



# The value of amphotericin B in the treatment of invasive fungal infections<sup>☆</sup>

Michael Klepser PharmD, FCCP\*

Ferris State University, Kalamazoo, MI 49008, USA

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Polyenes;  
Resistance

**Abstract** Over the last 20 years, there has been an increase in the total number of invasive fungal infections (IFIs) and in infections caused by rare and emerging pathogens. This is due in part to the growing population of immunocompromised patients at risk of developing fungal infections. Three classes of antifungal agents are widely used for the treatment of systemic fungal infections: polyenes, azoles, and echinocandins. Polyenes were the first antifungal agents developed and have a long-standing history in the treatment of IFIs. The use of conventional amphotericin B has been limited because of toxic side effects, which have been reduced by the lipid formulations of amphotericin B. Treatment options for invasive mycoses have expanded with the recent introduction of the second-generation triazoles (voriconazole and posaconazole) and the echinocandins (caspofungin, micafungin, anidulafungin). Despite the increased number of antifungal drugs, resistance issues present a problem in the treatment of IFIs. Although some fungal pathogens display innate resistance, others have developed resistance secondary to selective pressure. This article briefly reviews the changing epidemiology of fungal infections and associated risk factors, resistance issues with commonly administered antifungal agents, and treatment options for IFIs, with a focus on polyenes.

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## 1. Invasive fungal infections (IFIs): changing epidemiology and risk factors

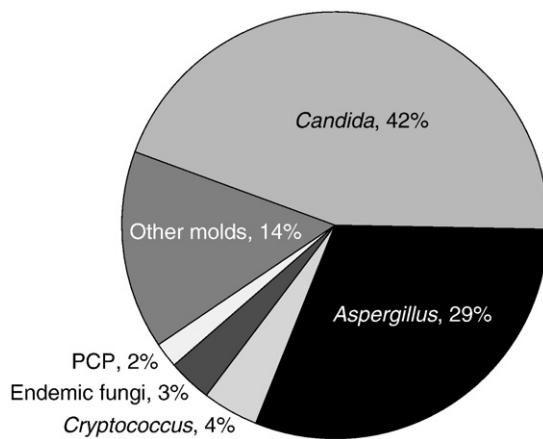
The population of patients at risk of invasive mycoses has been increasing as a result of infections, malignancies, and advances in medicine that allow more patients to undergo transplantation procedures, receive aggressive immunosuppressive therapies, and in general create a more susceptible patient population. *Candida* and *Aspergillus* species remain

the cause of most fungal infections (Fig. 1) [1], but other previously less common and emerging fungal pathogens are being increasingly diagnosed in patients at risk of IFIs. *Candida albicans* is implicated in approximately 50% of patients with candidiasis [2,3]; however, infections caused by other species, such as *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida parapsilosis*, and *Candida lusitanae*, are rising [4–7]. In the case of invasive aspergillosis, *Aspergillus fumigatus* is the causative agent responsible for roughly 80% of cases [8,9]. Infections caused by other *Aspergillus* species, including *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus ustus* have been increasingly documented [10,11]. There has also been a rise in infections caused by non-*Aspergillus* molds, such as *Fusarium* and *Scedosporium* species, as well

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\* Tel.: +1 269 387 7298.

E-mail address: MichaelKlepser@ferris.edu.



**Fig. 1** Types of fungal pathogens responsible for invasive mycoses among solid organ and hematopoietic stem cell transplant recipients. PCP, *Pneumocystis jirovecii* (*carinii*).

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as Zygomycetes [10,12]. At some institutions, infections caused by *Fusarium* species and Zygomycetes have increased 2-fold or more over the last 20 years [10,13,14]. Risk factors associated with invasive fungal infections are summarized in Table 1.

