Overview of Treatment Approaches for Fungal Infections

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KEYWORDS

• Antifungal • Fungal infections • Invasive mycoses • Amphotericin • Triazoles • Echinocandins • Flucytosine

KEY POINTS

There are 4 main groups of antifungals and each one has a specific mechanism of action: polyenes and azoles disrupt the cell membrane, echinocandins affect the cell wall synthesis, and pyrimidine analogues block the DNA synthesis.

- Amphotericin B is still the drug of choice to treat empiric severe and invasive fungal infections due to its broad spectrum of activity.
- Triazoles are the preferred agents for the treatment and prevention of invasive aspergillosis in most patients, and for many endemic mycoses.
- Echinocandins are usually preferred among other antifungals for their activity against *Candida* spp.
- Fluocytosine is generally used in combination of amphotericin B to treat refractory *Candida* infections and cryptococcal meningitis.

INTRODUCTION

Fungi are eukaryotic organisms that cause both endemic and severe infections, predominantly in the immunocompromised and debilitated host. Yeasts (eg, *Candida* spp), molds (eg, *Aspergillus* spp), and dimorphic fungi (eg, *Histoplasma capsulatum*) are the 3 groups in which fungi are generally classified.

Structurally, fungi are usually formed by a cell membrane surrounded by a fungal cell wall. The cell membrane is mostly formed from ergosterol and zymosterol (fungi equivalents of cholesterol), whereas mannoproteins, chitin, and beta-glucans are the main components of the fungal wall. These elements not only confer rigidity to the fungus but can also alter the host immunity, causing some patients' exuberant inflammatory reactions responsible for tissue injury and other systemic manifestations, such as respiratory failure and even death.[1–3]

Antifungals are commonly used drugs for the treatment and prophylaxis of most fungal infections and can be divided into 4 main groups: polyenes, azoles (triazoles and imidazoles), echinocandins, and pyrimidine analogues. They have different mechanisms of action, which result in different spectrums of activity. Polyenes and azoles disrupt the cell membrane, echinocandins affect the synthesis of the cell wall, and pyrimidine

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analogues block the DNA synthesis. This is important because additive effect may be achieved by combining different antifungal classes, particularly in very severe or invasive disease.

Understanding the precise use of the established and new antifungal agents is critical because fungal infections are on the rise. The increased mobility of patients to endemic fungal regions, together with an aging population with more chronic conditions, malignancies, transplants, and autoimmune diseases that require the use of potent immunosuppressant agents, represent the main contributors to this increase. This article reviews the main characteristics, clinical uses, and secondary effects of the main antifungals used in clinical practice to treat systemic and chest fungal infections.

Amphotericin B

Developed in the 1950s, amphotericin B (AmB) is a natural product of *Streptomyces nodosus*. Despite being among oldest drugs available to treat fungal diseases, it is still the drug of choice for severe and invasive fungal infections due to its broad spectrum of activity. It is effective for most clinical isolates of *Candida* spp and *Aspergillus* spp, *Cryptococcus neoformans*, endemic mycosis, *Zygomycetes*, and brown-black molds. However, there are well known AmB-resistant organisms, including chromoblastomycosis, *Aspergillus terreus*, *Candida lusitaniae*, *Scedosporium* spp, *Trichosporon* spp, and some *Fusarium* spp.[4]

AmB belongs to the polyenes group and it has been classically accepted that it exerts action by binding to ergosterol. AmB-ergosterol binding was thought to disrupt the fungal cell membrane by creating pores that allow the efflux of electrolytes and other molecules, causing the death of the organism. Recent evidence suggests that AmB also forms large, extramembranous aggregates that kill yeast by extracting ergosterol from lipid bilayers.[5] The AmB effect is not specific to ergosterol and in mammalian cells may also exhibit altered cholesterol content, causing cell damage, which is responsible for some of its known toxicity. Resistance to AmB is rare and has been attributed to a decreased content of ergosterol or other sterols in the fungal membrane.

AmB is poorly absorbed and, therefore, is commonly administered intravenously (IV). Deoxycholate is used to solubilize AmB and is responsible for some of the well-known drug-toxicities, particularly the nephrotoxicity. To avoid that, lipid formulations have been developed (liposomal AmB, AmB lipid complex, and AmB colloidal dispersion) and are generally preferred because they are more potent and have lower incidence of nephrotoxicity and other infusion-related reactions. Direct or local instillation (intraperitoneal, intrathecal, intravitreal, and bladder irrigation), as well as inhaled administration, are also available. Inhaled lipid formulations are favored over the deoxycholate preparation because the former has been shown to affect surfactant proteins.[6–8]

If nephrotoxicity develops, it usually improves after discontinuation of therapy. However, permanent effects may occur, particularly in patients receiving doses greater than 5 gm of AmB or when AmB is used in conjunction with other nephrotoxic drugs. Hydration and sodium repletion before initiation of AmB may decrease the risk of nephrotoxicity; frequent monitoring of renal function and avoidance of concomitant administration of other nephrotoxic agents is recommended. However, alternative safer options are generally preferred when available. Recommended monitoring includes regular cell blood count (CBC), serum electrolytes (magnesium and potassium), and renal and liver function tests.[9]

Infusion-related toxicities are also common, consisting mostly of fever, chills, hypotension, nausea, vomiting, and bronchospasm. Life-threating hyperkalemia and arrhythmias has been described after rapid infusion and, therefore, infusion over 2 to 6 hours is recommended.[10] Pulmonary toxicity is a concern with concomitant infusion of leukocytes and should be avoided.[11]

Despite the aforementioned secondary effects, IV liposomal formulation of AmB is a primary indication for empiric treatment of neutropenic fever, cryptococcal meningitis, *Zygomycetes*, and severe infections caused by endemic mycosis (*Histoplasma*, *Blastomyces*, *Coccidioides*, and *Sporothrix*).[9,12] It is an alternative to voriconazole for initial and salvage therapy for invasive aspergillosis. The inhaled formulation has been shown to be protective against the development of invasive aspergillosis in neutropenic patients with cancer and current guidelines recommend it use for prophylaxis in patients with prolonged neutropenia and lung transplant.[13] Inhaled AmB is also recommended as adjunctive therapy in the setting of tracheobronchial aspergillosis associated with anastomotic endobronchial ischemia or ischemic reperfusion injury due to airway ischemia associated with lung transplant.[13]

AmB is usually the preferred antifungal for severe fungal infections during pregnancy and is considered by the US Food and Drug Administration (FDA) as a class B agent. Infant risk cannot be ruled out and breast feeding is not recommended while receiving AmB.[9,14,15]