



New Antifungal Agents

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Amphotericin B deoxycholate has been the standard therapy for critically ill patients with invasive fungal disease. However, despite its acceptance in the past as the “gold standard” of therapy, outcomes in patients treated with amphotericin B deoxycholate can be extremely poor. The toxicity and lack of efficacy of amphotericin B is particularly striking in patients with severe underlying immune defects (such as those undergoing bone marrow transplantation) and patients with widely disseminated infection. New therapeutic agents have been introduced to fill these significant, unmet medical needs. Lipid formulations of amphotericin B the newer azoles and new classes of antifungal agents such as the echinocandins, which have activity against a broad spectrum of pathogens and offer the potential of significantly decreased toxicity. While new therapies such as the lipid formulations of amphotericin B have resulted in improved outcome in some patients, these agents have a extremely high cost of acquisition, and optimal dosing is unfortunately not established. The lipid formulations of amphotericin B have been most studied for patients with fever and neutropenia with no large-scale trials evaluating their efficacy in a randomized, prospective manner. Thus, they remain approved for use as salvage agents for invasive mycoses. Newer triazole antifungals (such as voriconazole, and posaconazole) have improved activity against resistant yeasts and moulds, particularly *Aspergillus*, which they were developed to target. A recent study compared voriconazole with AmB followed by other licensed therapy and found significantly more responses and improved survival in patients with acute invasive aspergillosis receiving voriconazole. These results extended to high risk patients and those with extensive infection so that voriconazole is now recommended as primary therapy for most patients with invasive aspergillosis. Notable, these azole antifungals induce the cytochrome P450 enzyme systems, so the potential exists for significant drug interactions, including immunosuppressive agents such as cyclosporine and tacrolimus. When voriconazole is administered with these agents, specific dose reductions from 50% to 30% are recommended for cyclosporine and tacrolimus, respectively. The major toxicities of voriconazole include a specific transient visual toxicities have occurred in approximately 30% of patients treated with voriconazole, although this adverse event does not appear to be associated with long-term toxicity and rarely leads to drug discontinuation. In addition, liver function abnormalities occur in 10-15%, gastrointestinal intolerance and rash are less common. Posaconazole is undergoing regulatory review but is limited by the fact it is only available in an oral suspension and has a saturable absorption mechanism. However, good efficacy was seen in a salvage therapy trial particularly against *Aspergillus* and against agents of Zygomycosis, for which it is the only azole with appreciable activity.

Finally, a new class of antifungal drugs, the echinocandins (including caspofungin, micafungin and

anidulafungin), has been introduced; these drugs are targeted to inhibit the fungal cell wall. These agents have fungicidal activity against *Candida* including species other than *C. albicans*. Caspofungin was as effective and significantly less toxic than amphotericin in treating invasive candidiasis, including candidemia. These agents also have been shown to have activity as salvage therapy for aspergillosis. While their specific role in treating invasive aspergillosis has yet to be defined, particularly encouraging work in animal models suggests synergistic activity when combined with the newer azoles, such as voriconazole, in sterilizing tissues. The introduction of new antifungals also makes it possible to consider combination therapy in order to improve the outcome in these critically ill patients, and clinical trials evaluating potential combinations are in progress. Prompt recognition of fungal infection combined with intensive antifungal therapy is needed for successful therapy of patients with invasive fungal infections.

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