Antifungal agents

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ABSTRACT

- The four main classes of antifungal drugs are the polyenes, azoles, allylamines and echinocandins.
- Clinically useful "older" agents include topical azole formulations (for superficial yeast and dermatophyte infections), first-generation triazoles (fluconazole and itraconazole, for a range of superficial and invasive fungal infections), amphotericin B formulations (for a broad range of invasive fungal infections) and terbinafine (for dermatophyte infections).
- Clinically important "newer" agents include members of the echinocandin class (eg, caspofungin) and second-generation triazoles (eg, voriconazole and posaconazole).
- Voriconazole and posaconazole have broad-spectrum activity against yeasts and moulds, including *Aspergillus* species. Posaconazole is the only azole drug with activity against zygomycete fungi.
- Caspofungin and the other echinocandins are effective in treating *Candida* and *Aspergillus* infections.
- The azoles are relatively safe, but clinicians should be aware of drug–drug interactions and adverse effects, including visual disturbances (with voriconazole), elevations in liver transaminase levels, and skin rashes. Caspofungin has minimal adverse effects.
- Combination antifungal therapy may be appropriate in selected patients with invasive fungal infections, but is empiric and driven by individual physician practice.

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After a long period following the release of the first triazole antifungal agents (fluconazole and itraconazole, in the early 1990s) and lipid amphotericin B (AMB) formulations (mid 1990s), several new antifungal drugs have become available. These include members of a new class of agent (the echinocandins) and a new generation of an existing class (second generation triazoles).[1,2] Their arrival is timely, given the rise in infections caused by non-*albicans Candida* species and moulds. Many of these fungi are less susceptible to, or are resistant to, older antifungal agents.[2-4]

Clinically, it is useful to categorise fungal infections into superficial (involving skin or mucous membranes) and invasive fungal infections (IFIs). Most superficial infections are caused by dermatophytes and yeasts, and are present both in the community and in hospitalised patients. IFIs cause potentially life-threatening disease in critically ill and immunocompromised individuals, and in people with indwelling medical devices.[3,5,6] With the shift to managing serious illnesses outside hospitals, the population at risk of developing IFIs is no longer restricted to hospitalised patients. Early treatment is a key factor in minimising the associated high mortality.[7,8]

This article summarises the therapeutic uses of "older" antifungal drugs (eg, AMB deoxycholate, first-generation triazoles) as well as second-generation triazoles and echinocandins. At the time of writing, three agents, voriconazole, posaconazole and caspofungin, have been licensed for use in Australia, with anidulafungin on the horizon. Discussion of the prophylactic use of antifungal drugs is beyond the scope of this article, but is the subject of a number of reviews and meta-analyses.[9-11]

Classes of antifungal agents

Most antifungal drugs interfere with biosynthesis or integrity of ergosterol, the major sterol in the fungal cell membrane. Others cause disruption of the fungal cell wall. Based on their mechanism of action,[12] the major agents can be grouped into five classes:[1] polyenes; azoles; allylamines; echinocandins; and other agents, including griseofulvin and flucytosine.

Antifungal agents

Azole antifungal agents

These are the most widely used antifungal drugs, and act primarily by inhibiting the fungal cytochrome P450 enzyme, 14α-demethylase. There are two groups in clinical use: the imidazoles (ketoconazole, miconazole, clotrimazole, and econazole) and the triazoles (fluconazole, itraconazole, voriconazole, and posaconazole). As the triazoles have greater affinity for fungal compared with mammalian P450 enzymes, their safety profile is significantly improved over the imidazoles. The use of imidazoles is limited to treating superficial mycoses and is only briefly discussed (see "Superficial fungal infections"). The triazoles have broad application in therapy of both superficial and IFIs. Box 1 presents the drug profiles of the four clinically important triazoles; detailed pharmacological and efficacy data are available in recent articles and in the relevant product information.[13-19]

First generation triazole agents

Fluconazole has good overall activity against *Candida* species and *Cryptococcus neoformans*. However, resistance to the drug is encountered in certain non-*albicans Candida* species such as *C. krusei* and some isolates of *C. glabrata*.[4] It is available as oral and intravenous formulations (Box 1). Itraconazole has activity against yeasts and some moulds (including *Aspergillus*), but is disadvantaged by variable bioavailability and an unpleasant taste. In Australia, two oral formulations (the intravenous preparation is not licensed) are available: capsule, and oral solution. The bioavailability of the capsule form is highly influenced by concomitant food intake, and there is considerable intra- and inter-patient variability in plasma drug concentrations;[20] the solution form has a more favourable pharmacokinetic profile.[21] Fluconazole is commonly given once daily, but can be prescribed twice daily for larger total daily doses. Itraconazole is usually given twice daily (Box 1).

