EDITORIAL
Optimising antifungal therapy for individual patients

The Australian guidelines by Slavin et al. published in this issue of the Internal Medicine Journal on p. 192 represent an addition to similar guidelines from Germany,2,3 the UK4 and the USA5 but have incorporated some of the important recent advances in clinical mycology. Here we reflect on the indications for the recently introduced antifungal drugs, the more contentious areas and the implications of the Australian guidelines for patients in a variety of clinical scenarios.

Amphotericin B deoxycholate (AmB) has, until recently, been the standard of care for invasive fungal infections (IFI) and associated syndromes such as persistent febrile neutropenia. It has a broad spectrum of activity, which includes Aspergillus spp. (except A. terreus), Candida spp., Fusarium spp. and the zygomycetes but not Trichosporon spp. or Scedosporium spp. AmB is associated with dose-limiting toxicity, the consequences of which are not trivial. AmB-induced renal failure is associated with increased morbidity and mortality, which has significant financial implications; this detracts from its tolerance of AmB, primarily based on the better characteristics levelled at the voriconazole study was that a more appropriate comparator may have been a lipid preparation of amphotericin B, primarily based on the better tolerability of these agents and, therefore, enabling a longer treatment course.12 The various lipid preparations are clearly associated with less toxicity than AmB but do the higher doses that the lipid preparations allow translate to superior efficacy? An analysis of salvage data as well as the only comparative trial13 suggests that conventional and lipid amphotericin B preparations cannot be distinguished in terms of efficacy in invasive aspergillosis. This probably reflects the attainment of maximal effect at relatively modest doses but whether this is true will undoubtedly be borne out in future trials examining much higher doses of the lipid preparations.

It is appropriate to recommend caspofungin for the treatment of invasive aspergillosis in circumstances where voriconazole or amphotericin are precluded or failing, although comparative data are not available at the present time. Caspofungin is the first of a class of new antifungal agents, the echinocandins, with a novel mode of action and a unique structure. The key characteristics of the echinocandins are i.v. use only, predictable kinetics allowing reliable once-a-day dosing, very low toxicity, paucity of significant drug interactions and activity against Candida spp. and Aspergillus spp.14 Caspofungin may be appropriate in the setting of significant renal impairment, hepatic dysfunction or in the circumstance of significant drug interactions.

Itraconazole is not mentioned in the guidelines for the primary treatment of invasive aspergillosis, which is probably appropriate, but it is indicated for salvage or long-term consolidation therapy. Itraconazole is devoid of some of the side-effects associated with voriconazole such as retinal flashes and a photosensitive rash. It also has a good long-term usage safety record. Itraconazole does not have the randomised trial database of voriconazole but it does have solid data to support its use in primary15 and salvage therapy16 for invasive aspergillosis, with response rates no worse than amphotericin B and a particular role in more chronic forms of aspergillosis. As with voriconazole, drug interactions are a significant issue and the limitations that apply to i.v. voriconazole also apply to the i.v. cyclohextrin formulation of itraconazole.

The term ‘empirical therapy’ implies the treatment of patients deemed to be at risk of IFI (usually persistently febrile neutropenia) who do not have any specific features to support its presence. Empiric therapy should be distinguished from prophylaxis on the one hand and pre-emptive therapy on the other, the latter referring to a patient at risk of IFI who possesses some surrogate clinical, radiological or laboratory marker to suggest the presence of IFI. Patients deemed to require pre-emptive treatment should be managed as if they have definite disease. In the absence of early and reliable surrogate markers of IFI, empirical therapy remains an important...
component of care and AmB continues to play an important role in this regard.

The problem with empirical therapy is the exposure of a large number of individuals, many without IFI, to potentially toxic and expensive drugs. In this setting a compromise must be struck between drug toxicity, cost and efficacy and this is reflected in the guidelines where a distinction is drawn between the dose of liposomal amphotericin B recommended for empirical therapy and that for proven or probable infection. As far as empirical therapy is concerned, the extent of drug toxicity is possibly just as important as the primary antifungal effect in determining the final outcome as the association between AmB-induced renal failure and mortality serves to remind us. It is likely that less toxic drugs such as caspofungin will assume an increasingly important role. There is evidence, currently in abstract form, to support at least the non-inferiority but superior tolerability of caspofungin compared with liposomal amphotericin B given at 3 mg/kg for the treatment of persistently febrile neutropenic patients.

