Review
Optimizing antifungal choice and administration

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Abstract

Background:
The antifungal armamentarium includes a number of drug classes and agents within each class. Successful IFI management depends on optimal matching of drug choice with the individual patient and causative pathogen, and maximizing effectiveness of the selected drug through appropriate dosing and toxicity management.

Objective:
This review is intended to provide a brief overview of key factors involved in optimizing antifungal choice and administration for patients with invasive fungal infections (IFIs).

Findings:
Antifungals differ in spectrum of activity, and these differences are critical when selecting the antifungal most likely to provide success for a patient with an IFI. When the species has not yet been identified, an analysis of regional epidemiology and risk factors can provide clues as to the most likely pathogen. For severely immunocompromised patients, a fungicidal agent may be preferred over a fungistatic agent, although more research is needed in this area. Triazoles, particularly itraconazole and posaconazole, exhibit great interpatient pharmacokinetic variability related to absorption. Steps can be taken to maximize absorption when using these agents. Voriconazole concentration is affected by polymorphisms in the major metabolic enzyme, cytochrome P450 2C19. Triazoles, and to a lesser extent other antifungals, are also subject to drug–drug interactions, which needs to be considered when selecting a particular antifungal agent for use in a severely ill patient on polypharmacy. Therapeutic drug monitoring may be a useful adjunct for patients receiving itraconazole, voriconazole, or posaconazole. When the IFI involves a pharmacologically protected site, such as the central nervous system (CNS) or eye, 5-fluorocytosine, fluconazole, or voriconazole are generally preferred. Echinocandin penetration is typically inadequate for IFIs of the CNS or eye. Antifungal agents also differ in their toxicity profiles, and these issues also need to be considered and managed when making an antifungal choice.

Conclusion:
Successful management of IFIs relies in part on the accurate selection of an antifungal agent for the infection. Drug characteristics can help in the selection of drug therapy. These characteristics include the drug’s spectrum of activity, pharmacokinetics, pharmacodynamics, toxicity profile, and distribution to the infection site. Matching the drug profile to the patient and fungal species contribute to optimal management of infection.

Introduction
Clinicians now have multiple drugs from several antifungal drug classes for the management of invasive fungal infections (IFIs). These include four drugs of the polyene class (amphotericin B [AmB] deoxycholate and three lipid-based amphotericin B formulations: amphotericin B colloidal dispersion [ABCD], amphotericin B lipid complex [ABLC], and liposomal AmB [L-AMB]); four triazole drugs (itraconazole, fluconazole, voriconazole, and posaconazole); three echinocandins (caspofungin, micafungin, and anidulafungin), and...
### Spectrum of activity

A critically important consideration is the agent's spectrum of activity. Antifungal classes, and even agents within the same class, often exhibit differential activity against particular fungal pathogens (Table 1). For example, different antifungals show variable activity against different *Candida* spp. *C. albicans* and *C. tropicalis* are susceptible to all agents, but triazoles show minimal or variable activity against *C. glabrata*, and echinocandins exhibit the greatest activity. Both polyenes and (particularly) echinocandins are active against *C. krusei*, while only voriconazole and to a lesser extent posaconazole exhibit reasonable activity. Polyenes and triazoles demonstrate good activity for *C. parapsilosis*, while echinocandins are less active against this pathogen.

Polymorphisms exhibit reduced activity against *C. parapsilosis*, while echinocandins are less active against this pathogen. Polyenes and triazoles do not exhibit activity against *C. lusitaniae*. The echinocandins exhibit reduced activity against *C. parapsilosis* and *C. guilliermondii*.

Although important, identification at the species level is often not available in most microbiology laboratories until several days into the course of treatment; delayed or inadequate initial antifungal therapy has been linked to poorer outcomes. Hence, ‘hitting the target right first time’ requires an understanding of local epidemiology patterns, and using this in conjunction with antifungal spectrum of activity to guide initial drug selection. *Candida* spp. distribution and patterns of resistance can vary not only by clinical service but also globally and by geographic regions. In the United States, the most recent survey has demonstrated the continuing emergence of drug resistance.

5-fluorocytosine (5FC, also known as flucytosine), a pyrimidine analog. Additional agents are in development.

The azoles are available as either intravenous (IV) or oral formulations (with the exception of posaconazole, which does not currently have an IV formulation, and itraconazole, which has an IV formulation in Europe but not the United States); the polyenes and echinocandins can only be administered parenterally; and 5FC is only available in an oral preparation. Besides route of administration, other variables differentiate antifungal agents, and can be important when selecting the most suitable agent.

This review examines how to utilize these differentiating characteristics to optimize antifungal choice and administration for patients. Ideally, data from randomized controlled, head-to-head clinical trials would be available when selecting an agent (e.g., Herbrecht *et al.*, comparing voriconazole and AmB for invasive aspergillosis [IA]), but often these data are not available. Hence, understanding of drug characteristics assumes greater importance for drug selection.

