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**Where next for therapy against invasive fungal infections in Asia?**

Emerging fungal infections arising in a rapidly expanding population of patients requiring treatment with immunosuppressant drugs or immunocompromised by HIV-AIDS are proving an increasing challenge for healthcare services in South East Asia and the Western Pacific. But a growing understanding of the relative roles of the new generation of antifungal agents against key *Candida* and *Aspergillus* species is helping to direct treatment in the most effective way.

Speakers at the *New Directions in the Treatment of Fungal Infections* symposium, supported in part by an educational grant from Schering-Plough, highlighted the importance of tailoring treatment to patient characteristics as well as to fungal species.

**Professor Boonmee Sathapatayavongs**, from Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, reported that in her own hospital, *Candida albicans* has moved from the seventh most common blood isolate in 1997 to the fourth most common in 2007 – behind *E.coli*, *S. aureus* and *K. pneumoniae*. Non-*albicans* species, such as *C. tropicalis*, *C.glabrata* and *C. parapsilosis* are also rising, with increased fluconazole-resistant in both *albicans* and non-*albicans* species.

Professor Sathapatayavongs explained that invasive aspergillosis is usually caused by *Aspergillus fumigatus* and, to a lesser but growing extent to *A. flavus*, *A. niger*, and *A. terreus*. She added that the non-*fumigatus* species are more resistant to amphotericin B, especially *A. terreus*.

## **Experience in Thailand**

A retrospective review at Ramathibodi Hospital identified 94 cases of invasive aspergillosis (IA) from 2000-2005, 35 proven, 10 probable and 49 possible. Patient predisposing factors were neutropenia in 39%, chemotherapy in 34% and steroid treatment in 25%. The lungs were infected in 68%, the sinus in 17% and the CNS in 5%, and mortality was high – at 47%.

Professor Sathapatayavongs pointed out that the emergence of fungal infection in Asia as a life threatening consequence of immunosuppressant treatments reflects what is being seen around the world with, for example, significant increases in *Fusarium* species, *Scedosporium*, and *Zygomycetes*. She suggested that these trends are likely to be associated with widespread prophylactic and therapeutic use of amphotericin B and older azoles in previous decades.

In the HIV era, she said, endemic mycoses had changed from a few disseminated cases to hundreds of diagnosed patients and, in South East Asia, *Penicillium marneffeii* is now recognised as an important pathogen added to the list of infections for AIDS defining illnesses, similar to *Histoplasma capsulatum* in the USA.

*Cryptococcus neoformans* is another important pathogen in HIV-infected people and, in Thailand, it has been the second most common AIDS-defining illness, after tuberculosis, Professor Sathapatayavongs told delegates. Although the introduction of highly active antiretroviral therapy (HAART) has been associated with a reduction in AIDS-related fungal infections, other underlying conditions, such as diabetes, renal failure, cirrhosis/liver failure, near-drowning (as seen following the Tsunami) and thalassemia/haemoglobinopathy, can all predispose to invasive fungal infection.

Professor Sathapatayavongs reported that nearly 100 cases of human pythiosis have now been reported in Thailand, all related to thalassaemia or haemoglobinopathy. Mainly involving the lower extremities, patients show symptoms and signs of arterial insufficiency, ranging from intermittent claudication and resting pain to gangrenous ulcer and gangrene. The infection is unresponsive to amphotericin B and itraconazole, and effective treatment remains elusive. But, as Professor Sathapatayavongs pointed out, if such cases are being seen in Thailand, they are almost certainly occurring in other parts of South East Asia. So physicians need to be watchful for this and other fungal infections associated with changing microbial epidemiology and/or clinical practice.

### **New generation triazole antifungals**

The newer triazoles, posaconazole and voriconazole, have provided a valuable broadening of antifungal activity against emerging fungal infections, but there are still gaps in understanding about their use in combination treatment and as salvage therapy, as well as the potential for azole cross resistance, concluded **Dr Monica Slavin**, from the Royal Melbourne, Alfred Hospitals, Melbourne, Australia, presenting on behalf of Professor Tania Sorrell, from the Centre for Infectious Diseases and Microbiology, at the University of Sydney, Australia.

In terms of spectrum of activity, Dr Slavin explained that each new azole offers some advantage over previous agents. Thus, itraconazole is active against *Aspergillus* and *Phaeohyphomycetes* as well as the *Candida*, *Cryptococcus* and *Cocci* against which fluconazole is active, while voriconazole has added *Pseudallescheria* and *Fusarium* to the list of fungal infections which can be addressed. The latest introduction, posaconazole, now offers additional activity against *Zygomycetes*.

