Choosing the most suitable antifungal for a sick patient is not easy. Pharmacists should be aware of the factors influencing this choice and the side effects and monitoring requirements of each drug

Invasive fungal infections management

By Katie Hatton, DipGPP, MRPharmS, Preet Panesar, DipClinPharm, MRPharmS, and Mark Gilchrist, MSc, MRPharmS

Before 2000, there was a limited choice of drugs for the treatment of invasive fungal infections. Since then, the launch of five new medicines (anidulafungin, caspofungin, micafungin, posaconazole and voriconazole), in addition to existing drugs such as amphotericin, fluconazole and flucytosine, has broadened antifungal treatment options considerably. However, the increased number of antifungals has brought with it the challenge of choosing the appropriate one for a given clinical circumstance. In the absence of clear treatment guidelines this can be difficult; local clinical experience and patient comorbidities will influence choice.

Antifungal therapy accounts for a substantial proportion of hospital anti-infective drug budgets. In the current climate of limited resources, pharmacists can take an active role in the financial management of these medicines in the NHS.

It is important to remember that fungi, like mammalian cells, are eukaryotes. This means that finding medicines that are selectively toxic to fungi (and therefore minimise human toxicity) is a challenge for drug developers.

Clinical pharmacists can advise on antifungal choice and on monitoring and managing the adverse effects associated with antifungals. In addition, the licensing of antifungal drugs for the treatment of invasive infections varies and should always be taken into consideration when choosing a medicine.

This article considers factors which may influence choice of antifungals and sets out monitoring requirements to help pharmacists support the appropriate and safe clinical use of these medicines. The use of medicines for the prophylaxis of fungal infections and management of non-invasive fungal infections is outside the scope of this article.

Figure 1: Spectrum of activity of antifungal medicines

<table>
<thead>
<tr>
<th>Fungal species</th>
<th>Antifungal medicine</th>
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<tbody>
<tr>
<td></td>
<td>Fluconazole</td>
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<tr>
<td>Yeasts</td>
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<tr>
<td>Candida spp</td>
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<tr>
<td>C albicans</td>
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<tr>
<td>C tropicalis</td>
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<td>C parapsilosis</td>
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<td>C krusei</td>
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<td>C glabrata</td>
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<tr>
<td>Cryptococcus neoformans</td>
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<tr>
<td>Moulds</td>
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<tr>
<td>Aspergillus spp</td>
<td></td>
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<tr>
<td>Fusarium spp</td>
<td></td>
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<tr>
<td>Scedosporium apiospermum</td>
<td></td>
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<tr>
<td>Diamorphic Fungi</td>
<td></td>
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<tr>
<td>Coccioides spp, Blastomyces, Histoplasma spp</td>
<td></td>
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<tr>
<td>Zygomycetes</td>
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</tbody>
</table>

- Active against fungal pathogen
- Partial activity against fungal pathogen
- No activity against fungal pathogen

SUMMARY

With the increasing number of patients developing invasive fungal infections, it is important for pharmacists to be able to advise on selecting and monitoring antifungal treatments.

Newer antifungals (eg, voriconazole, posaconazole and micafungin) have added to the existing treatment options (eg, amphotericin and fluconazole), but have also introduced the challenge of choosing the right antifungal for a given clinical circumstance. Generally, selection is based on indication, site of infection, patient comorbidities and local guidelines.

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Azole antifungals

The systemic triazole derivatives (fluconazole, itraconazole, posaconazole and voriconazole) have a varied spectrum of activity and, consequently, different licensed indications (see Figure 1, p177). The azole antifungals act by targeting ergosterol, which is an essential component of the fungal cell membrane. They inhibit the fungal cytochrome P450 enzyme 14-alpha-demethylase, preventing the conversion of lanosterol to ergosterol — this causes inhibition of fungal growth and replication (see Figure 2).² Practice points for azole antifungals can be found in Box 1.

Selection Fluconazole, itraconazole and voriconazole are available in both oral and parenteral formulations (unlike posaconazole, which is only available in an oral preparation). Generally, the bioavailability of the oral preparations is good. Fluconazole² and voriconazole have good penetration into the central nervous system.

Dosing When treating invasive fungal infections, the maximum tolerated dose of azole should be used, for example fluconazole (oral or intravenous) 400-800mg daily. A loading dose is required when using fluconazole or voriconazole.³

Renal and hepatic considerations Usually, no dose adjustment is required for patients with renal impairment, except for fluconazole in patients with severe renal dysfunction.³ Another exception is the use of IV voriconazole for patients with moderate-to-severe renal impairment (creatinine clearance <50ml/min) since accumulation of the IV vehicle, SBECD, can occur.³ Oral voriconazole should be administered to these patients unless an assessment of the risk and benefit justifies the use of IV voriconazole.