Second generation triazole agents

Voriconazole and posaconazole are second-generation triazoles with an extended spectrum of activity against yeasts, *C. neoformans* and moulds, including *Aspergillus, Scedosporium* and *Fusarium* species.[15,18] Voriconazole is active against fluconazole-resistant *Candida* species, although cross-resistance has been observed.[15] Posaconazole, licensed in May 2007, is the broadest spectrum

1 Drug profiles of fluconazole, itraconazole, voriconazole and posaconazole

Formulation	Metabolism and excretion	Tissue/CSF penetration*	Oral bioavailability	Dosing	Adverse effects[13-19]	Dose reduction in renal failure	Dose reduction in hepatic failure
Fluconazole: oral/IV	Half-life, 24 hours; protein binding, 11%. Excretion: > 80% unchanged drug in urine†	+++ / +++	> 90%	100–400 mg, orally/IV, daily‡	Gastrointestinal upset (5%); hepatotoxcity (5%–20%)	Required	Not required
Itraconazole: oral	Cytochrome P450 (extensive); half-life, 20 hours; protein binding, 95%. Excretion: renal (< 1%)	+++ / +/–	Variable (capsule, enhanced with food; solution, 30% increased compared with capsules)	100–400 mg, orally, daily	Skin rash (5%–19%); headache; rarely blood dyscrasias	Not required	Data not available§
Voriconazole: oral/IV	Cytochrome P450 (extensive); half-life, ⩾ 24 hours; protein binding, 58%. Excretion: renal (< 2%)	++++ / ++++	96%	4–6 mg/kg, IV twice daily; then 200–300 mg, orally, twice daily	Stevens–Johnson syndrome, hair loss, electrolyte disturbances (eg, hypokalaemia), cardiovascular effects (eg, QT_c prolongation, arrythmias), hallucinations. Visual disturbances (30%, usually transient)	Oral: not required. IV: if creatinine clearance < 50 mL/min, use oral formulation§	Not required for acute hepatic injury; half maintenance dose in cirrhosis (Child–Pugh A and B); drug not recommended in severe cirrhosis (Child–Pugh C)
Posaconazole: oral	Cytochrome P450; half-life, 35 hours; protein binding, > 98%. Excretion: faeces (77%), renal (< 0.2%)	++++ / +/–	Variable (enhanced with food)	200 mg, orally, four times daily		Not required	Data not available¶

* Refers to penetration into tissue other than cerebrospinal fluid (CSF) / penetration into CSF: +/–= low; + = moderate; ++ = good; +++ = very good; ++++ = excellent. † The major fluconazole excretion route is renal,[16] but some drug is metabolised by cytochrome P450. ‡ Doses used in clinical trials, and which vary with clinical indication.[16] Higher doses can be used for severe infection. § Because of limited pharmacokinetic data in patients with hepatic insufficiency, no recommendation for dose adjustment can be made. ¶ In patients with moderate to severe renal dysfunction, accumulation of the intravenous vehicle occurs, and oral voriconazole is preferred. ◆

azole to date. Cross-resistance with fluconazole is uncommon, and posaconazole is the only azole with clinical activity against zygomycete fungi.[14,17] Both drugs are available as oral formulations and are easily administered (Box 1); voriconazole is also available for intravenous use (in a sulfobutyl betadex sodium vehicle). Voriconazole is administered twice daily. Posaconazole is usually prescribed initially in four divided doses to achieve adequate plasma levels, but may be given twice daily in non-life-threatening situations.[14] Its absorption is improved when taken with food or nutritional supplements (Box 1).

