New Antifungal Agents in Pediatric Practice

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Clinical needs for new antifungal agents have steadily increased with the rise and alteration in spectrum of invasive mycoses in children and neonates having AIDS, malignancies and undergoing immunosuppressive therapies. Several new options are now available for management of serious fungal infections. The aim of this review is to summarize the key features of the new antifungal agents and novel targets being investigated for the treatment of fungal infections, with special reference to its use in the treatment of pediatric fungal infections. New triazoles have broad spectrum of activity with voriconazole presently being the drug of choice against invasive aspergillosis, and posaconazole is the possible first substitute of amphotericin B against zygomycosis. Echinocandins with new mode of action of inhibition of fungal cell wall polysaccharide synthesis are effective in treating candidemia and invasive candidiasis. Some of these agents are however, still awaiting FDA approval for their use in pediatric practice.

Keywords: *Antifungal, Antimicrobial, Mycoses, Treatment.*

Invasive fungal infections (IFI) in the immunocompromised children with hematological malignancies and hematopoetic stem cell transplant (HSCT) recipients and the neonates, especially the very low birth weight infants (VLBW) and the extremely low birth weight (ELBW) infants is associated with significant morbidity, mortality and high health care costs(1-5).

While *Candida* and *Aspergillus* species are the most common causes of opportunistic fungal infections in India(6,7), previously uncommon, emerging fungal species such as *Fusarium, Pichia* and *Scedosporium* spp. are also being increasingly reported worldwide(8-10). This emergence of lesser-known fungal pathogens coupled with the increased antifungal drug resistance in commonly encountered fungal pathogens, has prompted a considerable expansion in the choice of antifungal drugs. Currently 4 classes of drugs are available for treating IFIs: polyenes, triazoles, echinocandins and nucleoside analogues. Among these, the echinocandins are an entirely new class of drugs and the triazoles have undergone significant development with a new and improved generation of azoles being added to the list (posaconazole, ravuconazole and voriconazole), while several others are being developed (isavuconazole, albaconazole). Many of these new drugs have already been licensed in many countries around the world including India, and are being used for the treatment of pediatric IFI. However, pediatric dosage finding and safety evaluations of several of these compounds are incomplete and data show that significant differences in pharmacokinetic properties exist between pediatric and adult patients. The purpose of this review is to describe the new antifungal agents with special reference to the status of their clinical development and use in pediatric patients. The new antifungal agents and their use are detailed in ***Tables*** **I** and **II**.

NEW AZOLES

Azoles exert their antifungal activity by binding to the ergosterol biosynthetic enzyme, lanosterol 14-α demethylase and inhibiting ergosterol synthesis. Earlier members of this group had a rather narrow spectrum of activity against some but not all yeasts, with itraconazole demonstrating some activity

TABLE I CHARACTERISTICS OF NEW ANTIFUNGAL AGENTS

Drug	Antifungal activity					Route
	Candida spp.	Cryptococcus spp.	Aspergillus spp.	Other hyalohypho-mycetes	Zygomycetes	
Voriconazole	+	+	+	+/–	–	iv/po
Posaconazole	+	+	+	+/–	+/–	po
Ravuconazole	+	+	+	+/–	+/–	iv/po
Caspofungin	+	-	+	–	–	iv
Anidulafungin	+	-	+	–	–	iv
Micafungin	+	-	+	–	–	iv

iv = Intravenous, po = per oral

against molds. New generation triazoles have an expanded spectrum of action with cidal activity against a broad spectrum of molds and enhanced activity against *Candida* spp. and other yeasts. The new azoles that have been developed include voriconazole, posaconazole and ravuconazole; and isavuconazole and albaconazole are under study. While all azole derivatives share the common mechanism of action, each possesses a unique affinity for the various fungal cytochrome P450 enzymes and thus a unique spectrum of activity and safety profile. However, the common mechanism of action leads to cross-resistance among azoles.

Voriconazole. It has been developed from fluconazole by adding a α-methyl group and substituting a fluoropyrimidine ring for one of the azole groups. This achieved fungicidal activity against *Aspergillus* and other molds but not against *Zygomycetes*(11). United States Food and Drug Administration (FDA) approved it for the treatment of primary acute invasive aspergillosis and serious infections caused by *Scedosporium* spp. and *Fusarium* spp in 2002, and in 2005 approved its use for the treatment of candidemia in adult patients without neutropenia. It can be used as both oral and intravenous formulations and is currently available in India.