For patients with impaired hepatic function, it is important to consider the underlying cause. There are no formal guidelines for adjusting azole doses in patients with hepatic impairment, although some manufacturers make specific recommendations. In practice, a dose reduction or alternative drug should be considered for patients with hepatic transaminase levels more than three times the upper limit of normal.³

Adverse effects Adverse effects of the azoles commonly seen in practice include gastrointestinal disturbances, such as nausea and abdominal pain, and hepatobiliary effects, such as elevated transaminases and hyperbilirubinaemia.

Interactions Pharmacokinetic drug-drug interactions with azoles are common. The azoles are known to inhibit the cytochrome P450 enzymes CYP3A4, CYP2C9 and CYP2C19 to varying degrees. Although most drug-drug interactions are manageable, concomitant use is contraindicated with drugs that are metabolised via the enzyme CYP3A4 and are known to prolong the QT interval.³

Absorption of itraconazole capsules is impaired by drugs that increase the gastric pH. Therefore these drugs should be avoided if possible.³ Food can also affect the absorption of azole antifungals; for example, itraconazole capsules should be taken with food whereas the oral liquid should be taken on an empty stomach.³ The absorption of posaconazole is increased by a high-fat meal.

Therapeutic drug monitoring Therapeutic drug monitoring (TDM) of serum levels of azole antifungals is not required routinely. However, it may be considered for itraconazole, voriconazole and posaconazole where non-compliance is suspected, if a patient is responding poorly to therapy or if subtherapeutic levels are suspected due to drug interactions.

Polyenes

The only systemic polyene in widespread clinical use for the treatment of invasive fungal infections is amphotericin B, which is derived from Streptomyces nodosus. Amphotericin is thought to exert its effect via an interaction with ergosterol in the cell membrane, which causes a change in membrane permeability, allowing leakage of cellular components and, ultimately, leading to cell death (Figure 2).³ Practice points for amphotericin can be found in Box 2 (p179).

Selection For the treatment of invasive fungal infections amphotericin can only be given by the IV route. In the UK...
it is available in three formulations — a non-lipid deoxycholate complex (Fungizone) and two different lipid formulations (Abelcet [lipid complex] and AmBisome [liposomal]).

Fungizone, often termed “conventional amphotericin”, is the original formulation launched over 40 years ago. Crystalline amphotericin is insoluble in water so, in the Fungizone formulation, it is solubilised through the addition of sodium deoxycholate, a detergent, to create a colloidal dispersion suitable for IV administration. However, despite being a highly effective medicine, Fungizone is associated with several serious adverse effects (including hypokalaemia, arrhythmias and nephrotoxicity) and has complex dilution and administration requirements.

Lipid formulations of amphotericin were subsequently developed to minimise toxicity, predominantly nephrotoxicity. The lipid formulation AmBisome has been demonstrated to have significantly less nephrotoxicity than Fungizone but is still associated with dose-limiting renal toxicity. Lipid formulations of amphotericin were subsequently developed to minimise toxicity, predominantly nephrotoxicity. The lipid formulation AmBisome has been demonstrated to have significantly less nephrotoxicity than Fungizone but is still associated with dose-limiting renal toxicity. However, despite being a highly effective medicine, Fungizone is associated with several serious adverse effects (including hypokalaemia, arrhythmias and nephrotoxicity) and has complex dilution and administration requirements.

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In September 2007 the National Patient Safety Agency released a rapid response report, highlighting the potentially lethal problems that can arise if non-lipid and lipid formulations of amphotericin are confused. Consequently, most pharmacies now only keep one lipid formulation of amphotericin and, generally, do not hold stocks of Fungizone. To avoid confusion, IV formulations of amphotericin should always be prescribed by brand name.

Dosing Patients can develop serious allergic-type reactions to amphotericin, including anaphylaxis, so a test dose should be given before the first dose of any IV amphotericin preparation is administered. The patient should then be observed for a set time (usually 30 minutes) before the remainder of the dose is administered.

Amphotericin maintenance dosing is weight-based and varies considerably between brands of the drug. The dose should always be carefully checked with the prescribed brand.

Renal and hepatic considerations Caution should be exercised when prescribing amphotericin for patients with pre-existing renal impairment, either acute or chronic. In such cases an alternative antifungal with appropriate spectrum of activity and penetration is often preferred.

Concomitant administration of IV amphotericin with other nephrotoxic drugs may potentiate the effect of drug-induced nephrotoxicity in some patients. Likewise co-administration of drugs known to cause hypokalaemia (eg, diuretics) may enhance the potential for drug-induced hypokalaemia. Patients should be monitored closely for adverse effects; monitoring electrolytes (especially potassium and magnesium) and renal function is particularly important.