Adverse effects

In general, the triazoles are relatively safe, even when used for prolonged periods. The main adverse reactions are shown in Box 1. All triazoles can cause hepatotoxicity, but only 5%–7% of patients require treatment cessation. Hepatic reactions range from mild transient elevations in transaminases to clinical hepatitis, cholestasis and liver failure.[2,15,16] These reactions are idiosyncratic, so there is no cross-sensitivity between triazoles. The major drawback associated with triazole use relates to their metabolism by the hepatic cytochrome P450 (CYP) enzyme system (mainly CYP2C9, CYP2C19 and CYP3A4). Triazole levels are affected by other drugs metabolised by this pathway.[13,15,17] Because triazoles also inhibit CYP enzymes, plasma levels of any drug metabolised by these enzymes may be elevated (see Box 2 for the major drug interactions). Concomitant use of a triazole and such a drug, where not contraindicated, must be accompanied by monitoring of plasma drug levels (Box 2). The potential for drug–drug interactions is greatest for itraconazole and voriconazole,[16-19] but lower for posaconazole and fluconazole, as these azoles are not metabolised to the same extent by the CYP system (Box 1).[14,16] Conversely, CYP isoenzyme inducers substantially decrease plasma triazole levels. The most clinically significant interaction occurs with rifampicin, where concomitant use with itraconazole, voriconazole and posaconazole is contraindicated (Box 2). Where possible, rifampicin should not be used in conjunction with fluconazole.

AMB formulations

AMB formulations are commonly used to treat fungal infections. All have a similarly broad spectrum of activity against a wide range of fungal pathogens.

AMB deoxycholate

Conventional AMB or AMB deoxycholate has long been used to successfully treat various yeast, cryptococcal and mould infections.[22,23] Unfortunately, its clinical use is hindered by intrinsic toxicity and the requirement for intravenous administration. Dose-dependent nephrotoxicity is frequently encountered with therapeutic doses (Box 3). Although renal failure is usually reversible,

2 Major drug interactions encountered with triazole agents

	Degree of interaction					
	FLU	ITC	VOR	POS	Effect	Clinically significant
Substrates of CYP3A4 and CYP2C9*	++	+++	+++	++	Increased plasma concentrations of other drug substrates	Yes (some contraindicated)
Inducers of CYP3A4 and CYP2C9†	++	+++	+++	++	Decreased plasma concentrations of triazoles	Yes (some contraindicated)
Warfarin	++	+++	+++	++	Increased prothrombin time	Yes
Phenytoin	+++	+++	+++	+++	Increased phenytoin levels, decreased triazole levels	Yes
Rifampicin	+++	+++	+++	+++	Decreased triazole levels	Yes (contraindicated with ITC, VOR, POS)
Proton-pump inhibitors	++	++	+++	++	Increased proton-pump inhibitor levels, decreased triazole absorption	Yes
Cyclosporine	++	++	+++	++	Toxicity, renal failure	Yes
Tacrolimus	++	++	+++	++	Toxicity, renal failure	Yes
Sirolimus	++	++	++++	++	Toxicity, renal failure	Yes (contraindicated with VOR)
Statins	++	+++	+++	++	Increased statin levels	Yes

FLU = fluconazole; ITC = itraconazole; POS = posaconazole; VOR = voriconazole. + = mild, ++ = moderate, +++ = high, ++++ = very high. * Includes but not restricted to cisapride (contraindicated with FLU, ITC, VOR POS), terfenadine, astemizole, pimozide, quinidine, ergot alkaloids (contraindicated with ITC, VOR), sirolimus (contraindicated with VOR), tacrolimus, cyclosporin, statins, warfarin, omeprazole, phenytoin, benzodiazapines, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and sulfonylurea oral hypoglycaemics. † Includes rifampicin (contraindicated with ITC, VOR, POS), rifabutin (contraindicated with ITC, VOR), long-acting barbiturates (contraindicated with VOR), phenytoin, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors. ◆

permanent renal failure may occur. Infusion-related adverse reactions and thrombophlebitis are common even with preventive measures (Box 3).[22,23]

Lipid preparations of AMB

Two of three marketed lipid formulations of AMB are licensed in Australia: liposomal AMB and AMB lipid complex (Box 3). Their development has substantially reduced, but not eliminated, nephrotoxicity; other AMB-associated adverse effects also occur less frequently (Box 3). Other advantages include the ability to administer larger doses of AMB. Although at least as efficacious as conventional AMB in treating IFIs, lipid formulations have not been shown to be more effective.[23] They are substantially more expensive than conventional AMB, but despite this, have become the "standard of care" for seriously ill patients with actual or potential renal compromise. The choice of antifungal agent, or between different formulations of a particular drug, depends primarily on the specific pathogen and clinical setting. With expensive drugs, the cost–benefit ratio should be considered on an individual patient basis. A number of pharmacoeconomic analyses of the use of lipid-associated AMB and triazole agents have been published.[24,25]