For the future, Dr Slavin reported that ravuconazole, which is in phase II clinical trials has evidence of activity against azole-resistant *Candida* and *Rhodotorula*,

while albaconazole in phase I/II trials has activity against *Scedosporium prolificans* and *Paecilomyces*. Isavuconazole, which is in phase III studies, has similar activity to that of posaconazole, but with less activity against Zygomycetes, she added.

### **Recent aspergillosis guidance**

For today's treatment of invasive and CNS aspergillosis, Dr Slavin drew attention to the recent Infectious Diseases Society of America (IDSA) guidelines which recommend voriconazole as first line treatment, following studies demonstrating its favourable effects compared with amphotericin B [1]. In candidaemia, the azole has been shown to be as effective as an amphotericin B/fluconazole regimen, but with fewer toxic effects [2].

For empirical treatment of invasive aspergillosis, the situation is harder to interpret, Dr Slavin explained, as a comparison with liposomal amphotericin B failed to show non inferiority of voriconazole. This means that voriconazole cannot be recommended for treatment of febrile neutropenia, but can be supported for the early treatment of invasive aspergillosis. The challenge, therefore, is to differentiate between the two situations in order to determine optimal treatment. The increased toxicity and drug interactions associated with voriconazole, compared to other azoles, also needs to be borne in mind.

Turning to posaconazole, Dr Slavin discussed the results of the recent trial showing that the drug reduces invasive aspergillus infection (IFI) and improves survival compared with fluconazole/itraconazole when used as prophylaxis in patients undergoing treatment for acute myelogenous leukaemia (AML) or myelodysplastic syndrome [3]. Dr Slavin pointed out that the design of the study meant that patients could be taking fluconazole or itraconazole, depending on the protocols in use at the treatment centres, and some patients were known to have a positive galactomannan test, so it could be argued that this was an early treatment rather than a prophylaxis study. But she stressed the importance of the

improved survival shown in the study, given the generally poor prognosis of such AML patients – a benefit recognized in the recent IDSA recommendation for posaconazole as prophylaxis against IA in high risk patients.

Describing the results of a second posaconazole prophylaxis study in stem cell transplant patients with graft versus host disease, Dr Slavin explained that there had been a reduction in IFI/IA while patients were on treatment, though there was no accompanying mortality benefit [4]. She added that further analysis had provided reassuring evidence that patients with AML and GVHD in these studies were achieving comparable plasma levels of the drug to those seen in healthy volunteers.

Concluding her presentation with a summary of the use of voriconazole and posaconazole as salvage therapy, Dr Slavin reported a promising response rate of about 60% with posaconazole in zygomycosis, and rates of around 40% with voriconazole and posaconazole in aspergillosis. But she stressed that further research is needed.

### **Using pharmacodynamics to optimise efficacy**

Greater understanding of the pharmacodynamics of antifungal agents will enable clinicians to choose the most potent and safe drug dosing regimen, predicted **Dr David Andes**, from the Division of Infectious Diseases Medical Microbiology and Immunology, at the University of Wisconsin, Madison, USA.

He explained that the minimum inhibitory concentration (MIC) of an antimicrobial drug which prevents microbial growth is a good indicator of potency, but it says nothing about the time course of activity. Thus, for some drugs, outcome is optimised when the concentration is well above the MIC while, for others, the concentration only needs to be a little above the MIC, but for a longer period of time, i.e. total exposure or area under the curve (AUC) is most important.

Professor Andes described three patterns of activity with antifungal drugs. As an example of the first pattern, the activity of amphotericin and the echinocandins is based on concentration dependent killing, with each increase in concentration of amphotericin or echinocandins, resulting in enhancement of the rate and extent of fungal killing. For echinocandins, dose fractionation studies show that the optimal approach is to give a large amount of drug less frequently.

In the second pattern, the antifungal activity of flucytosine is not enhanced by increasing the dose of drug, and optimal efficacy is seen when small, frequent doses are administered, keeping the concentration just above the MIC.

In the third pattern (time dependent killing), exemplified by the triazoles, increasing concentration does not enhance killing, but prolonged persistent effects are seen even after the concentration falls below the MIC, so outcome is dependent on the amount of drug that is given rather than the frequency. The AUC in relation to the MIC is therefore the driving parameter.

