

## Review Article

## Advances in Therapy of Invasive Mycoses

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**ABSTRACT**

**Introduction:** Concurrent with the advances in medical and transplant technologies, and emergence of HIV/AIDS as a major public health problem, the number and type of immunosuppressed individuals has increased. This has resulted in an increasing incidence of opportunistic mycoses. To meet this challenge, the field of antifungal therapeutics has made unprecedented progress in recent years. In this article, we have reviewed some of the major advances that have taken place in this area.

**Methods:** MEDLINE database was searched using the following key words: amphotericin B, lipid formulations of amphotericin B, triazoles, voriconazole, posaconazole, echinocandins, caspofungin, micafungin, anidulafungin, clinical trials and combination therapy since the year 2000.

**Results:** Based on the information retrieved through the

search, the following inferences could be drawn: (i) voriconazole is as effective as amphotericin B, followed by fluconazole for the treatment of candidemia in non-neutropenic patients with fewer side effects, (ii) caspofungin is better tolerated and is as effective as amphotericin B in treating invasive candidiasis and thus may be preferred in patients with renal impairment, (iii) caspofungin or amphotericin B is still a preferred therapy for candidemia in neutropenic and critically ill patients, and (iv) voriconazole has replaced amphotericin B in some centers as the drug of choice for treating invasive aspergillosis including patients with CNS involvement.

**Conclusions:** With the introduction of new antifungal agents, the options for treating invasive mycoses have considerably expanded with improved therapeutic outcomes. Attention is now being focused to evaluate efficacy of these agents in combination therapy.

**KEYWORDS:** anidulafungin, caspofungin, lipid formulations of amphotericin B, micafungin, posaconazole, voriconazole

**INTRODUCTION**

Invasive mycoses pose a major diagnostic and therapeutic challenge. They have emerged as important causes of morbidity and mortality among immunocompromised patients, particularly infecting those who have undergone bone marrow or organ transplantation, or become infected with acquired immunodeficiency syndrome<sup>[1,2]</sup>. Absence of specific signs and symptoms and limitations of specificity and sensitivity of the currently available diagnostic tests make early diagnosis difficult, thus delaying timely initiation of appropriate antifungal therapy. Together with the progress made in medical and transplant technologies, the number and diversity of immunosuppressed individuals has increased, and so are the types of fungal pathogens infecting them. In fact, some of the mould infections that infect the immunosuppressed population today were not even described as pathogens 20 or 30 years ago<sup>[3,4]</sup>. In this context, Professor Howard A. Buechner<sup>[5]</sup>, as early as 1971, wrote that “—the role of the fungus is emerging with frightening rapidity and the

physician who formerly had merely a nodding acquaintance with these disorders will soon find themselves compelled to take a more active role in their early detection and proper treatment”. To meet these growing complications of modern medicine, the field of antifungal drug research has made considerable progress. Fluconazole and itraconazole, introduced in 1980s, were the first alternatives to amphotericin B with activity against *Candida* and *Aspergillus* species, respectively<sup>[6, 7]</sup>. Fluconazole continues to be a first line therapy option for invasive candidiasis in non-neutropenic patients, besides its well recognized prophylactic use in selected high-risk patients<sup>[7, 8]</sup>. While the role of itraconazole in the treatment of invasive candidiasis remains to be rationalized, it is being used as an alternative to amphotericin B for empirical treatment in persistently neutropenic cancer patients (excluding allogeneic transplant recipients) and in allergic bronchopulmonary aspergillosis patients to prevent *Aspergillus* colonization<sup>[6, 9]</sup>.

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The development of lipid formulations of amphotericin B, and more recently introduction of novel echinocandin derivatives (caspofungin, micafungin and anidulafungin) and modified triazole agents (voriconazole, posaconazole and ravuconazole) with expanded antifungal spectrum, are some of the milestones in antifungal drug development. These discoveries have opened-up new therapeutic options<sup>[10]</sup>. The purpose of this article is to review most recent information available on the treatment of invasive fungal infections.

## METHOD

A MEDLINE search for English language database was made using the following key words: lipid formulations of amphotericin B, triazoles, voriconazole, posaconazole, echinocandins, caspofungin, micafungin, anidulafungin, clinical trials and combination therapy since the year 2000 onward. The information so retrieved was analyzed and condensed to write this review.

