New antifungal agents

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With the relentless increase in invasive fungal infections, particularly in critically ill and immunocompromised patients, it is good to know that there are new additions to the antifungal armamentarium. These include not only new formulations of existing drugs and the development of new triazole agents, but also the introduction of a new class of antifungal drug.

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Like other azoles, the new triazoles act by inhibiting the fungal cytochrome P450 enzyme lanosterol 14-alpha-demethylase, which prevents the conversion of lanosterol to ergosterol and disrupts the integrity of the fungal cell membrane (*Figure 1*). Drug interactions with other cytochrome-dependant agents are likely. New agents have a broader spectrum of activity while retaining the excellent safety profile of fluconazole. Activity against fluconazole-resistant yeasts has been reported but there is the potential for cross-resistance to develop.

Voriconazole

This drug is licensed for the treatment of invasive aspergillosis and is undergoing phase III trials for other infections. It has good activity against *Candida* spp. including those resistant to fluconazole, although the minimum inhibitory concentration (MIC) may be higher in non-albicans species. It has a broad spectrum of activity against most moulds and yeasts, including emerging mycoses such as *Fusarium* spp. and *Scedosporium* spp., although clinical data are limited. No useful activity against mucorales infections has been demonstrated.

Both oral and intravenous preparations are available. Absorption is good after oral administration and bioavailability is high, at up to 96% of the dose. The elimination half-life of voriconazole is 6 hours. It is metabolized in the liver with less than 5% of unchanged drug excreted in the urine. Side effects are few and include elevated hepatic transaminases (10–15%), skin rashes (1–5%) and transient,

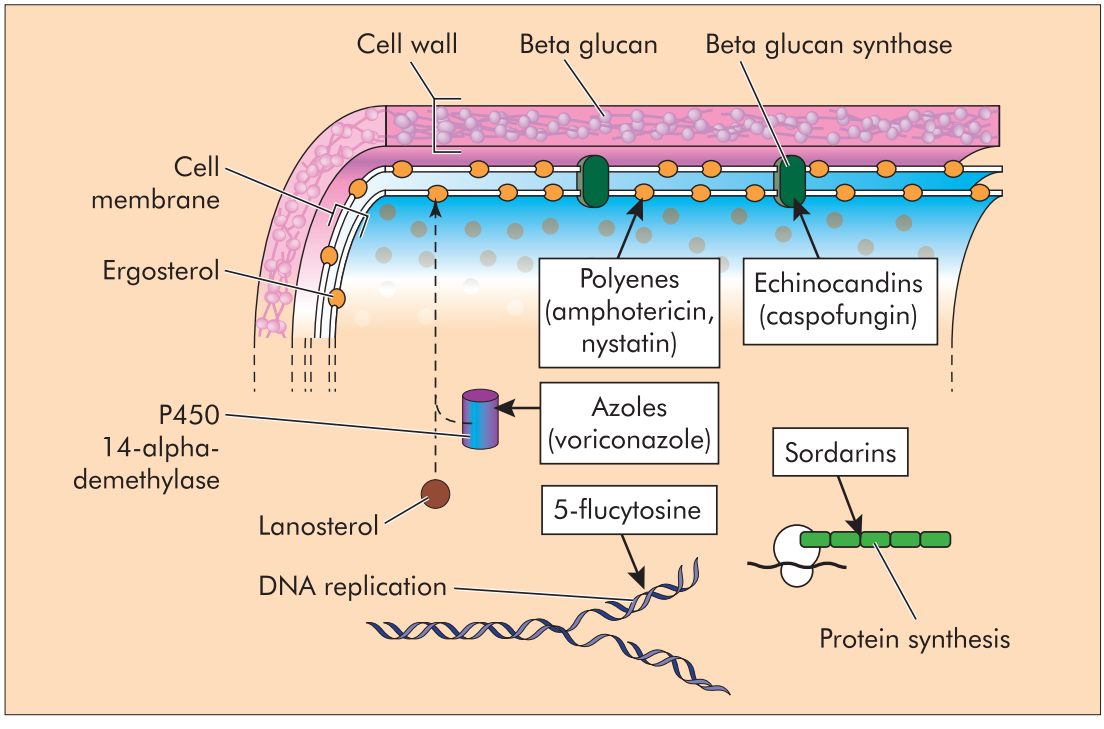

Figure 1. Sites of action of antifungal agents.

