

New Strategy for Fungal Infections

Ben E. De Pauw

*Departments of Bloodtransfusion and Hematology, University Medical Center St Radboud Nijmegen,
HB Nijmegen, The Netherlands*

Abstract

An alarming increase in the number of invasive fungal infections has been observed. This is due to more aggressive bone marrow ablative regimens as well as to intensive use of corticosteroids and other immunosuppressants in numerous disorders. Principally amongst seriously ill non-cancer patients *Candida* has become a very prominent isolate. The attributable mortality from candidemia ranges from about 40% in patients with candidemia alone to over 90% for those who have acute tissue invasion with or without fungemia. Secondary bloodstream infections, which evolve from infectious foci such as wounds, carry a higher mortality than do primary, catheter-related infections. Many patients die within the first 48 hours after establishing the diagnosis. If applicable, a return of the granulocytes is an important prognostic feature, just as timely commencement of antifungal agents. Until recently fluconazole and amphotericin B were seen as a first line options for the treatment of disseminated candidosis. However, whereas more than 15 years ago, 80% infections by yeasts were due to *C. albicans*, in the 1990's non-albicans species have now become responsible for at least half of them, presumably related to the intensive prophylactic use of fluconazole. Development of the lipid formulations, with their improved therapeutic index raised hope for the future, but evidence on their general efficacy is still rather limited. Moreover, the results published on the treatment of non-albicans species have been rather disappointing up until now. On the other hand, the high expectations on the activity of the new candins against *Candida* species, including those resistant to the azoles and polyenes, appear justified. These compounds have a mechanism of action totally different from the traditional antifungals. Data on an improved outcome of candidemia if a central venous catheter is removed promptly are conflicting. To avoid untimely death, most specialists nowadays prescribe systemic empirical antifungal therapy to immunocompromised patients who fail to respond to adequate broad spectrum antibacterial treatment or show any sign of an invasive fungal infection. Given its broad spectrum of activity, amphotericin B at a dose of 1 mg/kg per day is still the drug of choice for such purposes; the lipid preparation should be reserved for patients who can not tolerate the conventional formulation. Fluconazole can be an option for cases with a low risk of invasive mould infections but its lack of activity against *Aspergillus* species is a major drawback. The other traditional antifungal agent registered for use for the treatment of invasive aspergillosis is itraconazole. A randomized study in neutropenic patients comparing itraconazole with amphotericin B hinted at equivalence but did not reach a statistical endpoint. Unfavorable drug interactions has led to failure in many a patient. The new azoles, voriconazole and posaconazole possess an expanded spectrum of activity. Voriconazole, which now has been filed for approval in many countries, was shown to be clearly superior to amphotericin B in the first-line treatment of invasive pulmonary aspergillosis. It also offers promise for the treatment of some hitherto notoriously difficult-to-treat infections by rare organisms such as *Scedosporium* and *Fusarium* species. A phase II trial assessing the activity of caspofungin in the treatment of refractory invasive aspergillosis provided results that warrant a further evaluation of its potency for rescue purposes and in an empirical setting, where both moulds and yeasts can be encountered.