## LITERATURE REVIEW

### Amphotericin B and its lipid formulations

Amphotericin B deoxycholate was licensed in 1959 on the basis of open-label, non-comparative data for the treatment of invasive, life-threatening fungal infections. Despite severe *in vivo* toxicity of the drug, it has been used extensively with or without 5-fluorocytosine for treatment of invasive mycoses<sup>[11,12]</sup>. In recent studies it has been documented that dose related toxicity of amphotericin B limits its overall efficacy as an antifungal agent<sup>[13,14]</sup>. In one such study, 30% patients receiving amphotericin B developed nephrotoxicity, which was associated with a six-fold increase in mortality and substantially increased hospital cost<sup>[14]</sup>. This necessitated the need to develop lipid formulations of amphotericin B which are markedly less nephrotoxic but possess comparable therapeutic efficacy as the parent compound. These lipid formulations have been approved by FDA for treating patients with invasive mycoses who are refractory or intolerant to conventional amphotericin B and also provide a safer option for empirical therapy of presumed fungal infections in febrile neutropenic patients. Currently three lipid formulations, namely amphotericin B colloidal dispersion (Amphocil / Amphotec), amphotericin B lipid complex (Abelcet) and liposomal amphotericin B (AmBisome) are commercially available for therapeutic use<sup>[15]</sup>. While the optimal dosage of lipid formulations are yet to be defined, high acquisition cost and potential toxicity associated with larger doses have restricted their use<sup>[16]</sup>.

## AZOLES

Azole antifungals inhibit the cytochrome P 450 3A dependent enzyme 14 [alpha]-demethylase, a critical enzyme in the ergosterol biosynthesis. This leads to the depletion of ergosterol in the cell membrane and accumulation of toxic intermediate sterols causing increased membrane permeability and inhibition of fungal growth. Modification of existing triazoles has led to obtaining agents with increased spectrum and activity against moulds<sup>[17,18]</sup>.

## VORICONAZOLE

Voriconazole (V-Fend, Pfizer Ltd., UK) is an extended spectrum triazole that is approved for therapy of invasive aspergillosis, *Fusarium* spp and *Scedosporium* spp. and more recently for patients with *Candida* esophagitis and candidemia including infections with *C. glabrata* and *C. krusei*. Voriconazole is more potent than fluconazole against *Candida* spp and it is active against *Coccidioides immitis*, *Histoplasma capsulatum* and *Blastomyces dermatitidis*, as well as emerging fungi<sup>[19,20]</sup>. It has become the recommended primary therapy for invasive aspergillosis including central nervous system infection and showed improved outcomes in several clinical trials (Table 1)<sup>[21-25]</sup>. In a randomized trial, voriconazole therapy led to better responses and improved survival and resulted in fewer severe side effects than the amphotericin B<sup>[22]</sup>. In another randomized, multicenter trial, voriconazole appeared to be as efficacious as liposomal amphotericin B for the empiric treatment of fungal infections in patients with febrile neutropenia. Breakthrough infections were less frequent in voriconazole recipients than liposomal amphotericin B (1.9% versus 5.0%,  $p = 0.02$ )<sup>[24]</sup>. Voriconazole has also been evaluated for its efficacy in invasive candidiasis and the results of three clinical trials are summarized in Table 2<sup>[21,26,27]</sup>. The drug also showed promise as a salvage agent for the treatment of invasive candidiasis, even in the setting of previous azole therapy and infection due to *C. krusei* which is intrinsically resistant to fluconazole<sup>[26]</sup>. Voriconazole cleared blood cultures as quickly as amphotericin B / fluconazole (median time to negative blood culture was 2.0 days) in non-neutropenic patients<sup>[27]</sup>. Voriconazole has little activity against zycomycetes<sup>[28]</sup>. Cases of zygomycosis have been reported in the setting of voriconazole prophylaxis<sup>[29]</sup>.