Although the incidence of invasive candidiasis (a broader term than candidaemia) in a range of clinical settings continues to rise mortality is falling. This is probably the result of the widespread use of fluconazole prophylaxis and improvements in the management of associated risk factors such as the duration of neutropenia, the use of central venous catheters and total parenteral nutrition. Invasive candidiasis remains an important diagnostic entity in the critical care setting. There is a well-recognised deficiency of conventional microbiological techniques and although both molecular and serological tests have been widely advocated, they remain to be fully validated and integrated into routine practice.

AmB is clearly an effective drug for the treatment of invasive candidiasis but, once again, it is limited by its associated toxicity. There is good evidence from randomised trials that AmB and fluconazole are equally efficacious and the response rates to fluconazole range between 56% and 70%. Fluconazole has been extensively used because of its favourable side-effect profile and availability in both i.v. and oral formulations. We agree with the recommendation that an alternative drug to fluconazole should be chosen in circumstances of prior exposure or where local epidemiological factors make a fluconazole-resistant infection a significant concern. An alternative initial drug to fluconazole might also be indicated if the incorrect treatment could have serious consequences, such as for patients who are critically ill or neutropenic. It is always possible, of course, to switch back to fluconazole if deemed clinically appropriate or if there are subsequent microbiological data to support this course of action.

What then are the possible choices in circumstances where fluconazole is deemed inappropriate or has failed? For empirical therapy in the at-risk surgical or intensive care unit patient, toxicity and cost are the dominant concerns making the choice between amphotericin B, a lipid amphotericin preparation, caspofungin and voriconazole somewhat difficult but possibly favouring caspofungin. For a documented yeast infection, drug efficacy is the primary concern in which case there is good data to support the use of caspofungin and conventional amphotericin B. There are surprisingly few data to guide the appropriate dose of the lipid preparations but most clinicians tend to use 3–5 mg/kg. Similarly, voriconazole may be appropriate but its efficacy in comparison with fluconazole is uncertain as the trials are not completed.

Thus, the dominance of AmB as the unequivocal drug of choice for a range of IFI and related syndromes is drawing to an end. Voriconazole is superior for the treatment of invasive aspergillosis; caspofungin and the lipid amphotericin preparations are less toxic for empirical therapy in the persistently neutropenic patient and fluconazole and caspofungin are efficacious and non-toxic choices for the treatment of invasive candidiasis. There are a few remaining indications for AmB, which include the primary therapy of cryptococcal meningitis (preferably with flucytosine) and mucormycosis. Other indications include the treatment of patients in established renal failure who can be treated with conventional AmB rather than a lipid preparation, salvage therapy for refractory disease and the treatment of invasive aspergillosis where other agents are precluded.

The guidelines will require regular review. Two new azoles, ravinconazole and posaconazole, are in development as well as two echinocandins, micafungin and anidulafungin. There are important questions to answer regarding the role of combination therapy and the importance of the appropriate sequence of antifungal agents. Improving the precision of mycological diagnosis will minimise the need for unnecessary therapy. We believe the guidelines for the therapy of IFI will be a useful guide for clinicians and institutions to help decision making at a time when the introduction of new drugs poses difficult questions in terms of their relative efficacy, toxicity and cost.

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W. W. HOPE
and
D. W. DENNING
Education and Research Centre
Wythenshawe Hospital
Manchester, UK

REFERENCES
3 Link H, Blumenstengel K, Bohme A, Cornely O, Kellner O, Nowrousian MR et al. [Antimicrobial therapy for fever of unknown origin in neutropenia. Standard recommendations of the Work Group of Infections in Hematology and Oncology of the