The annual incidence of invasive candidiasis is estimated at 72-228 per million population [1] and is associated with a mortality rate of 10%-49% [15-17]. Zaoutis et al estimated that candidemia results in a mean increase of \$39,331 in hospital charges [17]. A cost-effectiveness analysis among patients in the intensive care unit found empiric caspofungin therapy to be the most effective treatment strategy for invasive candidiasis but also the most expensive (\$295,115 per discounted life-year saved). Invasive mycoses caused by *Aspergillus* species range between 12 and 34 infections per million population [1]. Invasive aspergillosis has a mortality rate as high as >85%, and an evaluation of 1209 aspergillosis cases at multiple medical centers found that 62% of patients with *Aspergillus* infections die within 3 months of a positive culture [18,19]. An analysis conducted using hospital discharge data estimates a mean total hospital charge of \$96,731 for patients diagnosed with primary or secondary aspergillosis [20]. The prevalence of less common fungal pathogens is low; for instance, Zygomycetes cause approximately 1.7 infections per million population annually. However, the effects on patients who are at risk are devastating; patients with disseminated zygomycosis have a 96% mortality rate [21]. Costs associated with treatment of rare or emerging fungal infections remain to be evaluated but are expected to be considerably high.

Over the past 2 decades, there has been an increase in the number of antifungal drugs available for the treatment of IFIs. The spectrum of activity of antifungals in the 3 classes of drugs (polyenes, azoles, and echinocandins), resistance issues associated with antifungal drugs, and treatment options are discussed in the following sections.

**Table 1** Risk factors associated with invasive fungal infections

| Fungal pathogen                                                                          | Major risk factors                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Candida</i> species                                                                   | <ul style="list-style-type: none"> <li>• Advanced age or premature births</li> <li>• Hematological malignancies</li> <li>• Neutropenia, <math>\geq</math> 8-day stay in the intensive care unit</li> <li>• Abdominal surgery</li> <li>• Broad-spectrum antibiotics and immunosuppressive drugs</li> <li>• Total parenteral nutrition</li> <li>• Vascular catheters</li> </ul> |
| <i>Cryptococcus neoformans</i>                                                           | <ul style="list-style-type: none"> <li>• Human immunodeficiency virus</li> <li>• Corticosteroid therapy</li> <li>• Hematological malignancies</li> <li>• Solid organ transplants</li> </ul>                                                                                                                                                                                   |
| <i>Blastoschizomyces capitatus</i><br><i>Trichosporon</i> and <i>Rhodotorula</i> species | <ul style="list-style-type: none"> <li>• Hematological malignancies</li> <li>• Neutropenia</li> <li>• Hematological malignancies</li> <li>• Catheterization in immunocompromised patients</li> <li>• Immunosuppressive drugs</li> <li>• Corticosteroids</li> </ul>                                                                                                            |
| <i>Aspergillus</i> , <i>Fusarium</i> , and <i>Scedosporium</i> species                   | <ul style="list-style-type: none"> <li>• Hematological malignancies</li> <li>• Neutropenia</li> <li>• Hematopoietic stem cell and solid organ transplants</li> <li>• Graft-versus-host disease</li> <li>• Immunosuppressive drugs</li> <li>• Corticosteroids</li> </ul>                                                                                                       |
| Zygomycetes                                                                              | <ul style="list-style-type: none"> <li>• Hematological malignancies</li> <li>• Diabetes with acidemia</li> <li>• Iron overload</li> <li>• Bone marrow, hematopoietic stem cell, and solid organ transplants</li> </ul>                                                                                                                                                        |

## 2. Overview of antifungal drugs: focus on polyenes

### 2.1. Azoles

Fluconazole, itraconazole, and the new triazoles, voriconazole and posaconazole, are the azoles most commonly used to combat systemic fungal infections. Azoles exert their primary action by inhibiting the synthesis of ergosterol, by inhibiting the enzyme lanosterol 14  $\alpha$ -demethylase [22]. Azoles are typically fungistatic against yeasts and fungicidal against molds. Except for fluconazole, azoles commonly used to treat systemic fungal infections have activity against most *Aspergillus* species [23-27]. Azoles also have activity against most *Candida* species, *Cryptococcus neoformans*, and dimorphic fungi [24]. Activity against Zygomycetes, *Fusarium* and *Scedosporium* species is variable among the different azole drugs (Table 2) [23,24,26,28,29].

Azoles interact with human cytochrome P (CYP) 450 enzymes, thus increasing the potential for drug-drug-

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