Voriconazole is available in oral and intravenous formulations. Its oral bioavailability is 96%. It is distributed into brain, lung, kidney, liver and spleen and metabolizes via hepatic CYP isoenzymes. Drug-drug interactions are common necessitating careful monitoring of serum levels of interacting drugs. The major side effects of the drug

**Table 1:** Efficacy of voriconazole for patients with invasive aspergillosis

Study	Study design	No. of subjects	Primary antifungal	Duration	Comparator	Results	Comments
Perfect et al. <sup>[21]</sup>	Salvage	142	Vori, 6 mg/kg 2 times daily iv on day 1 (loading dosage), followed by 4 mg/kg 2 times daily iv for atleast 3 days, then switched to 200 mg 2 times daily po; or Vori, 400mg 2 times po (loading dosage), followed by 200 mg 2 times daily po	iv group, 1 -138 days (median duration, 18 days); for po group, 1 - 326 days (median duration, 69 days)	None	Clinical response rate, 44%	
Herbrecht et al. <sup>[22]</sup>	Multicenter, randomized	277	Vori, 6, mg/kg 2 times daily iv (loading dosage), 4 mg/kg 2 times daily (maintenance dosage)	2-84 days (mean duration, 77 days)	AmB, 1-1.5 mg/kg iv once daily for 1 - 84 days (median duration, 10 days)	Rate of successful outcome, 52.8% for Vori group and 31.6% for AmB group (difference, 21.2%, 95% CI, 10.4% - 32.9%); survival rate: 70.8% vs. 57.9%, respectively (95% CI, 40%-88%; p = .02)	Vori group had fewer adverse events (343 vs. 432; p =.02) and fewer severe adverse events (26 vs. 45; p=.008); the duration of treatment was much longer for the Vori group
Denning et al. <sup>[23]</sup>	Multicenter, open-label, noncomparative salvage	116	Vori, 6, mg/kg 2 times daily iv (loading dosage), 3 mg/kg 2 times daily po (maintenance dosage); and then 200 mg 2 times per day po	54 - 250 days (median duration, 133 days); iv group, 1 -40 days; po group, 2 - 219 days	None	Clinical response rate, 48% (only 14% of subjects had complete response)	Vori as effective as AmB followed by Flu; Vori was more effective against <i>Candidatropicalis</i> (32% vs. 6% success rate) (p = .032)

Abbreviations: Vori- Voriconazole, AmB- Amphotericin, Flu - Fluconazole, po = per oral

are transient visual disturbance (about 30%), rash and hepatitis.

**Indications:** Invasive aspergillosis, esophageal candidiasis, and refractory infections caused by *Scedosporium apiospermum* and *Fusarium* species.

**Dosage:** Intravenous route: adults: 6 mg/kg q12h X 1 day, then 4 mg/kg q12h; children: 6 mg/kg q12h X 1day, then 4-5 mg/kg q12 h; infants: 8 mg/kg q12h X 1 day, then 6 mg/kg q12h. Oral route: adult and children > 40 kg: 400 mg q12h X 1 day, then 200-300 mg q12h; < 40kg: 200 mg q12h X 1 day, then 100-150 mg q12h. (Note: more pediatric studies are needed to determine optimal doses).

## POSACONAZOLE

Posaconazole (Noxafil, Schering-Plough Inc., NJ) was approved in Europe in October, 2005 for treating invasive fungal infections in adult patients who had refractory disease or who were intolerant of certain commonly used antifungal agents. It is an oral second generation triazole with broad-spectrum antifungal activity<sup>[30,31]</sup>. A primary advantage over voriconazole is its activity against zygomycetes<sup>[31]</sup>. It has been shown to retain activity against many *Candida* and *Aspergillus* isolates that exhibited resistance to voriconazole, fluconazole,

and amphotericin B, although instances of cross-resistance in some *Candida* isolates have been reported<sup>[32]</sup>. Recently, posaconazole has been used as salvage therapy in 24 patients with active zygomycosis. Eleven out of them had CNS involvement<sup>[33]</sup>. The success rates were 79% in patients who were refractory to the standard drug. It has also been found useful as salvage treatment for invasive *Fusarium* infection with success outcome of 48%<sup>[34]</sup>. In a well-designed multi-center trial, Vaquez et al<sup>[35]</sup> demonstrated that posaconazole was as efficacious as fluconazole in the treatment of oropharyngeal candidiasis in HIV-infected patients. It was more effective in sustaining clinical success after treatment was stopped. In September, 2006, FDA has approved oral suspension of posaconazole for prophylaxis against invasive *Aspergillus* and *Candida* infections in severely immunosuppressed patients > 12 years of age. This is the first antifungal agent ever approved by FDA for the prevention of invasive aspergillosis. The drug appears safe and well tolerated, even when administered for long periods. Pharma-cokinetics of posaconazole in children are unknown. Posaconazole is extensively distributed into tissues and metabolized through liver. Inhibition of CYP3A4 but not other CYP450 enzymes by posaconazole may cause less drug interactions. It might be an appropriate alternative