AMB formulations are given as single daily doses by slow (2–4 hours) intravenous infusion (see Box 3 for usual dosing schedules). Conventional AMB oral suspension or lozenges are not absorbed, but may be used for oral candidiasis (see later). AMB is extensively bound to tissue, although the relationships between serum and tissue concentrations and clinical efficacy or toxicity are unclear. Penetration into cerebrospinal fluid (CSF) is poor, and yet AMB is effective in treating certain causes of fungal meningitis (eg, cryptococcosis).[22]

Echinocandins

There are three clinically important echinocandins. Caspofungin is the first to be licensed in Australia. Micafungin is only approved in Japan and the United States. Anidulafungin is currently undergoing review for marketing in Australia. All three show good in vitro activity against *Candida* and *Aspergillus* species, but are not active against *C. neoformans* or non-*Aspergillus* moulds.[13,26]

Caspofungin is as effective as conventional AMB for treating mucosal and systemic candidiasis, and is approved for treating such infections.[13,26-28] It is also effective as salvage therapy for invasive aspergillosis, but has yet to be evaluated for primary treatment of mould infections.[13,26] Penetration into tissue is good, although CSF levels are low. Caspofungin is available only as an intravenous formulation (oral bioavailability, < 0.2%). Owing to the long half-life, it can be administered once daily. The recommended dose is a 70 mg loading dose followed by 50 mg daily. Dose adjustment in renal impairment is not required. However, in moderate hepatic insufficiency (Child–Pugh score B), dose reduction is recommended; after the initial loading dose, the subsequent daily dose should be 35 mg.[28]

Toxicity associated with echinocandins is infrequent because their action is specific to fungal cell walls (glucan is not found in mammalian cells). They are not metabolised via the cytochrome P450 enzymes, so there are minimal drug–drug interactions. An exception is cyclosporin, for which concomitant use is not recommended because of the risk of raised liver transaminase levels. Hepatitis is otherwise rare. Other adverse effects include histamine release reactions (irritation at infusion site, headache, rash; 15%–20%) and fever (10%–35%).[13,26]

Terbinafine

Topical and oral preparations of this allylamine drug are widely used to treat nail and skin infections, and terbinafine is the treatment of choice for onychomycosis (Box 4). The usual dose is 250 mg once daily. There are also anecdotal reports of its value in certain invasive mould infections (eg, scedosporiosis) in combination with either a triazole or AMB formulation.[29,30] It is generally well tolerated, but may cause gastrointestinal upset, taste disturbance and transient elevation of liver enzymes. Dose reduction is required in the presence of chronic liver disease.

3 Drug profiles of amphotericin B (AMB) formulations

Parameter	AMB deoxycholate	AMB lipid complex	Liposomal AMB
Dosage* (mg/kg per day)	0.5–1.5	5	3–5 (or higher)
Maximum serum concentration†	—	Lower	Higher
Infusion-related toxicity‡	High (50%–60%)	Moderate (20%–40%)	Mild (10%–20%)
Decrease in serum potassium	++++	++	++
Anaemia	++++	+	+
Nephrotoxicity	++++ (up to 80%)	+ (15%–25%)	+ (10%–20%)
Prevention of infusion-related toxicity§	Required	Required	Generally not required

* Commonly prescribed treatment doses; dose varies with pathogen. High-dose liposomal AMB required for zygomycete infection (⩾ 5 mg/kg per day). † In comparison with AMB deoxycholate. ‡ Includes fever, chills, headache, joint and muscle pain, and hypotension. Before therapy, a test dose is recommended to identify patients in whom severe infusion-related reactions might occur. § Usually comprises "cocktail" of antipyretic, antiemetic and antihistamine drugs. Value of corticosteroids not proven. ◆

Flucytosine

Flucytosine should not be administered as a single agent because of rapid development of resistance. Its role is limited to use in combination with an AMB formulation for treating cryptococcal meningitis.[31] It is available as oral and intravenous formulations, with more than 90% of an oral dose absorbed. Gastrointestinal effects are uncommon, but bone marrow toxicity and hepatotoxicity may occur. Monitoring of serum drug levels is required.