There are no formal recommendations for dose adjustments of amphotericin for patients with hepatic impairment. However, close monitoring of liver function tests (LFTs) are recommended throughout treatment. If LFTs become significantly elevated (eg, more than three times the upper limit of normal) therapy should be reviewed and alternative treatments considered.

**Adverse effects** Common adverse effects associated with amphotericin include fever, renal dysfunction and electrolyte disturbance, particularly hypokalaemia and hypomagnesaemia. For AmBisome, doses above 3mg/kg daily have been linked to a higher incidence of adverse effects. However, clinical practice suggests that using higher doses may be beneficial for patients with fungal meningitis or for those who are critically ill.

**Echinocandins** The echinocandins (caspofungin, anidulafungin and micafungin) are semi-synthetic lipopeptides originally derived from fermentation broths of various fungi. These antifungals inhibit the synthesis of beta(1,3)-glucan, which is an essential component of the cell wall of many fungi.
filamentous fungi but is not present in mammalian cells (see Figure 2, p178). The echinocandins are generally thought to be fungicidal against Candida spp but fungistatic against Aspergillus spp. Practice points for echinocandins are set out in Box 3.

Selection All three echinocandins have similar spectrums of activity but they have different pharmacokinetic profiles, which influence the choice of one drug over another. The licensed indications vary considerably between the three drugs and micafungin is the only echinocandin licensed for use in neonates.2 None of the echinocandins are absorbed when administered orally. Micafungin is the only echinocandin that does not require storage in a refrigerator.

Dosing A loading dose is recommended for caspofungin and anidulafungin and weight-based maintenance doses are required for micafungin and caspofungin.1

Renal and hepatic considerations No dose adjustments are required for patients with renal impairment. The dose of caspofungin should be reduced for those with moderate hepatic impairment. There is limited experience with caspofungin in severe hepatic impairment.2 In contrast, for micafungin, no dose adjustment is necessary for patients with mild or moderate hepatic impairment and there are currently insufficient data available to support its use in severe hepatic impairment.2

No dosing adjustments are required for anidulafungin for patients with mild, moderate or severe liver impairment, but patients should be monitored for evidence of worsening hepatic function.2

Adverse effects Adverse effects within the class are limited, although all can cause deranged LFTs. Close monitoring of liver function is recommended and, if LFTs increase to more than three times the upper limit of normal, or the Child-Pugh score increases, consideration should be given to stopping the drug or switching to an alternative medicine. Additionally, micafungin has a specific warning highlighting the risk of developing hepatocellular tumours.2

Interactions The potential for drug interactions may also impact on choice of echinocandin. Anidulafungin is not considered to have any clinically significant drug interactions.2 Caspofungin and micafungin have the potential to interact with medicines metabolised via the cytochrome P450 isoenzymes.2

Flucytosine Flucytosine was originally developed as an anticancer drug and was subsequently found to have activity against yeasts. Flucytosine is a competitive inhibitor of uracil metabolism. The drug is converted intracellularly to 5-fluorouracil where it is incorporated into fungal RNA and exerts its effect (see Figure 2, p178).2 Secondary resistance can develop rapidly during treatment and therefore it is generally administered as adjuvant therapy in combination with another antifungal. One of the main advantages of the drug is that it crosses the blood-brain barrier and therefore remains a first-line treatment option for cryptococcal meningitis in conjunction with amphotericin.1 Practice points for flucytosine can be found in Box 4.

Dosing Flucytosine dosing is weight-based and, generally, divided into four IV doses per 24 hours. TDM should be considered for all patients, especially those with changing renal function.

Renal and hepatic considerations Flucytosine requires dose modification for patients with renal dysfunction.2 There are no formal recommendations for dose adjustments for patients with hepatic impairment.2 However, in clinical practice, a dose reduction or alternative medicine should be considered for patients with hepatic transaminase levels more than three times the upper limit of normal.

Adverse effects Flucytosine can cause severe haematological disturbances, such as thrombocytopenia, leucopenia, agranulocytosis and aplastic anaemia. It should therefore be used with caution in patients with bone marrow suppression or blood dyscrasias. All patients receiving flucytosine require close monitoring of full blood count and renal and hepatic function.2

Future therapies Although several new antifungal drugs have been licensed in the past five years, some patients remain difficult to treat. The main reasons for this include: antifungal resistance (intrinsic or acquired); drug interactions; organ dysfunction preventing the use of some medicines; poor penetration into sites such as the eyes and urinary tract; and adverse effects. Research into new therapies is ongoing, some of which is described below.