**Table 2:** Clinical trials investigating the efficacy of voriconazole in patient with invasive candidiasis

Study	Study Design	No. of Subjects	Primary Antifungal	Duration	Comparator	Results	Comments
Perfect <i>et al.</i> <sup>[54]</sup>	Salvage	87	Vori, 6 mg/kg 2 times daily iv on day 1 (loading dosage), 4 mg/kg 2 times daily iv (maintenance dosage); after 3 days, patient can switch to 200 mg 2 times daily po Vori, 4-20 mg/kg per day	For iv therapy, 1-138 days (median duration, 18 days); for po therapy, 1-326 days (median duration, 69 days) 1-314 days (mean duration, 36 days; median duration, 60 days)	None	Clinical response rate, 55%	
Ostrosky-zeichner <i>et al.</i> <sup>[55]</sup>	Salvage	52	Vori, 6 mg/kg 2 times daily iv (loading dosage), 3 mg/kg 2 times daily iv (maintenance dosage); after 3 days, patient can switch to 200 mg 2 times daily po	8 weeks	None	Clinical response rate, 56% overall, 44% for patients with <i>C. albicans</i> infection, and 70% for patients with <i>Candida krusei</i> infection	Vori as effective as AmB followed by Flu; Vori was more effective against <i>Candida tropicalis</i> (32% vs. 6% success rate) ( $P = .032$ )
Kulberg <i>et al.</i> <sup>[56]</sup>	Multicenter, randomized	370	Vori, 6 mg/kg 2 times daily iv (loading dosage), 3 mg/kg 2 times daily iv (maintenance dosage); after 3 days, patient can switch to 200 mg 2 times daily po	8 weeks	AmB, 0.7-1 mg/kg per day iv for 3-7 days, then Flu, 400 mg per day	Successful outcome in 41% of patients in both arms.	

Abbreviations: Vori - Voriconazole, AmB- Amphotericin B, po = per oral, flu = fluconazole

**Table 3:** Clinical trials investigating the efficacy of echinocandins in patients with invasive candidiasis and candidemia

Study	Study design	No. of subjects	Primary antifungal	Duration	Comparator	Results	Comments
Mora-Duarte <i>et al.</i> <sup>[57]</sup>	Prospective, randomized	224	Cas, 70 mg iv loading dose, then 50 mg/day iv	1-28 days (mean duration, 12.1 days; median duration, 11 days)	AmB, 0.6-1 mg/kg per day iv for 1-28 days (mean duration, 11.7 days; median duration, 10.0 days)	Clinical response rate, 73.4%(Cas) vs. 61.7% (AmB); 95% CI -0.7 to 26.0; after adjustment for neutropenic status and the APACHE II score, the difference in the proportion of patients with a favourable response was 12.7% (95.6% CI, -0.7 to 26.0; $p=0.19$ )	There were significantly fewer drug-related adverse events in the Cas group than in the AmB group; laboratory abnormalities occurred in 24.3% vs. 54.0% of subjects ( $p=0.02$ ); withdrawal of therapy because of adverse effect occurred in 2.6% vs. 23.2% ( $p=0.003$ )
Ostrosky-zeichner <i>et al.</i> <sup>[57]</sup>	Multicenter, open label	126	Mica, 50-200 mg per day iv (adults)	5-42 days	None	Clinical response rate, 84.5%; patients who received 75-150 mg/day had higher success rate Clinical response rate, 85.7%	Best results with <i>Candida glabrata</i> infection, study included 20 pediatric patients; 29 patients also received other antifungals
Kohno <i>et al.</i> <sup>[58]</sup>	Multicenter, open label, dose comparison	7	Mica, 25-75mg per day iv	7-29 days (mean, duration, 16 days)	None	Clinical response rate, 85.7%	
Krause <i>et al.</i> <sup>[54]</sup>	Open-label, dose variable	83	Ani, 50mg, 75mg, or 100 mg per day iv	14-42 days	None	Clinical response rate for patients receiving Ani at 50 mg, 75 mg, and 100 mg per day was 84%, 90%, and 89%, respectively; at follow-up 2 week later, success rates were 72%, 85%, and 89%, respectively	No statistical significance between different doses, however trend toward higher success rates in the groups of 100 and 150 mg, compared to the 50 mg group

