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EDITORIAL

Optimising antifungal therapy for individual patients

The Australian guidelines by Slavin *et al.*[1] published in this issue of the *Internal Medicine Journal* on p. 192 represent an addition to similar guidelines from Germany,[2–5] the UK[6] and the USA[7] 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 low initial cost.[8,9] There is no doubt, however, that AmB remains central to the antifungal policies of many institutions and it is, therefore, timely to reflect on the indications for AmB in the context of an increasing antifungal armamentarium, which includes the azoles, echinocandins and lipid amphotericin preparations.

AmB was the standard of care for invasive aspergillosis until a recent trial clearly demonstrated the superiority of voriconazole.[10] This was the first therapeutic trial in any IFI that had shown an unequivocal mortality benefit. Voriconazole, a structural congener of fluconazole, was specifically designed to achieve anti-*Aspergillus* fungicidal activity. Unfortunately, however, voriconazole is less well tolerated than the parent compound in that it has a number of highly significant drug interactions, exhibits non-linear kinetics and may be associated with a greater degree of hepatic dysfunction. CYP polymorphisms of 2C19 in 5% of Caucasians and 10–20% of non-Indian Asians results in reduced drug metabolism and the prospect of higher than anticipated drug levels. The i.v. preparation is solubilised in a cyclodextrin excipient but this accumulates in renal failure, which limits the utility of the voriconazole in this setting.[11] Providing there are no contraindications, voriconazole should be considered the drug of choice for invasive aspergillosis but in certain situations careful consideration needs to be given to the individual risks and benefits.

What then is the role of the lipid preparations in the management of invasive aspergillosis? One of the criticisms 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 trial[13] 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 primary[15] and salvage therapy[16] 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. cyclodextrin 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.[9] 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.[17]

Although the incidence of invasive candidiasis (a broader term than candidaemia) in a range of clinical settings continues to rise[18] mortality is falling.[19,20] 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%.[21–23] 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[24] and conventional amphotericin B.[22] 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, ravuconazole 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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REFERENCES

1 Slavin MA, Szer J, Grigg AP, Roberts AW, Seymour JF, Sasadeusz J *et al.* Guidelines for the use of antifungal agents in the treatment of invasive *Candida* and mould infections. Intern Med J, 2004; 34: 192–200.

2 Cornely OA, Bohme A, Buchheidt D, Glasmacher A, Kahl C, Karthaus M *et al.* Prophylaxis of invasive fungal infections in patients with hematological malignancies and solid tumours – guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 2003; 82: S186–200.

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

German Association of Hematology and Oncology]. Dtsch Med Wochenschr 1999; 124: S3–8.
4 Maschmeyer G, Beinert T, Buchheidt D, Einsele H, Heussel CP, Kiehl M *et al.* Diagnosis and antimicrobial therapy of pulmonary infiltrates in febrile neutropenic patients – guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 2003; 82: S118–26.
5 Bohme A, Ruhnke M, Buchheidt D, Karthaus M, Einsele H, Guth S *et al.* Treatment of fungal infections in hematology and oncology – guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 2003; 82: S133–40.
6 Denning DW, Kibbler CC, Barnes RA. British Society for Medical Mycology proposed standards of care for patients with invasive fungal infections. Lancet Infect Dis 2003; 3: 230–40.
7 Stevens DA, Kan VL, Judson MA, Morrison VA, Dummer S, Denning DW *et al.* Practice guidelines for diseases caused by Aspergillus. Infectious Diseases Society of America. Clin Infect Dis 2000; 30: 696–709.
8 Bates DW, Su L, Yu DT, Chertow GM, Seger DL, Gomes DR *et al.* Mortality and costs of acute renal failure associated with amphotericin B therapy. Clin Infect Dis 2001; 32: 686–93.
9 Wingard JR, Kubilis P, Lee L, Yee G, White M, Walshe L *et al.* Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. Clin Infect Dis 1999; 29: 1402–7.
10 Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347: 408–15.
11 Food and Drug Administration. Background document for the Antiviral Drug Products Advisory Committee Meeting, 4 October 2001. Food and Drug Administration, Center for Drug Evaluation and Research, Division of Special Pathogen and Immunologic Drug Products [cited 11 Dec 2003]. Available from: URL: http://http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_02_FDA-voriconazole.pdf
12 Karthaus M. Voriconazole versus amphotericin B for invasive aspergillosis. N Engl J Med 2002; 347: 2080–81.
13 Bowden R, Chandrasekar P, White MH, Li X, Pietrelli L, Gurwith M *et al.* A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. Clin Infect Dis 2002; 35: 359–66.
14 Denning DW. Echinocandin antifungal drugs. Lancet 2003; 362: 1142–51.
15 Denning DW, Lee JY, Hostetler JS, Pappas P, Kauffman CA, Dewsnup DH *et al.* NIAID Mycoses Study Group Multicenter Trial of oral itraconazole therapy for invasive aspergillosis. Am J Med 1994; 97: 135–44.
16 Stevens DA & Lee JY. Analysis of compassionate use itraconazole therapy for invasive aspergillosis by the NAID Mycoses Study Group criteria. Arch Intern Med 1997; 157: 1857–62.
17 Walsh T, Sable C, Depauw B, Donowitz G, Maertens J, Baden L *et al.* Abstract M-1761. A randomized, double-blind, multicentre trial of caspofungin v liposomal amphotericin B for empirical antifungal therapy of persistently febrile neutropenic patients. Interscience Conference on Antimicrobial Agents and Chemotherapy; 2003; Chicago, USA.
18 Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003; 348: 1546–54.
19 McNeil MM, Nash SL, Hajjeh RA, Phelan MA, Conn LA, Plikaytis BD *et al.* Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. Clin Infect Dis 2001; 33: 641–7.
20 Kibbler CC, Seaton S, Barnes RA, Gransden WR, Holliman RE, Johnson EM *et al.* Management and outcome of bloodstream infections due to Candida species in England and Wales. J Hosp Infect 2003; 54: 18–24.
21 Rex JH, Pappas PG, Karchmer AW, Sobel J, Edwards JE, Hadley S *et al.* A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. Clin Infect Dis 2003; 36: 1221–8.
22 Rex JH, Bennett JE, Sugar AM, Pappas PG, van der Horst CM, Edwards JE *et al.* A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. N Engl J Med 1994; 331: 1325–30.
23 Phillips P, Shafran S, Garber G, Rotstein C, Smaill F, Fong I *et al.* Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. Canadian Candidemia Study Group. Eur J Clin Microbiol Infect Dis 1997; 16: 337–45.
24 Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J *et al.* Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002; 347: 2020–9.