Given orally on an empty stomach, the drug is rapidly and almost completely absorbed but food lowers the drug's bioavailability and delays absorption. The pharmacokinetics of voriconazole in children appears linear in contrast to non-linear pharmacokinetics in adults. This was based on single dose, open-label, two-center study involving children ages 2-11 years (mean 5.9 years); and a multi-dose, open, multicentric study in two age cohorts (age2-6, and 6-12 years with mean age 6.4 years). These studies showed that a pediatric dose of approximately 11mg/kg administered every 12h are approximately bioequivalent to an adult dosage of 4mg/kg given every 12h(12). Other variables such as CYP2C19 genotype, body weight, kidney and liver functions also affect plasma concentrations of the drug achieved after a given dosage. Selection of a fixed dose therefore yields a wide variety of plasma concentrations and there is a need of therapeutic drug monitoring for patients being treated with voriconazole(13,14). Though, voriconazole has not received FDA approval for use in children 2-11 years of age, it is approved in the European Union on the basis of compassionate use data(15). Voriconazole has not yet been formally tested in neonates due to the visual adverse events reported in adults and children. There is a major concern over its effect on the developing retina(16). Recently a case series of safe voriconazole use in critically ill newborn with cardiac disease has been reported from India(17). No significant drug interaction despite use of several cardiac drugs or any side effect was observed.

The largest clinical study of voriconazole in the pediatric population was an open-label compassionate-use evaluation of voriconazole in 58 children with proven or probable invasive fungal infection; refractory to or intolerant of conventional antifungal therapy. Voriconazole was administered

TABLE II TREATMENT OPTIONS FOR INVASIVE FUNGAL INFECTIONS

Clinical Condition	Underlying disease/ condition	Drug of choice	Adverse effects	Alternate drug
Prophylaxis for IFI[a]	Neutropenic patient with malignancy/HSCT	Posaconazole	GI intolerance, CYP450 drug interactions	Itraconazole/ fluconazole
Empiric therapy for IFI	Neutropenic patient with malignancy/HSCT and clinical and/or radiological signs of IFI without any laboratory evidence; Possible IA[b]	Caspofungin	Fever, rash, headache hematological abnormalities, hepatotoxicity, GI abnormalities	LAmB
Preemptive/targeted therapy for IFI	Neutropenic patient with malignancy/HSCT and clinical signs of IFI with laboratory evidence of fungal infection; Probable or proven IA[c]	iv Voriconazole	hepatotoxicity, cheilitis, photophobia, blurry vision, CYP450 drug interactions	iv LAmB
Prophylactic therapy for candidiasis in the ICU[d]	Neutropenic patients	Fluconazole[e]		
Empiric/targeted treatment for invasive candidiasis	Neutropenic/ HSCT	Caspofungin	Fever, rash, headache hematological abnormalities, hepatotoxicity, GI abnormalities	LAmB
	Non-neutropenic/ ICU patients	Echinocandin[f] (should be changed to fluconazole once sensitivity data is obtained)	Fever, rash, headache hematological abnormalities, hepatotoxicity, GI abnormalities, thrombophlebitis, epistaxis, mucositis	LAmB

IFI = Invasive fungal infection, HSCT=Hematopoetic stem cell transplant, GI= gastrointestinal, CYP 450= cytochrome P 450, IA=invasive aspergillosis, LAmB=Liposomal Amphotericin B, iv = intravenous, ICU=Intensive care unit,

[a]Some of the therapeutic options are based on trials or FDA recommendations in adults, as sufficient pediatric data is unavailable. Please see text for details.

[b,c]Guidelines for diagnosis according to European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group (38).

[d]Prophylactic use of antifungals in ICU is recommended based on hospital epidemiology and is justified if incidence of invasive candidiasis in ICU reaches 10% in spite of active prevention (39).

[e]May select for fluconazole resistant non-albicans species.