Abbreviations: Cas- Caspofungin, Mica - Micafungin, Ani- Anidulafungin, AmB- Amphotericin

to amphotericin B for patients with impaired renal function. It is not removed by haemodialysis. Although cerebrospinal penetration is poor, reports of therapeutic efficacy in CNS mycoses have appeared<sup>[36,37]</sup>.

**Indications:** Under FDA review for oral treatment of aspergillosis, zygomycosis and fusariosis in patients refractory or intolerant to other therapies. It has also been used in *Fusarium* keratitis. Recently has been approved as prophylactic agent for invasive *Aspergillus* and *Candida* infections in severely immunosuppressed patients, such as hematopoietic stem cell transplant recipients with graft-versus-host disease and those with prolonged neutropenia.

**Dosage:** Oral route: adults: 200 mg q6h or 400 mg q12h. It should be administered after meal. Children doses are not yet established.

### RAVUCONAZOLE AND ALBACONAZOLE

Ravuconazole (Bristol-Myers, Squibb Inc, CT, USA) exhibits potent *in vitro* activity against *Candida* spp., *Aspergillus* spp., *C. neoformans*, *H. capsulatum* and *C. immitis*. Cross-resistance between fluconazole and ravuconazole was observed with *C. glabrata* and is variable among other *Candida* spp. Ravuconazole is less active than voriconazole against *Fusarium*, *Scedosporium* and *Trichosporon* spp., and it has no activity against *Rhizopus* or *Mucor* spp. Immunosuppressed animal models have confirmed efficacy against *Candida* spp., *Aspergillus* spp., and *H. capsulatum*<sup>[38,39]</sup>. Metabolism is primarily hepatic. Ravuconazole is well-tolerated in healthy adults. Drug interactions are uncommon. Ravuconazole and albaconazole are undergoing early clinical evaluation and their future is uncertain. For all newer triazoles, concerns about emerging drug-resistant fungi and the incidence and management of breakthrough infections will dictate their role in antifungal prophylaxis and treatment.

### ECHINOCANDINS

The echinocandins are a novel class of agents that irreversibly inhibit [ $\beta$ ]-1, 3-D-glucan synthase, the enzyme complex that forms glucan polymers in the fungal cell wall, but is absent in mammalian cells. They are active against *Candida*, *Aspergillus*, but not against *Cryptococcus*, zygomycetes and some other moulds. Interestingly, echinocandins are fungicidal against yeasts and fungistatic against moulds. Their limited toxicity and minimal drug-drug interactions make them an attractive option for treatment of invasive mycoses. Currently, these intravenous agents include caspofungin (Cancidas, Merck Research

Laboratories, NJ, USA), micafungin (Mycamine, Fujisawa Healthcare Inc. Japan), and anidulafungin (Eraxis, Pfizer Inc.).

