

Invasive aspergillosis: current and future challenges in diagnosis and therapy

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ABSTRACT

Invasive aspergillosis is an increasingly common disease. While there have been significant advances in the past decade, significant challenges remain in terms of diagnosis and therapy. Some of the recent advances are outlined and future opportunities to improve the unacceptable mortality that is currently associated with this infection are considered.

Keywords Amphotericin, aspergillosis, diagnosis, therapy, voriconazole

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In the last decade, there have been significant advances in the diagnosis and treatment of invasive aspergillosis. For example, a recent trial demonstrated a superior response rate and survival advantage for patients with invasive aspergillosis receiving voriconazole as compared with deoxycholate amphotericin B [1]. While this is encouraging, significant challenges remain, since the incidence of the disease is increasing and, despite best current practices, the mortality rate remains unacceptably high at 30–50% [1,2].

The trial of voriconazole and deoxycholate amphotericin B [1] was conducted in immunocompromised patients with proven and probable invasive aspergillosis. With use of a 12-week endpoint, a successful outcome was demonstrated in 52.8% of patients receiving voriconazole, as compared with 31.9% of those receiving amphotericin B [1]. A mortality advantage was also observed in patients receiving voriconazole; this is the first such report in an antifungal treatment trial. Despite concerns about differing durations of therapy, as well as the possibility of excessive interruptions in the amphotericin arm [3], the conclusion that voriconazole is superior to amphotericin B for treatment of invasive aspergillosis

has been welcomed by most clinicians. What are the exceptions and what insights into invasive aspergillosis does the trial provide?

Voriconazole, despite its clear efficacy, may not always be appropriate, since drug toxicity, interactions with other drugs, resistance and polymicrobial fungal infections all represent scenarios where its use is either contraindicated or unlikely to be unsuccessful.

Higher than anticipated levels of voriconazole may be seen in elderly patients [4], patients with hepatic impairment [4], or those with a genetic deficiency of the cytochrome P450 enzyme CYP2C19, which is the most important of three human cytochromes involved in voriconazole metabolism [4,5]. CYP2C19 polymorphisms appear to account for most interpatient variability in voriconazole levels [4,5], and a deficiency of this enzyme is seen in 5% of caucasians and 10–20% of Asians [4]. Where toxicity is of concern, voriconazole should be used only if the benefits outweigh the risks. In the situation of CYP2C19 polymorphisms, the only strategy to prevent toxicity is to systematically measure serum voriconazole levels, although this is not widely advocated at present.

Drug interactions represent a further obstacle to the routine use of voriconazole. For example, rifampicin induces enzymes responsible for voriconazole metabolism, so that efficacious levels are unobtainable [4]. In contrast, voriconazole potentially inhibits the metabolism of several drugs, with potentially serious toxic conse-

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quences, including astemizole, terfenadine, cispripide, and sirilimus [4,6], while others can be co-administered but require dose adjustments. This latter group includes tacrolimus, cyclosporin and warfarin [4].

Primary resistance of *Aspergillus* spp. to voriconazole appears to be uncommon [7] and currently does not influence the therapeutic decision. The rate of development of secondary resistance is unknown, but requires consideration when patients either fail voriconazole or have significant pre-exposure. Although described [8], cross-resistance with itraconazole does not appear to be common [9], and therefore itraconazole may be useful for salvage therapy in such situations.

Finally, documented or possible polymicrobial infections with yeasts or other filamentous fungi resistant to voriconazole (e.g., the Mucorales) also compromise routine use of voriconazole as monotherapy.

Is the benefit exhibited by voriconazole a class effect of azoles, and can the results be extrapolated to other azoles with activity against *Aspergillus* spp.? This is a complex question, and difficult to answer in the absence of comparative clinical trials. The azoles share a common fungal target, i.e., P450-dependent 14 α -demethylase. However, their clinical utility as anti-*Aspergillus* agents probably also depends on other factors, such as fungicidal activity, pharmacokinetic characteristics, compartmental pharmacokinetics, protein binding (and therefore free drug available), and the presence or absence of active metabolites, to name a few. These parameters vary considerably between agents, and between individuals, making comparisons complicated. Until further evidence is available, it seems that voriconazole should be used in preference to other azoles for invasive aspergillosis. Additional questions include the possible role of the echinocandins as primary agents, combinations of antifungal agents, and the appropriate sequence of antifungal regimens. The sequence of itraconazole and amphotericin B is probably detrimental [10], but it is not clear if this pertains to all azoles.

Diagnostic issues remain of paramount importance and relevance for invasive aspergillosis. A major challenge is how to incorporate diagnostic tests such as PCR and antigen tests into published criteria. Lack of test standardisation, difficulties in establishing the reference

standard, differences in test performance in different situations, and understanding how tests apply to different stages of the infectious process from colonisation through to tissue damage, represent substantial but not insurmountable obstacles to this process.

The development of diagnostic criteria has been conceptually difficult, so the recently published criteria for patients with haematological malignancy, cancer and bone marrow transplantation [11] represent a welcome advance, with subtle differences from other diagnostic criteria. Thus, the voriconazole trial allowed a halo or air-crescent sign to define probable invasive aspergillosis without any additional microbiological evidence in the setting of haematological malignancy, neutropenia or allogeneic bone marrow transplantation, but this is now deemed to be inadequate [11]. In the voriconazole trial, a halo or air-crescent sign without supporting microbiological evidence was previously classified in the same manner as a lung biopsy demonstrating hyphae consistent with *Aspergillus* spp. with no supporting microbiological evidence, despite the fact that the two may differ in terms of their positive predictive value for invasive aspergillosis.

These observations serve to make two points. First, diagnostic criteria are merely statements about the probability of a specific underlying biological process. It is also important that cases which do not conform to established criteria are not automatically excluded, but rather considered on their merits, as long as an understanding is reached on how they depart from standard criteria. Second, there are clearly many different and subtle manifestations of invasive aspergillosis which have implications for diagnostic tools, in terms of both their performance and the role they play in subclassifying invasive aspergillosis. Diagnostic criteria need to be simple and robust to achieve widespread acceptance, while remaining flexible enough to identify the subtleties of the infection and account for its protean manifestations in a wide range of hosts.

Infections caused by *Aspergillus* spp. remain one of the most challenging and exciting areas of medicine, since they encompass rapidly developing diagnostic and therapeutic modalities. The ultimate aim is to minimise morbidity and mortality in a disease which has been notoriously difficult to diagnose and treat.

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