Superficial fungal infections

Fungal infections of the skin (level of evidence $E3_1$) or mucosa (E2) can usually be successfully managed by topical imidazole preparations (see Box 5 for level-of-evidence codes).[32] Topical nystatin preparations may also be effective for skin or mucosal candidiasis, including uncomplicated vulvovaginal infections (Box 4). For recurrent yeast infections, oesophageal candidiasis and infection unresponsive to topical agents, treatment with an oral triazole drug is indicated, with fluconazole being the drug of choice (E2) (Box 4). In these cases, species identification of the pathogen and determination of antifungal susceptibility are recommended. If resistance to fluconazole develops, either caspofungin (E2) or voriconazole (E2) may be used. Terbinafine is the treatment of choice for dermatophyte infections where systemic treatment is indicated (E2) (Box 4). Although griseofulvin can be used, safer and more effective alternatives are preferred.

Invasive fungal infections

Treatment of IFIs is usually initiated in hospitals, but is increasingly continued in the outpatient setting. Box 6 presents guidelines, based on national and international recommendations, for the use of antifungal agents in treating the major systemic mycoses. Specific treatment details for various IFIs are given in recently published articles.[19,30,31,33-35]

4 Guidelines for antifungal therapy of superficial fungal infections

Condition	Causative pathogens	Treatment recommendations
Tinea pedis/cruris	Dermatophytes	Topical azoles*
Tinea corporis	Dermatophytes	Usually requires oral azole (itraconazole preferred) or terbinafine (E2)
Onychomycosis	Dermatophytes, yeasts	Terbinafine (preferred) (E1) or oral azole (itraconazole) (E2)
Cutaneous candidiasis	*Candida* spp.	Topical azoles* ($E3_1$) Topical nystatin ($E3_1$)
Vulvovaginal candidiasis†	*Candida* spp.	Topical azoles* or topical nystatin ($E3_1$); single dose oral fluconazole; 7-day course of oral fluconazole[16] (E2)
Oral candidiasis†	*Candida* spp.	Topical nystatin or amphotericin B; systemic fluconazole in immunocompromised patients (E2)
Oesophageal candidiasis	*Candida* spp.	Systemic fluconazole (E2); echinocandin (E2) or newer triazoles (E2) if indicated

* Clotrimazole, miconazole, econazole most commonly used. All formulations (creams, powders, troches) available without prescription. † Refers to treatment of uncomplicated, non-recurrent disease. ◆

5 Level of evidence codes

Evidence of the statements made in this article is graded according to the National Health and Medical Research Council (NHMRC) system[32] for assessing the level of evidence:

E1: Evidence obtained from a systematic review of all randomised controlled trials.

E2: Evidence obtained from at least one properly designed randomised controlled trial.

$E3_1$: Evidence obtained from well designed pseudo-randomised controlled trials (alternate allocation or some other method).

$E3_2$: Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control studies, or interrupted time series without a parallel control group.

$E3_3$: Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.

E4: Evidence obtained from case series, either post-test, or pre-test and post-test. ◆

Invasive candidiasis, which includes bloodstream infections (candidaemia), is the most frequently encountered IFI. Although *C. albicans* remains the commonest causative species (40%–50% candidaemias),[36] clinicians should be alert to the rise in infections due to azole-resistant *Candida* species. In patients with candidaemia, it is essential to exclude dissemination of infection to other

body sites (eg, endopthalmitis, endocarditis, or osteomyelitis), as this influences treatment duration and has prognostic implications. *Aspergillus fumigatus* and other *Aspergillus* species are common pathogenic moulds and cause major morbidity, especially in neutropenic, and organ-transplant patients.[3,6] Other moulds, such as *Scedosporium* and the zygomycetes, albeit less common, are associated with high mortality (at least 60%) depending on site of infection and host factors.[3,6] In all cases, accurate identification of the pathogen is critical to selecting appropriate antifungal therapy (Box 6) given the resistance of emerging fungi to many antifungal agents. Endemic mycoses caused by dimorphic fungi are rare; only histoplasmosis can be acquired in Australia.