[f]Caspofungin is preferred in pediatric population (40).

as a loading dose of 6mg/kg every 12h on the first day of therapy, followed by 4mg/kg every 12 h on subsequent days. When possible, the conversion to oral therapy was made with a dose of 100mg or 200mg twice a day for patients weighing <40kg or ≥40kg respectively. After a 93-day median duration of therapy, complete or partial response was observed in 43% of children with aspergillosis, 50% with candidemia, and 63% with scedosporiosis. Treatment related adverse effect occurred in over 5% of patients, and were transaminase or bilirubin elevation in 13.8% of patients, rash in 13.8%, abnormal vision and photosensitivity reaction in 5% patients each; while 5% patients discontinued therapy due to intolerance(15).

Posaconazole. An oral 2nd generation azole, was approved by the FDA in 2006 for the prophylaxis of

invasive *Aspergillus* and *Candida* infections in patients at increased risk for these infections due to hematopoietic stem cell transplant, graft versus host disease, and hematological malignancies with prolonged neutropenia from chemotherapy. This drug is not yet commercially available in India. Posaconazole is similar in structure to itraconazole and has a broad-spectrum of activity *in vitro* against a wide array of yeasts, moulds, and especially the *Zygomycetes*, for which treatment options are limited. Unlike voriconazole, absorption is better when administered with fatty meals with extensive distribution in the tissues. It is only used as a compassionate release agent in oral formulation. It is active *in vivo* in several experimental models of pulmonary, cerebral, and disseminated aspergillosis(18,19). Randomized comparative studies of efficacy and safety of posaconazole in HIV-infected adults with oropharyngeal candidiasis indicate that it is as effective as fluconazole and well tolerated. A 40-80% response rate has been shown in patients with a wide variety of IFIs including cryptococcosis, candidiasis, phaeohyphomycosis, aspergillosis and fusariosis(15,20,21). Limited efficacy data are available in children. Posaconazole plasma levels were compared between juvenile (aged 8-17 years) and adult (aged 18-64 years) patients participating in an open-label phase III study. Posaconazole, 800 mg/day was given as salvage therapy for proven or probable IFI, refractory to standard antifungal therapy. Posaconazole concentrations in plasma were similar for juvenile and adult patients, suggesting that clinical outcomes are expected to be similar in adults and juvenile group with refractory invasive fungal infection(22). There is no data available on the safety and efficacy of posaconazole in neonates.

Ravuconazole. It is a derivative of fluconazole with potent activity against *Candida* spp*., Aspergillus* spp*., C. neoformans, H. capsulatum* and *C. immitis in vitro.* It is fungicidal, has 47-74% bioavailability with linear pharmacokinetics, and possesses long half-life of approximately 100h. Activity of ravuconazole against *Fusarium* and *Scedosporium* is less than that of voriconazole and cross-resistance between fluconazole and ravuconazole has been observed with *Candida glabrata* and other *Candida* spp(23). The drug has no activity against *Rhizopus* or *Mucor* spp. The safety and tolerability of ravuconazole has been tested in a handful of adult patients and was found to be similar to that of fluconazole. Unfortunately, no pediatric data is available.

BAL-8557. It is the water-soluble pro-drug that gets cleaved to BAL-4815 (isavuconazole). This new azole has very high (98%) plasma protein binding in humans and has potent *in vitro* activity against *Aspergillus* spp. including *A. fumigatus, A. flavus, A. terreus* and *A. niger.* It has lower MIC and MIC_{50} values than those of voriconazole for the majority of *Candida* spp. tested, including *C. glabrata* and *C. krusei*, and exhibits activity against dermatophytes and *Zygomycetes*(24, 25, 26). Several randomized clinical trials are evaluating the safety and efficacy of this drug for the treatment of invasive *Candida* infections (23).

Additional triazoles such as albaconazole are undergoing early clinical evaluation and their future is uncertain. For all new triazoles, concerns about emerging drug-resistant fungi and the problem of management of breakthrough infections will dictate their role in future antifungal prophylaxis and treatment.

B. ECHINOCANDINS

This is an entirely new class of antifungal agents that exert their activity by noncompetitive inhibition of 1, 3-β-D-glucan, an essential fungal cell wall polysaccharide. Structurally, they are characterized by a cyclic hexapeptide core linked to a lipid side chain that is variably configured. Echinocandins are fungistatic (due to blockade of cell wall synthesis) against *Aspergillus* and fungicidal (due to loss of cell wall integrity) against *Candida* activities. The unique mechanism of action has dual benefit: fewer side effects as cell walls are lacking in human cell, and possibility of successful combination with agents acting on cell membrane as combination therapy. All drugs in this group have poor bioavailability and have to be administered intravenously.