New amphotericin formulations New pegylated formulations of liposomal amphotericin have
demonstrated better efficacy than standard liposomal amphotericin in mouse models, although no improvements in mortality have been seen. A novel formulation of hydrophilic, heparin-surfaced nanoparticles containing amphotericin, known as amphotericin hydrosomes, have been designed to target infected sites by local adhesion. Amphotericin hydrosomes have been estimated to be seven times less toxic than conventional amphotericin in a murine model, but there are no published clinical results.

**Liposomal nystatin** Nystatin is only available as a topical preparation because of issues around solubility and toxicity with parenteral formulations. Recently, a new liposomal formulation of nystatin has been shown to have less toxicity than the original parenteral formulation (although renal toxicity appears to be similar to that of conventional amphotericin) while preserving antifungal activity. The pharmaceutical company involved is not pursuing further research with liposomal nystatin at present.

**New azoles** Isavuconazole and ravuconazole are two newazole antifungals that have a broad spectrum of activity, long half-life and large volume of distribution. Additionally, there are good in vitro data supporting their efficacy in treatment of invasive aspergillosis and candidiasis. Both compounds are in early phase III development. Another new azole, albcaconazole, has shown very potent activity against Candida spp, Cryptococcus spp and Aspergillus spp.

**New echinocandins** Aminocandin is an IV echinocandin with in vitro activity against Candida spp and Aspergillus spp. It has a long half-life, which may allow for a wide dosing interval — less frequently than once a day. An oral echinocandin is also currently under development, which would expand therapeutic use of this group of drugs outside hospitals.

**Nikkomycins** Nikkomycins inhibit the synthesis of cell wall chitin, a polysaccharide found in most fungi but not in mammalian cells, leading to osmotic lysis and cell death. The class was first described in 1976 and came out of research that aimed to discover fungicides for agricultural use. In experimental fungal models nikkomycin Z demonstrates only a modest activity against opportunistic fungi; however, synergistic activity against Candida spp, Cryptococcus spp and Aspergillus spp has been observed in vitro when the drug is combined with either fluconazole or itraconazole.

**Sordarins** Sordarins are compounds that affect the translocation of protein synthesis by inhibiting elongation factor 2, an essential factor for fungal protein synthesis. They also halt the addition of amino acid residues to the growing peptide chain. In vitro models suggest minimal activity against Aspergillus spp and in vivo studies in mice have yielded poor data.

**Pradimicins and benanomycins** Pradimicins and benanomycins disrupt the fungal cell membrane by binding to terminal D-mannosides. They have shown some in vitro and in vivo activity against Aspergillus spp, but further study is needed to investigate potential use as monotherapy or combination therapy for invasive aspergillosis.

**Combination and sequential therapy** The development of new antifungal drugs creates the potential for the use of combination regimens to help reduce the mortality associated with invasive fungal infections, particularly with invasive aspergillosis.

Based on the treatment of other infectious diseases, such as HIV, tuberculosis and cryptococcal meningitis, combination therapy for fungal disease seems logical — it could improve efficacy and enable the use of lower doses of other antifungals. However, laboratory and clinical data on combination therapy or sequential therapy for invasive aspergillosis are few; a range of effects from synergy to antagonism are reported (and there is also the potential for increased toxicity and cost).

**Immunotherapy** Immunotherapy is designed to increase the number of phagocytic cells, modulate the kinetics or actions of those cells at the site of infection, or activate the fungicidal activity of phagocytes to kill fungal cells more efficiently. Attacking the host immune response instead of the fungus itself is an attractive idea yet, to date, only data derived from in vitro studies using animal models suggest
improvement with immunomodulators and data from many of the clinical studies lack statistical power.

**Checking antifungal prescriptions**

For pharmacists involved in the management of invasive fungal infections, there are four key checks which should be considered for each prescription of an antifungal medicine:

- **Dose** — is a loading dose required? Are the loading and maintenance doses weight-based? Is adjustment required for co-existing renal or hepatic dysfunction?
- **Administration** — does the antifungal have specific administration instructions? Is a test dose required?
- **Monitoring** — what are the side effects? What parameters need to be monitored?
- **Interactions** — identify and manage drug-drug, drug-patient and drug-food interactions

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**Invasive fungal infections**

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To complete the module, you will need to log in to the site. If you are a new visitor, it is simple to register as a user (free to all Royal Pharmaceutical Society members).

**Questions**

This month’s Lifelong Learning questions are based on the CLINICAL FOCUS articles on invasive fungal infections, which were commissioned from independent authors.

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April’s Lifelong Learning module on lung cancer closes on 28 June 2011

The April 2011 CLINICAL FOCUS articles on lung cancer are linked to a learning@lunch flex module from the Centre for Pharmacy Postgraduate Education — further information at www.cppe.ac.uk/learning@lunch

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**References**