Antifungal Agents

Spectrum of Activity, Pharmacology, and Clinical Indications

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KEYWORDS

• Antifungal • Spectrum of activity • Azole • Echinocandins • Amphotericin B • Pharmacokinetics • Indications • Toxicity

KEY POINTS

- The currently available antifungal agents vary significantly in terms of spectrum of activity. The echinocandins exhibit potent activity against *Candida*, whereas the newer triazoles offer an extended spectrum of activity that includes *Aspergillus* and emerging filamentous pathogens.
- The pharmacokinetic properties differ among the antifungal drugs. Important considerations include absorption, tissue site penetration, impact of organ dysfunction on dosing, routes of metabolism, and the need for therapeutic drug monitoring.
- Many triazoles are metabolized via hepatic CYP450 enzymes. Drug–drug interactions are frequent and common enzyme polymorphisms may lead to unpredictable drug levels.
- Drug dosing and Food and Drug Administration–approved clinical indications for individual antifungal drugs are reviewed.

INTRODUCTION: THE EVOLUTION OF ANTIFUNGAL DRUG THERAPY

Continued advancement of medical science offers life-saving treatment options for a variety of hematologic, oncologic, and rheumatologic conditions. Immunosuppression, a common therapeutic side-effect, predisposes patients to invasive fungal infections, which are escalating in prevalence.[1,2] The development of effective, well-tolerated antifungals has lagged behind the advances of antibacterial therapy. Amphotericin B deoxycholate, an antifungal developed in the 1950s, marked a major therapeutic advance (**Box 1**). Although very effective for the treatment of numerous

Disclosure Statement: The authors have nothing to disclose.
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Infect Dis Clin N Am 30 (2016) 51–83
http://dx.doi.org/10.1016/j.idc.2015.10.012 **id.theclinics.com**
0891-5520/16/$ – see front matter

Box 1
History of antifungal therapy

- The first antifungal, amphotericin B deoxycholate, was introduced in 1958. It offers potent, broad-spectrum antifungal activity but is associated with significant renal toxicity and infusion reactions.
- Flucytosine, a pyrimidine analogue introduced in 1973, is active against *Candida* and *Cryptococcus*. Its use is limited by emergence of drug resistance and toxicity.
- The first-generation azole drugs, including fluconazole and itraconazole, became available in the 1990s. These agents offer the advantage of oral administration and have good activity against yeast pathogens. Due to CYP450 interactions, there are many drug–drug interactions.
- Lipid-based amphotericin B formulations were introduced in the 1990s and maintain the potent, broad-spectrum activity of the deoxycholate formulation with less toxicity.
- The echinocandin drugs became available in the 2000s and offer excellent activity against *Candida* with few drug–drug interactions; however, they are available in parenteral form only.
- The second-generation of azole drugs, including voriconazole, posaconazole, and isavuconazole, were brought to market beginning in the 2000s. The major advantage of these agents is the extended spectrum of activity against filamentous fungi.

invasive fungal infections, it is not without cost. Side-effects, including renal failure, electrolyte abnormalities, and infusion reactions, often limit its use.[3] However, for many years, amphotericin B remained the sole option for the treatment of invasive mycosis. In the 1970s, flucytosine, a pyrimidine analogue, was introduced. Its use has been limited by rapid emergence of resistance when used alone, as well as associated toxicities, including bone marrow suppression. In the mid-1990s, new lipid-based amphotericin B formulations were brought to market. Compared with the initial deoxycholate formulation, these have improved side-effect profiles with reduced nephrotoxicity and remain the mainstay for treatment of many life-threatening fungal infections.

In addition to the advent of the lipid-based amphotericin B formulations, another major advance of the 1990s was the addition of the triazole drug class (see **Box 1**). Compared with the amphotericin B formulations, the azole drugs are significantly better tolerated. The first-generation azole drugs (fluconazole-1990, itraconazole-1992) demonstrate excellent activity against *Candida* spp. The spectrum of itraconazole activity also includes endemic fungi, such as histoplasmosis. However, the original triazoles agents are inferior to amphotericin B for treatment of invasive filamentous fungal infections, such as aspergillosis and mucormycosis. The second-generation azole drugs (voriconazole-2002, posaconazole-2006) are broad-spectrum agents, with additional activity against filamentous fungi while retaining anti-*Candida* activity.[4,5] The newest azole released in 2015 (isavuconazole) has similarly broad activity with more favorable pharmacologic properties, allowing for improved bioavailability, more predictable drug levels, and fewer drug interactions.

The newest antifungal class, the echinocandins, was introduced in 2001 with caspofungin. Micafungin and anidulafungin were soon to follow. These agents exhibit potent activity against *Candida* spp, including many azole-resistant organisms and *C glabrata*. In addition, they demonstrate modest activity against *Aspergillus* spp. Favorable attributes of the echinocandin drugs include their excellent side-effect profiles and few drug–drug interactions. However, only parental formulations are available for this drug class.