Caspofungin. The drug was previously approved for use in adults for empiric therapy of presumed fungal

infections in febrile neutropenic patients, for the treatment of candidemia and esophageal candidiasis, and for treatment of refractory invasive aspergillosis. As of July 2008, caspofungin has received FDA approval for pediatric use. The details of pharmacokinetics, dosing and clinical efficacy has been published earlier in *Indian Pediatrics*(27).

Even though dosage and pharmacokinetics of caspofungin in neonates remain unclear and no clinical trial data is available, there are several reports of use of caspofungin in neonates with invasive *Candida* infection. It appears from these reports that caspofungin could be considered an alternative therapy for neonatal candidiasis refractory to conventional antifungal therapy(28).

Micafungin and Anidulafungin. These drugs are other echinocandins with spectra of activity similar to caspofungin. Both drugs are undergoing clinical trials and are still not available in India. These new echinocandins achieve highest concentration in lung, followed by the liver, spleen, and kidney. Micafungin reaches brain at undetectable or low level, but anidulafungin reaches in measurable concentration. Micafungin has been approved by FDA in 2005 for therapy of esophageal candidiasis and for prophylaxis of *Candida* infection in hematopoietic stem cell transplant recipients. FDA approved Anidulafungin in 2006 for therapy of candidemia and esophageal candidiasis.

In recent years, several pediatric studies have been completed using micafungin. A phase I single-dose, multi-center, open-labeled neonatal study evaluated three dosages (0.75mg/kg/day, 1.5mg/kg/day, and 3mg/kg/day) in two infant groups (weighing 500-1000g, and >1000g). The mean serum concentration of micafungin was lower in smaller infants and serum half-life was shorter and clearance was more rapid (29). A similar phase I pediatric (2-12 years old) febrile neutropenia study found that doses up to 4mg/kg/day were well tolerated without any side effect(30). In general, the terminal half-life of micafungin does not change appreciably in pediatric versus adult patients, and the volume distribution is only slightly higher in children(31). Micafungin in combination with second antifungal agent in pediatric and adult bone marrow transplant recipients with invasive aspergillosis revealed an overall complete or partial response of 39.1% of adult patients and 37.5% of pediatric patients(32). In an open-label non-competitive study of new or refractory candidemia including 15.1% pediatric patients, the overall complete or partial response was 85.1% in adult patients and 72.2% in pediatric patients(33). There is no accepted dosage schedule of micafungin in pediatric patients available yet.

The pharmacokinetics of anidulafungin showed approximately six-fold lower mean peak concentration in plasma, and two-fold lower AUC values compared with values for similar doses of caspofungin and micafungin. Results of a multicenter, ascending-dosage study of trial of anidulafungin in neutropenic pediatric patients have recently been published. Patients were divided into two age cohorts (2 to 11 years and 12 to 17 years) and were enrolled into sequential groups to receive 0.75 or 1.5 mg/kg of body weight/day. The drug was well tolerated in pediatric patients with only mild to moderate adverse effects. It was found that the drug can be dosed based on body weight and pediatric patients receiving 0.75mg/kg/day or 1.5mg/kg/day were found to have pharmacokinetics similar to adult patients receiving 50 or 100mg/day respectively (34). This is in contrast to caspofungin, which requires a dosage adjustment based upon a calculation of body surface area rather than a weight-adjusted scale.

Aminocandin (HMR3270). This is a semi-synthetic fermentation product from *Aspergillus sydowi,* and is similar in structure to the other members of the echinocandin class. It has demonstrated potent activity against both *Candida* and *Aspergillus* spp. (including itraconazole resistant strains). MIC results for molds are however species specific being very low for *Aspergillus fumigatus* (MIC_{90} 0.5 mg/L) but not active against *Scedosporium* spp., *Fusarium* spp. and the *Zygomycetes*(35).

CONCLUSION

The advances in antifungal therapy have been impressive in the last few years and new therapeutic strategies have had significant impact on the mortality of IFI (36). This has great implications in

the field of pediatric antifungal therapy, especially since the number of children receiving chemotherapy and HSCT continue to increase. However there is need for more clinical trials to study the use of these new agents and their efficacy in different clinical conditions, specifically in the pediatric age group.

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