Professor Andes pointed out that, despite the disparity of size, the results of mouse studies of antifungal agents are predictive of the human situation because, in both cases, the drug target is the fungal organism. The AUC to MIC needed for efficacy in the mouse is therefore the same as in humans.

For example, extensive research with fluconazole and, more recently with voriconazole, has demonstrated that optimal clinical outcome with azoles is achieved when the AUC:MIC ratio is over 25.

In the case of the echinocandins, achieving an AUC:MIC of 10-20 seems to be important in animals, though this has yet to be confirmed in human studies.

Dr Andes concluded that, by using pharmacodynamic targets such as these, it should be possible to predict the highest MIC where a good clinical outcome can be achieved.

### **Similarities and differences of echinocandins**

As a class, the echinocandins have more similarities than differences, they are well tolerated and very active against Candida infection, and they have potential application in biofilms. They may be useful in invasive aspergillus, but data are currently limited to salvage studies, and more information is needed about how the echinocandins can be combined with other antifungal agents, their use in children, likelihood of resistance and the opportunities for intermittent and prophylactic treatment.

This was how **Dr Monica Slavin**, from the Royal Melbourne, Alfred Hospitals, Melbourne, Australia, summed up at the end of her review of the current and future role of the echinocandins.

She explained that the echinocandins are similar in that they are all available only as IV formulations, they have a long half life making them suitable for once daily administration, and they exhibit strong protein binding over 90%, so they are not dialysed. Low levels reach the CSF compared to plasma (only 1%) and they are generally well tolerated, with no dose adjustment needed in renal failure, and liver function abnormalities occurring in 1-8% of patients. A rare problem is histamine release in 1-2%, causing rash and sometimes hypotension and angioedema which can be dramatic and concerning when it does occur.

Focusing on the main differences between the echinocandins, Dr Slavin explained that anidulafungin has the longest half life, at 52 hours, and because it is diluted in alcohol, has an effect comparable to drinking a glass of wine when administered. Unlike caspofungin and micafungin it is metabolised in the plasma rather than the liver.

Features which distinguish caspofungin from the other two drugs are that dose needs to be reduced in liver failure and, when combined with inducers of CYP3A, levels of caspofungin are reduced. Caspofungin also increases levels of cyclosporin A when the two agents are combined.

Dr Slavin told delegates that, based on their MIC, fungicidal and clinical activity, echinocandins are highly active against *Candida albicans*, *glabrata*, *tropicalis*, *krusei* and *kefyr*, and very active against *C.parapsilosis*, *guilliermondii* and *lusitanae* and *Aspergillus fumigatus*, *flavus* and *terreus*. But the group is inactive against Zygomycetes, *Cryptococcus neoformans*, *Fudarium spp*, and *Trichosporon spp*.

Resistance has been reported, usually in association with clinical failure, especially with prolonged treatment or for infection in difficult sites, or in highly immunocompromised patients. The mechanism is not well understood.

### **Key clinical trials of echinocandins**

Turning to key clinical trials, Dr Slavin explained that, in invasive candidiasis, caspofungin has proved as effective as amphotericin B (success 72% vs. 63%) [5]. Micafungin has been shown to be non inferior to caspofungin (success 71% vs. 76%) [6], and anidulafungin has proved non inferior to fluconazole (success 76% vs. 60%) [7].

For IFI prophylaxis, the only randomised clinical trial (RCT) has been carried out in stem cell transplant patients, with micafungin superior to fluconazole. For empirical therapy, caspofungin has proved equivalent to amphotericin B, but no RCT data are available in IA patients. Caspofungin and micafungin have proved useful as salvage therapy in IA.

## **Future prospects with echinocandins**

Considerable work is still needed, said Dr Slavin, to determine the best use of echinocandins in children, though it appears that dosing may need to be on a mg/m<sup>2</sup> rather than a mg/kg basis.

She also pointed out that the promising effects of echinocandins against fungal cells in biofilms suggested that the drugs could have a role in preventing or treating infections in catheters. Intermittent prophylaxis, for example with the echinocandin with the longest half life, anidulafungin, also has potential for future developments.

No combination studies have yet been carried out, but a combination of an echinocandin with voriconazole or liposomal amphotericin B could be beneficial, given the additive activity seen in animal models of aspergillosis, concluded Dr Slavin.

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