



Recent Advances in the Management of Invasive Aspergillosis

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Invasive aspergillosis is a major cause of morbidity and mortality in immunosuppressed patients. Recent advances in early diagnosis as well as new therapeutic options may offer improved outcomes for this often lethal infection. Early diagnosis and therapy is critical to a successful outcome but a definitive diagnosis remains difficult to establish. Recent studies have demonstrated the utility of early detection of invasive pulmonary aspergillosis with CT scan of the chest with a “halo” sign in high risk patients that is highly suggestive of invasive mould infection. Non-culture based methods, including detection of galactomannan, glucan, or PCR have also been developed. Recent clinical studies show the potential advantage of these techniques but their optimal use remains under investigation.

Amphotericin B has been the standard therapy for invasive aspergillosis, but it is toxic and may not be successful in severely immunosuppressed patients. Overall mortality rates of invasive aspergillosis are approximately 60% but even higher rates of mortality of 80-90% occur in severely immunosuppressed patients such as those undergoing bone marrow transplantation or those with extensive infection including disseminated or central nervous system. Similarly, in a study of 595 patients with invasive aspergillosis favorable outcomes occurred in less than 25% of severely immunosuppressed patients who received amphotericin B therapy and death due to or with *Aspergillus* occurred in 66%. Lipid formulations of amphotericin B offer the advantage of reduced toxicity as compared with amphotericin B deoxycholate, but the optimal dosage and/or use of these compounds is not known. However, it is clear that breakthrough infections occur more commonly with lower doses of lipid amphotericin B so that higher doses of 5 mg/kg/d or more are frequently recommended for patients with extensive infection such as involving the central nervous system or with progressive infection. Another approach has been the development of the newer azoles, such as voriconazole or posaconazole, which have been targeted specifically to *Aspergillus*. These compounds offer the potential advantage of fungicidal activity against *Aspergillus* and -for voriconazole- both intravenous as well as highly bioavailable oral therapy. A recent global trial for the primary therapy of invasive aspergillosis showed the efficacy of voriconazole as compared with amphotericin B followed by other licensed therapy with both overall better outcomes and importantly improved survival. In this study overall favorable outcomes at 12 weeks occurred in 53% of those in the voriconazole arm as compared with 32% of those randomized to receive amphotericin B. Importantly those favorable results were seen even in the subgroups of patients with highest risk of mortality including those patients undergoing hematopoietic stem cell transplantation and in those with extrapulmonary infection. Notably, voriconazole was less toxic than amphotericin B although temporary visual disturbances were reported in 44% of the patients. Another approach has been the use of echinocandins to inhibit the *Aspergillus* cell wall. This drug class offers the advantage of few drug interactions and very minimal toxicity. In addition, its intravenous administration allows use in critically ill patients potentially in combination with other compounds. In one study of patients with progressive infection refractory to multiple antifungal agents, caspofungin was demonstrated to have a favorable response in over 40% with minimal toxicity,

which led to its approval as salvage therapy for this disease. Another study showed the potential for the echinocandin micafungin to prevent invasive mycoses in high risk stem cell transplant patients including potentially the development of invasive aspergillosis. Additional studies are ongoing to determine the optimal dosing and strategy for use of these compounds in invasive aspergillosis. Finally, interest in combinations of antifungal agents such as the echinocandins with either amphotericin B lipid preparations or with the newer azoles have received extensive interest due to the unmet medical needs in this disease and the potential for attacking the organism at multiple sites of action. Preclinical studies have suggested the benefit of this approach, clinical evidence remains largely anecdotal although trials evaluating combination therapy are in progress. While the optimal use of these newer diagnostic tools and new antifungal agents remains to be determined, prompt recognition combined with intensive therapy with these new agents may finally improve the outcome of patients with invasive aspergillosis.

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