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

Clin Microbiol Infect 2004; 10; 2–4

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, cisa-
pride, and sirolimus [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 vor-
iconazole appears to be uncommon [7] and 
currently does not influence the therapeutic 
decision. The rate of development of secondary 
resistance is unknown, but requires considera-
tion when patients either fail voriconazole or 
have significant pre-exposure. Although de-
scribed [8], cross-resistance with itraconazole 
does not appear to be common [9], and therefore 
itraconazole may be useful for salvage therapy 
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 14α-demethylase. However, 
their clinical utility as anti-Aspergillus agents 
probably also depends on other factors, such as 
fungicidality, pharmacokinetic characteristics, 
compartmental pharmacokinetics, protein bind-
ing (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 aspergil-
losis. A major challenge is how to incorporate 
diagnostic tests such as PCR and antigen tests 
into published criteria. Lack of test standardisa-
tion, 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 pub-
lished criteria for patients with haematological 
malignancy, cancer and bone marrow transplan-
tation [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 microbiolog-
al evidence in the setting of haematological 
malignancy, neutropenia or allogeneic bone mar-
row 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 classi-
fied in the same manner as a lung biopsy 
demonstrating hyphae consistent with Aspergillus 
spp. with no supporting microbiological evi-
dence, 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 remain-
ing flexible enough to identify the subtleties of 
the infection and account for its protean manifesta-
tions 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 develop-
ing diagnostic and therapeutic modalities. The 
ultimate aim is to minimise morbidity and mort-
ality in a disease which has been notoriously 
difficult to diagnose and treat.
REFERENCES