TABLE 1.
Comparison between new antifungal agents

Drug	Formulation	Spectrum	Dose	Use
Voriconazole	Oral and IV	Most yeasts, moulds including *Fusarium*	Oral 200 mg BD IV 3–6 mg/kg BD	Invasive aspergillosis, candidosis resistant to fluconazole. May be used as prophylaxis in neutropenic BMT patients
Caspofungin	IV	Most yeasts, moulds, dimorphic fungi and PCP. No action against *Cryptococcus neoformans*	Loading dose 70 mg then 50 mg/day.	Candidosis and invasive aspergillosis
Liposomal amphotericin B	IV	Most moulds, yeasts and *Leishmania donovani*	1–3 mg/kg/day	Disseminated candidosis, aspergillosis, and cryptococcal meningitis

BD = twice daily; BMT = bone marrow transplant; IV = intravenous; PCP = *Pneumocystis jiroveci*

dose-related visual disturbances (8–10%). The oral dose is 200 mg twice daily. The intravenous dose is 3–6 mg/kg given every 12 hours (*Table 1*). A study in patients with neutropenia and persistent fever compared voriconazole with liposomal amphotericin B. The overall success rates were 26% with voriconazole and 30.6% with liposomal amphotericin B. There were fewer documented breakthrough infections with voriconazole (1.9%) *vs* liposomal amphotericin B (5%) but non-inferiority was not demonstrated as a result of the complex multiple end points used in the study (Walsh et al, 2002).

Another study comparing voriconazole with conventional amphotericin B for the primary treatment of invasive aspergillosis showed improved survival and fewer side effects in the voriconazole group (Herbrecht et al, 2002). There were successful outcomes in 52.8% of patients in the voriconazole arm and 31.6% in the amphotericin B arm. The survival rate at 12 weeks was higher in the voriconazole group (70.8%) than the amphotericin B group (57.9%). Patients on voriconazole had fewer side effects, although visual disturbances were more common.

Posaconazole

This is available in an oral formulation only. It has a broad spectrum of activity including yeasts, moulds and dimorphic fungi. Early experience shows promise. It seems particularly efficacious against fusariosis and aspergillosis. Against yeasts, posaconazole may be slightly less potent than voriconazole but the drug offers significant potential as a prophylactic agent in high-risk groups.

Ravuconazole

It is available in both oral and intravenous formulations. It has a very long half-life of up to 100 hours. It has good activity against *Candida* spp., *Aspergillus* spp. and *Cryptococcus neoformans*, and modest activity against zygomycetes, *Fusarium* and *Sporothrix* spp.

ECHINOCANDINS

This new class of antifungals block synthesis of beta (1,3)-D-glucan of the fungal cell wall by non-competitive inhibition of the enzyme beta (1,3)-D-glucan synthase. They are available in intravenous formulations only and have good activity against all *Candida* and *Aspergillus* spp. and also dimorphic fungi such as *Blastomyces dermatitidis* and *Histoplasma capsulatum*. *Cryptococcus neoformans* are resistant to echinocandins. Activity against the 'cyst' but not 'trophozoite' form of *Pneumocystis jiroveci* (formerly *P. carinii*) has been reported but there are no clinical data for pneumocystiosis.

Caspofungin

This agent is highly protein bound. The half-life is 9–11 hours allowing once-daily dosing. It has linear kinetics, leading to accumulation after multiple dosing. Less than 3% is eliminated unchanged in the urine and significant drug interactions have not been reported. It is rapidly active and side effects are minimal. Dose reduction is not necessary in elderly patients or in cases of moderate renal impairment. Patients should receive a 70 mg loading dose followed by 50 mg/day. Caspofungin is not dialysable.

Caspofungin has been approved for the treatment of invasive aspergillosis in patients refractory or intolerant to other therapies and also for the treatment of invasive candida infections. A study comparing caspofungin with conventional amphotericin B for the primary treatment of invasive candidosis showed a favourable response in 71.7% of patients on caspofungin and 62.8% of patients on amphotericin B. There were significantly fewer adverse effects in the caspofungin arm (Mora-Duarte et al, 2002).

Micafungin (FK463)

This is under clinical trial in bone marrow transplant recipients, as primary prophylaxis in patients having fever during protracted neutropenia.

Anidulafungin

This is being studied in a phase III clinical trial for the treatment of oesophageal candidiasis. Further studies in invasive candidosis are planned.