### CASPOFUNGIN

Caspofungin was the first agent that became available for therapeutic use in the echinocandin class<sup>[40]</sup>. It is fungicidal *in vitro* against *Candida* spp. including azole-resistant species. Minimal inhibitory concentrations (MIC) are higher for *Candida parapsilosis* and *Candida guilliermondii*. Fungistatic activity has been demonstrated against *Aspergillus* spp. Caspofungin also has activity against *C. immitis*, *H. capsulatum* and *B. dermatitidis*. However, *Cryptococcus neoformans*, zygomycetes, *Fusarium* spp., *Scedosporium* spp. and *Trichosporon* spp. are relatively resistant. Caspofungin has been approved by FDA for adult patients refractory to or intolerant of standard antifungal agents for invasive aspergillosis and for primary therapy for *Candida* infections as well as empirical therapy for fever and neutropenia<sup>[40,41]</sup>. In a randomized, double-blind multinational trial caspofungin was compared with liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia<sup>[41]</sup>. Caspofungin was found to be as effective as liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. It has also been found effective and very well tolerated alternative for salvage treatment of invasive aspergillosis<sup>[42]</sup>. Recently, caspofungin has been recommended as a first line treatment option for candidemia<sup>[8]</sup>. It was found to be at least as effective as amphotericin B for the treatment of candidiasis and candidemia (Table 3)<sup>[43]</sup>. In children, caspofungin was effective and well-tolerated for persistent and progressive candidiasis in 10 neonates (9 pre-term). They were treated with a dose of 1 mg/kg for the first two days and 2 mg/kg thereafter. Nine out of 10 survived, but no pharmacokinetic data were obtained<sup>[44]</sup>. Walsh *et al*<sup>[45]</sup> studied pharmacokinetics, safety and tolerability of caspofungin in children with neutropenia using weight-based regimen and body surface area regimen. The drug was generally well tolerated and no serious side effects were observed. A dose of 1 mg/kg was found inadequate, and doses of 50 mg/m<sup>2</sup>/day were necessary to achieve appropriate drug levels. Although caspofungin is neither a substrate for nor an inhibitor of CYP450, some drug-drug interactions have been observed with cyclosporin, phenytoin, efavirenz, rifampin and other drugs. It appears to have low toxicity with few adverse effects, such as nausea, fever and flushing.

**Indications:** *Candida* infections: intra-abdominal abscesses, peritonitis and pleural space infections, candidemia, esophageal candidiasis; invasive aspergillosis in patients refractory or intolerant to other antifungal therapies; empiric therapy in febrile neutropenic patients.

**Dosage:** Intravenous: adults: load 70 mg, then 50 mg daily; children 50 mg/m<sup>2</sup> daily; neonates: 1 mg/kg daily X 2 doses then 2 mg/kg daily. (Note: more pediatric studies are required to determine optimal doses).

### MICAFUNGIN

Like caspofungin, micafungin exhibits identical spectrum of *in vitro* activity against *C. albicans*, non-*albicans* species and *Aspergillus* species but not against zygomycetes and *C. neoformans*. It has fewer drug-drug interactions and relatively less expensive than caspofungin<sup>[46]</sup>. It is efficacious against invasive candidiasis and aspergillosis. Although soluble in water, it has poor oral bioavailability. Its pharmacokinetics is similar in adults and children and metabolism is hepatic. It received FDA approval in March 2005 for esophageal candidiasis and for *Candida* infection prophylaxis in hematopoietic stem cell transplant recipients. Two clinical trials have been reported for the treatment of invasive candidiasis with micafungin (Table 3)<sup>[47,48]</sup>. In the first non-randomized, non-comparative study, micafungin was found safe and effective in the treatment of refractory and new cases of candidemia including those caused by *C. glabrata* with an overall success rate (complete and partial) of 83%<sup>[47]</sup>. In the second multicenter, open-label study, the clinical response for candidemia was 100% and for esophageal candidiasis 71%<sup>[48]</sup>. Recently, de Wet *et al*<sup>[49]</sup> conducted a randomized, double blind study comparing intravenous micafungin (150 mg/d) with intravenous fluconazole (200 mg/d) in the treatment of esophageal candidiasis. Micafungin was found to be as efficacious as intravenous fluconazole. In a randomized, double blind trial that included adults and children with neutropenia, micafungin compared favorably with fluconazole in preventing invasive fungal infections after hemopoietic stem cell transplantation (80% versus 73.5% respectively;  $p = 0.03$ )<sup>[50]</sup>.

**Indications:** Esophageal candidiasis, prophylaxis of *Candida* infections in patients undergoing stem cell transplantation.

**Dosage:** Intravenous (Mycamine): Adults: *Candida* infection prophylaxis in hematopoietic stem cell transplant patients: 50 mg/day over 1 h;

esophageal candidiasis: 150 mg/day over 1 h. Children: 3 mg/kg (more pediatric studies are needed to determine optimal dose).