### Table 1. Antifungal spectrum of activity against more common invasive fungal pathogens (data from Lewis, 2011; Denning and Hope, 2010; Dodds Ashley *et al.*, 2006; and Pfaller and Diekema, 2010).

<table>
<thead>
<tr>
<th>Polyenes</th>
<th>Triazoles</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td><em>C. guilliermondii</em></td>
<td>−</td>
<td>±</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td><em>A. fumigatus</em></td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td><em>A. flavus</em></td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td><em>A. terreus</em></td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><em>A. niger</em></td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td><em>A. nidulans</em></td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fusarium spp.</td>
<td>±</td>
<td>−</td>
</tr>
<tr>
<td>Scedosporium prolificans</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Scedosporium apiospermum</td>
<td>−/±</td>
<td>−</td>
</tr>
<tr>
<td>Mucorales</td>
<td>±</td>
<td>−</td>
</tr>
<tr>
<td>Blastomyces spp.</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Histoplasma spp.</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coccidioides spp.</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Plus signs (+) indicate the antifungal agent has activity against the specified organism; plus/minus signs (±) indicate the agent has variable or slight activity against the specified organism; and minus signs (−) indicate the agent does not have activity against the specified organism.

| Varities echinocandin activity against dimorphic fungi has been described in vitro, depending on whether they are in mycelial or yeast-like form. |

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Pharmacokinetics (PK) and therapeutic drug monitoring (TDM)

PK issues are also important considerations for drug selection and when trying to optimize drug levels for maximal benefit and minimal risk. PK variability is a particular concern with triazole therapy, where various factors affect absorption and bioavailability and where genetic polymorphisms of cytochrome P450 (CYP) 2C19 can alter voriconazole plasma levels. Drug–drug interactions and comorbidities (renal or hepatic insufficiency) can also have important PK effects.

Oral itraconazole and posaconazole show greater variability in absorption than oral fluconazole or voriconazole. The capsular form of itraconazole is associated with wide variability27–29, with markedly lower absorption and plasma concentrations when administered under fasting versus fed conditions30,31. Itraconazole solution demonstrates more predictable absorption and higher plasma concentrations compared to the itraconazole capsule formulation, particularly under fasting conditions12,33. Administration of itraconazole capsules with an acidic beverage has been shown to enhance absorption. Food also increases the bioavailability of the capsule form.34 Wide interpatient pharmacokinetic variability has also been observed with posaconazole35, and similar to itraconazole, absorption and bioavailability of posaconazole is markedly increased when administered with food or a nutritional supplement versus when fasting.36–39. Gastric acidity is also important for posaconazole absorption40. Finally, posaconazole absorption is saturable, thus despite a long elimination half-life, exposure is increased when administered as divided doses of 200 mg four times daily versus a single 800 mg daily dose.41,42. Intertreatment variability with voriconazole is primarily due to differences in metabolism related to CYP2C19 polymorphisms, rather than absorption issues, although voriconazole absorption is modestly reduced by administration with food.43. CYP2C19 is the major determinant of voriconazole metabolism and clearance, and patients who are homozygous extensive CYP2C19 metabolizers have markedly lower plasma concentrations than homozygous poor metabolizers or heterozygous extensive metabolizers.44,45 Fluconazole demonstrates predictable, linear PK that is unaffected by food or gastric acidity.46–48.

TDM has been proposed as a potential tool for optimizing therapy with itraconazole, voriconazole, and posaconazole35,49–52. Each of these drugs meet widely accepted criteria for TDM: unpredictable population PK, a relatively narrow therapeutic window, and a fairly well defined clinical therapeutic range.49,51 TDM recommended trough concentrations for voriconazole and posaconazole efficacy are each approximately >1 µg/mL.50,51,53–57 A recommended trough <5 µg/mL has been recommended to limit the likelihood of voriconazole toxicity; a toxicity trough associated with posaconazole has not been defined.31

Comorbid organ dysfunction, specifically renal or hepatic insufficiency, alters the PK of certain antifungals and impacts either drug selection or the dosing regimen design. Dose reductions of fluconazole or 5FC are recommended for patients with renal insufficiency. No dosing adjustments for any of the polyene formulations, oral voriconazole, posaconazole, or any of the echinocandins are required in patients with renal dysfunction.7 However, caution should be exercised when IV voriconazole is used in patients with a creatinine clearance (CrCl) <50 mL/min or with IV itraconazole in patients with CrCl <30 mL/min. This is because the cyclohexatin component of these parenteral formulations can accumulate in patients with renal disease, and some animal studies suggest very high cyclohexatin may be associated with renal toxicity.58 Voriconazole dose reduction is recommendations for patients with mild-to-moderate hepatic dysfunction.59 Similarly, caspofungin dose should be halved in patients with moderate hepatic insufficiency.60 No dosing adjustments are needed based on hepatic insufficiency for any other antifungal.7

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Optimizing antifungal choice and administration: An Ark.
Drug interactions and toxicity