SORDARINS

Sordarins inhibit fungal protein synthesis. They block the elongation step of protein synthesis by acting on elongation factor 2 (EF-2). Their spectrum includes *Candida* spp. (except *Candida krusei* and *Candida lusitaniae*), *Cryptococcus neoformans* and *P. jiroveci*. These agents show promise in the treatment of infections caused by these organisms but are unlikely to be used in the treatment of aspergillus infections based on preliminary animal data (Martinez et al, 2000).

NEW FORMULATIONS

Amphotericin B

Amphotericin B has significant nephrotoxicity. This has led to the development of lipid formulations of the drug and new methods of delivery.

Lipid formulations include liposomal amphotericin B, amphotericin B lipid complex and amphotericin B colloidal dispersion. Lipid formulations are as effective as conventional amphotericin B in treating febrile neutropenic patients and result in less nephrotoxicity and infusion-related reactions. They are substantially more expensive than conventional amphotericin B. The cost implications balanced against the risk of nephrotoxicity are the main factors that influence the decision to use lipid formulations of amphotericin B as the first-line antifungal agent.

Heating to 70°C for 20 minutes produces a superaggregated form of amphotericin B and reduces nephrotoxicity. No impact on antifungal activity has been demonstrated in vitro or in murine models but clinical experience is very limited (Kwong et al, 2001).

Similarly, delivery of drug via 24-hour infusions has also been reported to reduce nephrotoxicity although mild impairment of creatinine clearance and hypokalaemia were still reported.

COMBINATION THERAPY

Combination therapy with 5-fluorocytosine and amphotericin B has proven benefit in the treatment of cryptococcal meningitis, candidal peritonitis and endocarditis, but the evidence for benefit in other fungal infections is poor.

Studies suggest that fluconazole and 5-fluorocytosine can be used for the treatment of cryptococcal meningitis in patients intolerant of amphotericin B. The combination of amphotericin B and azoles remains controversial, with in vitro and animal studies suggesting antagonism. There have been no clinical trials to evaluate the combination of echinocandins and amphotericin B or echinocandins and azoles, but animal studies and isolated case reports suggest that these combinations may be more effective.

Finally, the cost of antifungal agents seems to play an important role in our treatment strategy. We need more studies looking into the cost effectiveness of the various agents, especially when used in combination. *Figure 2* compares the price of various antifungal agents. HM

Conflict of interest: Dr Barnes is a member of the Cancidas Advisory Board, Vfend Advisory Board and Gilead International Advisory Board.

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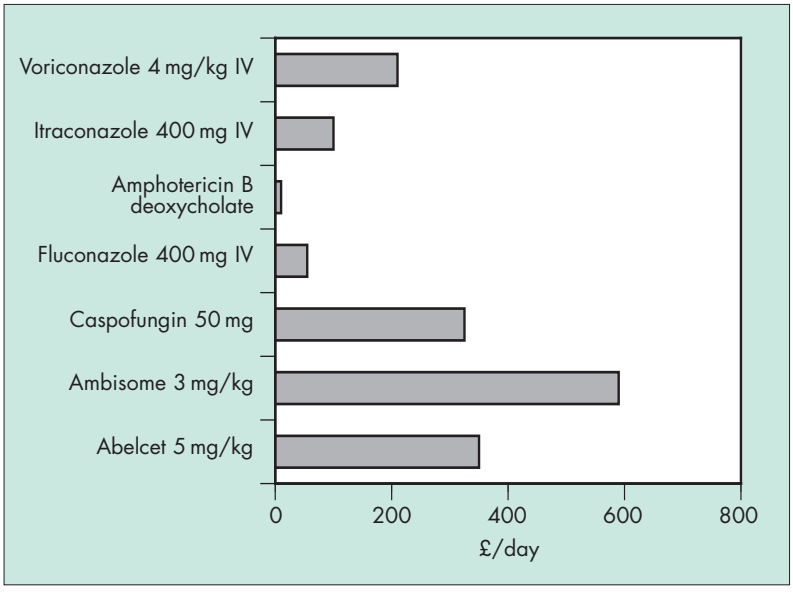

Figure 2. Comparison of acquisition costs. From British Medical Association and the Royal Pharmaceutical Society of Great Britain (2003). IV = intravenous.

KEY POINTS

- The options for antifungal treatment are increasing.
- New agents with activity against yeast and moulds are available.
- Rational use of these agents in at-risk patients should be determined.
- The cost and toxicity of the treatment need to be balanced with the benefit to patients at risk.