### ANIDULAFUNGIN

Anidulafungin (Eraxis) received FDA approval for treating candidemia in February 2006. The drug is active *in vitro* against most *Candida* spp with fungicidal activity, but like caspofungin, *C. parapsilosis* and *C. guilliermondii* are more resistant to this agent<sup>[51]</sup>. It is fungistatic against *Aspergillus* spp. and not active against *C. neoformans* or *B. dermatitidis*<sup>[52]</sup>. Although clinical experience is limited, anidulafungin is comparable to fluconazole in esophageal candidiasis<sup>[53]</sup>. At the end of randomized, double-blind study of 601 patients with endoscopically and microbiologically documented esophageal candidiasis, rate of endoscopic success for anidulafungin was 97.2% as compared to 98.8% in fluconazole group. This was found statistically non-inferior to that of fluconazole<sup>[53]</sup>. In a phase 2, randomized, dose-ranging study evaluating the safety and efficacy of anidulafungin in 123 invasive candidiasis and candidemia patients, at the end of treatment, the success rates were 84, 90, and 89% in the 50, 75 and 100 mg groups, respectively (Table 3)<sup>[54]</sup>.

**Indications:** Candidemia, esophageal candidiasis, abdominal abscesses, and peritonitis.

**Dosage:** Intravenous: Candidemia: adult: load 200 mg day 1, followed by a 100 mg daily dose, to continue for at least 14 days after last positive culture; esophageal candidiasis: load 100 mg day 1, followed by a 50 mg daily dose, continue for at least 14 days and for at least seven days following resolution of symptoms. Doses in children are not yet established.

### COMBINATION THERAPY

With the availability of voriconazole, lipid formulations of amphotericin B, and echinocandins, the possibilities of using combination antifungal agents have greatly increased. The combination of amphotericin B and 5-Flucytosine is well established for the treatment of cryptococcal meningitis<sup>[12]</sup>. Initial combination studies using azole antifungals and polyenes in animal models yielded synergistic, additive, indifferent or even antagonistic results<sup>[55]</sup>. A recently completed randomized, blinded clinical trial in candidemia patients suggested a trend towards improved outcomes among non-neutropenic patients receiving amphotericin B (0.6-0.7 mg/kg) and fluconazole (800 mg/day) versus fluconazole (800 mg/day) alone<sup>[56,57]</sup>. Results of this study

demonstrated a 69% success in favor of combination therapy ( $p = 0.043$ ) over monotherapy (56%). However, success rates utilizing a Kaplan-Meier time to failure analysis was not significantly different ( $p = 0.08$ ). The usefulness of combination of fluconazole with an echinocandin in *Candida* infections remains unclear.

Currently, invasive aspergillosis is the focus of combination therapy in experimental and clinical studies<sup>[58,59]</sup>. In a prospective, multicenter study comprising patients of proven and probable invasive aspergillosis, voriconazole and caspogungin combination therapy was considered preferable to lipid formulation of amphotericin B in a subset of organ transplant recipients, such as those with renal failure or *A. fumigatus* infection<sup>[60]</sup>.

Adjunctive immunotherapies and immune-reconstitution with a view to restoring or enhancing host defenses are other important strategies for the successful management of fungal infection. Reduction of immunosuppression level, where feasible, administration of recombinant cytokines and donor elicited granulocyte transfusion for neutropenic patients have been used with encouraging results in experimental and clinical studies<sup>[61]</sup>. Recently, there have been studies of adjunctive interferon and antibody therapy for cryptococcal meningitis<sup>[62]</sup>. More recently, Pahl *et al*<sup>[63]</sup> reported that an antibody fragment of heat shock protein 90 (Mycograb; manufactured by NeuTec Pharma, Manchester, UK) is effective in the treatment of human candidiasis. In a double-blind, randomized study involving 117 culture confirmed patients, a complete overall response was obtained in 48% patients in the amphotericin B group as compared to 84% in amphotericin B and Mycograb combination group, reducing *Candida* attributable mortality to > four-fold. This molecule has direct antifungal activity *in vitro* against *C. albicans* and *C. neoformans* through an unknown mechanism. This is a notable advance, giving a new direction to the field of antimicrobial therapy.

## CONCLUSION

Clinical mycology has entered into an era of unprecedented therapeutic development. Options for treatment of invasive fungal infections have increased with new agents that exhibit improved tolerability and increased range of activity. Now attention is being focused on examining the efficacy of these agents in combination with older or newer agents in randomized, controlled clinical studies. It is hoped that with the availability of new therapeutic alternatives, it will be possible to develop effective strategies to prevent and treat these life-threatening infections in the near future.

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