The likelihood for drug–drug interactions is greater with triazoles than other major antifungal classes. All the triazoles are substrates for one or more CYP450 enzymes, which creates the potential for bidirectional drug–drug interactions when these drugs are used concomitantly with other drugs that are also substrates for these enzymes. All triazoles are either moderate or strong inhibitors of CYP3A4, while fluconazole, and voriconazole also inhibit CYP2C9. Voriconazole is also a strong inhibitor of CYP2C19. Because of this, clinically relevant potential drug–drug interactions can occur when particular triazoles are coadministered with drugs that either induce or inhibit CYP450 isoenzymes or that are substrates for them. A large list of significant drug–drug interactions have been noted with triazoles (although less with posaconazole).

Drug–drug interactions need to be considered not only when initiating antifungal therapy, but also when discontinuing it. One will often need to adjust the dose of the remaining non-antifungal drug. Interestingly, at our institution, we sometimes use the voriconazole-elevating effects of coadministered omeprazole to increase voriconazole exposure in situations where simple dosage increases have minimal impact.

Drug–drug interactions involving other (non-triazole) antifungals have been reviewed elsewhere. Echinocandins are not appreciable substrates, inducers, or inhibitors of CYP450 isoenzymes, and exhibit few clinically relevant drug–drug interactions. Clinically relevant polyene drug–drug interactions are not associated with drug exposure per se, but rather with their polyene nephrotoxicity, additive nephrotoxic effects when coadministered with other nephrotoxic agents, and altered renal elimination or electrolyte imbalances due to these renal effects.

Toxicities associated with antifungal agents can also impact drug choice and monitoring. Toxicity associated with 5FC includes hepatitis and myelosuppression, especially at serum concentrations ≥100 μg/mL. Polyene antifungals exhibit dose-related nephrotoxicity which is reduced with newer lipid formulations of AmB compared to conventional AmB deoxycholate. Polyenes have also been linked with common infusion-related reactions and less frequently anemia. Furthermore, polyene-related nephrotoxicity increases the risk of serious 5FC-related adverse events such as bone marrow suppression when polyenes are coadministered with this 5FC. Triazoles are generally safe and well tolerated. The most common side effects are gastrointestinal. One important consideration with the triazole class is modest QTc prolongation. This is not typically important unless they are combined with other pharmacologic agents with similar conduction properties. Among the class, voriconazole is associated with greater but still low incidence of hepatotoxicity and also exhibits several unique side effects including visual disturbances and photosensitivity. Very high concentrations of voriconazole have also been associated with reversible neurologic toxicity, with 31% (5/16) of patients with trough levels >5.5 mg/L experiencing encephalopathy as a serious adverse event in one study, and none of 30 patients with trough levels ≤5.5 mg/L. Onset of encephalopathy ranged from 5 to 30 days following start of voriconazole therapy. Fluconazole is a well tolerated antifungal without significant toxicity. All triazoles are also teratogenic.

Echinocandins are generally well tolerated and exhibit few toxicities, the most common being occasional mild infusion-related reactions.

Distribution to infection sites

Distribution to the site of infection is another PK variable of potential importance when individualizing antifungal therapy. A number of pathogenic fungi have a propensity to disseminate to pharmacologically protected body sites – particularly the central nervous system (CNS) or eye, or urine with Candida spp. – and antifungals differ in their ability to penetrate these tissues. Of the triazoles, only fluconazole and voriconazole penetrate to any measurable degree into the CSF or intra-ocular compartments, while the echinocandins typically lack penetration or achieve very low levels in these tissues. 5FC exhibits excellent penetration to all common infection sites, while polyenes show only modest penetration into the CSF. Fluconazole and 5FC are the only antifungals that demonstrate any appreciable excretion into the urine for patients with asymptomatic Candida urinary tract infections.

Conclusions

Optimal IFI management depends on multiple factors, including rapid and accurate diagnosis and early treatment with an antifungal agent or antifungal combination best suited for the individual patient and causative pathogen. Once a suitable antifungal is selected, it is important to maximize effectiveness by managing its administration and taking the appropriate steps to maximize efficacy and reduce toxicity. Under certain circumstances, TDM may be useful. Knowledge of the agent’s spectrum of activity is essential, particularly when the species has been identified, but epidemiology patterns and risk factor evaluation are important guides when species identification is not available. Certain antifungals and dosages are better than others when the IFI involves a pharmacologically protected site. When selecting certain triazoles, an understanding of factors affecting absorption and ways to...
optimize exposure is essential, including an understanding of drug–drug interactions. Toxicity monitoring is important when using polyenes and 5FC, and to a lesser extent with certain triazoles. Risk of nephrotoxicity is a concern when considering polyene selection. Knowledge of all these factors contributes to an optimal therapy regimen for patients with an IFI.

Transparency

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Declaration of financial/other relationships

D.A. has disclosed that he has been a consultant to Astellas and Merck.

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