6 Guidelines for antifungal therapy of invasive fungal infections

Infection	Antifungal agent	Treatment duration
Yeast infections		
Candidaemia and other forms of invasive candidiasis	AMB, FLU, CAS and VOR equally effective (E2). Lipid AMB formulations can also be considered if neutropenic ($E3_1$). Tailor choice of agent to species of *Candida* and susceptibility result.	Candidaemia: 14 days after last positive culture or after resolution of all symptoms and signs if neutropenic (expert opinion). Other invasive candidiasis: varies with site of infection.[31]
Cryptococcosis	Initial therapy: AMB with or without flucytosine (for central nervous system disease and if not neutropenic) (E2). Maintenance therapy: FLU (E2), or other triazole (E4).	Induction therapy: 2–6 weeks. Maintenance therapy: 3 months to 1–2 years; varies with host status and disease extent (E2).
Mould infections		
Invasive aspergillosis	Initial therapy: VOR is treatment of choice (E2). If patient is intolerant to VOR, lipid AMB is preferred over conventional AMB (E2). Maintenance therapy: VOR (E2); POS (E4). Salvage therapy: CAS (E4).	Until complete response evident, along with recovery of immune deficit. Indefinite treatment if persistent immunosuppression (expert opinion).
Zygomycosis	Initial therapy: high-dose lipid AMB formulation (≥ 5 mg/kg per day) (E4). Maintenance therapy: POS (expert opinion).	Until complete response evident, along with recovery of immune deficit. Indefinite treatment if persistent immunosuppression (expert opinion).
Scedosporium infections	Initial therapy: VOR with or without terbinafine (E4). Maintenance therapy: VOR (E4).	Until complete response evident, along with recovery of immune deficit. Indefinite treatment if persistent immunosuppression (expert opinion).
Infections caused by dimorphic fungi	Initial therapy: AMB formulation (E2). Maintenance therapy: ITC (E2); FLU (E4), VOR (E4), POS (E4) second line.	Until complete response evident, along with recovery of immune deficit. Indefinite treatment if persistent immunosuppression (expert opinion).

AMB = amphotericin B; CAS = caspofungin; FLU = fluconazole; ITC = itraconazole; POS = posaconazole; VOR = voriconazole. ◆

Combination antifungal therapy

The only fungal infection for which combination therapy is of proven clinical benefit is cryptococcocal meningitis where treatment with AMB formulations *plus* flucytosine results in higher cure rates and more rapid CSF sterilisation.[31,37] However, with the availability of potent extended-spectrum azoles, safer AMB formulations and the novel echinocandins, combination antifungal therapy is conceptually appealing, especially for very ill patients with poor prognosis. There are, for instance, reports of successful outcomes following combination therapy with voriconazole and terbinafine for *Scedosporium prolificans* infection.[29,30] The cases for (eg, poor outcomes associated with monotherapy) and against (eg, increased drug toxicity) combination therapy have been comprehensively reviewed, particularly for the treatment of aspergillosis.[37-39] Studies in vitro and in vivo indicate triazole–echinocandin combinations are often synergistic, sometimes indifferent, although never antagonistic; however, combinations of a polyene (AMB) with a triazole show conflicting data.[37-39] As results of preclinical studies cannot be used to direct clinical decisions, and in the absence of prospective, comparative data in humans, selecting patients that could benefit from combination therapy should be done individually.

Adjunctive therapy

Surgery may be required in instances such as fungal endocarditis or for large isolated lesions (eg, pulmonary cryptococcomas) that persist despite antifungal treatment (E4).[31,34] Aggressive surgical debridement is also mandatory in zygomycete infections (E4); for these infections, there are anecdotal reports of successful outcomes with adjunctive hyperbaric oxygen therapy and, more recently, iron chelation therapy (E4). The role of adjuvant recombinant cytokine therapy such as granulocyte-macrophage-stimulating factor in improving the host immune response remains investigational. Most recently, an approach using a monoclonal antibody against a fungal heat shock protein in combination with lipid-associated AMB resulted in improved outcomes for patients with invasive candidiasis (E2).[40]

The future

The release of new antifungal agents with improved efficacy and safety profiles is good news for patients with both superficial and invasive fungal infections. Both the echinocandins and new triazoles represent significant advances. Clinicians now have an alternative to offer patients suffering from intractable fluconazole-resistant mucosal candidiasis and, for the first time, there is an oral treatment for zygomycoses (posaconazole). In addition, there is a well-tolerated effective oral treatment for aspergillosis (voriconazole). Nevertheless, important questions remain. Clinical studies of the echinocandins and posaconazole are underway to clarify

their niche in the antifungal armamentarium. The pharmacokinetics of the newer agents and their efficacy in paediatric populations also require clarification. Other areas that need to be addressed include whether the addition of cytokines to the newer agents improves outcomes, and how best to study, and translate into clinical use, antifungal drug combinations. The answers to these and other questions will help define the future directions in antifungal therapy.

Competing interests

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