



## Ask the Expert: Examining Controversies and Unanswered Questions in the Management of Invasive Fungal Infections

A continuing education (CE) activity entitled *Examining the Evidence in the Management of Invasive Fungal Infections: Case Study Approach* was presented as one of three CE in the Mornings topics at the 45th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in December 2010 (which are available at [www.ashpadvantage.com/cemornings](http://www.ashpadvantage.com/cemornings)). The program was presented by Peggy L. Carver, Pharm.D., FCCP. Attendees submitted questions about unresolved issues and controversies that were later addressed by Dr. Carver in a live webinar conducted on February 8, 2011. The highlights of the webinar pertaining to non-neutropenic patients are described in this e-newsletter, and highlights pertaining to neutropenic and transplant patients will be discussed in an e-newsletter to be released in May 2011.

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### Faculty Podcast Interviews

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## Epidemiology

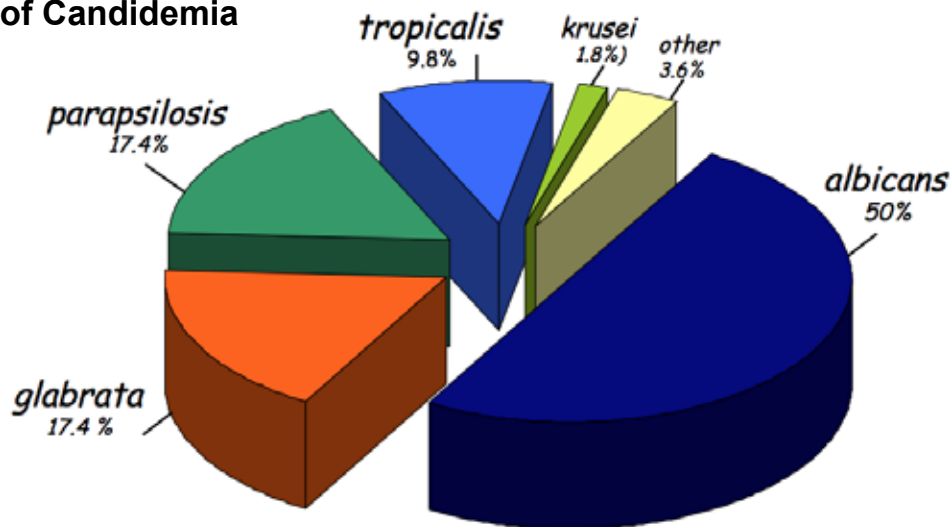
Invasive fungal infection is a major cause of morbidity and mortality in hospitalized patients, and *Candida* is the most common cause of invasive fungal infection.<sup>1-3</sup> Candidemia is the fourth most common cause of nosocomial bloodstream infections in the United States.<sup>3</sup> The *Candida* species most commonly isolated from patients with bloodstream infections are *Candida albicans* (50%), *Candida glabrata* (17%), and *Candida parapsilosis* (17%) (Figure on Page 2).<sup>4</sup> The prevalence of these species varies by the type of patient and hospital location (e.g., surgical intensive care unit versus neonatal intensive care unit).<sup>5</sup>

Risk factors for candidemia include colonization with *Candida* species, antibiotic or corticosteroid use, renal failure, diabetes mellitus, gastrointestinal (GI) disease, surgery (especially GI surgery), use of a foreign device (e.g., central venous catheter), prolonged use of mechanical ventilation or length of stay in the intensive care unit (ICU), and profound neutropenia.<sup>6</sup> *Candida glabrata* (*C. glabrata*) is cause for concern in non-neutropenic patients because of its high prevalence and resistance to fluconazole.<sup>7</sup>

According to 2009 guidelines from the Infectious Diseases Society of America (IDSA), fluconazole or an echinocandin is recommended for the treatment of candidemia and as empiric therapy for suspected invasive candidiasis in non-neutropenic patients, although fluconazole is preferred for infections due to *Candida parapsilosis* (*C. parapsilosis*).<sup>3</sup>



**Figure.**  
**Epidemiology of Candidemia**



Horn DL et al. *Clin Infect Dis*. 2009;48:1695-1703.

Wisplinghoff H et al. *Clin Infect Dis*. 2004;39:309-17.

Pfaller MA et al. *Clin Microbiol Rev*. 2007; 20:133-63.

Pfaller MA et al. *Diagn Microbiol Infect Dis*. 2010;68:278-83.

Source: Pfaller MA et al. *Diagn Microbiol Infect Dis*. 2010; 68:278-83.

An echinocandin is preferred for patients with or at high risk for infection due to *C. glabrata*, recent azole exposure, or moderately-severe or severe disease.<sup>3</sup>

The use of fluconazole to treat *Candida* bloodstream infections caused by non-susceptible strains currently is the subject of controversy. The fluconazole minimum inhibitory concentration (MIC) breakpoints used in Europe and the United States to establish whether *Candida* isolates are susceptible or resistant to the drug differ.<sup>8</sup> In Europe, *Candida* isolates with fluconazole MICs exceeding 8 mg/L are categorized as resistant to the drug. The Clinical and Laboratory Standards Institute (CLSI) in the United States defines a fluconazole MIC of 8 mg/L or less, 16-32 mg/L, and more than 64 mg/L as susceptible, susceptible-dose dependent, and resistant, respectively, for *Candida* species. The current (2009) IDSA guidelines do not explicitly address whether fluconazole or an echinocandin is preferred for isolates with fluconazole MICs in the susceptible-dose dependent range.

The CLSI fluconazole MIC breakpoints were derived primarily from studies of the drug in patients with human immunodeficiency virus infection and oropharyngeal candidiasis (usually *Candida albicans*), so the relevance for non-neutropenic patients with candidemia or candidiasis is questionable.<sup>8,9</sup> Recent analyses of clinical data in patients with candidemia have shown that fluconazole is reliably effective at daily doses at least 25- to 50-fold higher than the MIC.<sup>8,10</sup> Thus, in an adult with an average body weight and normal renal function, a 400-mg daily dose would suffice for a susceptible isolate with an MIC of 4 mg/L, but high-dose therapy with 800 mg/day would be required for an isolate with an MIC of 16-32 mg/L (i.e., one categorized as susceptible-dose dependent). The ratio of the fluconazole area under the exposure curve to MIC and the ratio of the dose to MIC both correlate with therapeutic success. However, the data used in these recent analyses were obtained primarily from *Candida* strains with MICs in the susceptible range. Therefore, the uncertainty surrounding use of fluconazole to treat *Candida* bloodstream infections caused by non-susceptible strains remains unresolved.



## ***C. glabrata***

In non-neutropenic patients, advanced age (>60 years), recent abdominal surgery, a time from ICU admission to the first positive blood culture of 7 days or less, recent cephalosporin use, the presence of a solid tumor, and the absence of diabetes mellitus have been identified as independent risk factors for *C. glabrata* bloodstream infections.<sup>11</sup> Delaying empiric antifungal treatment for more than 12 hours after drawing a positive blood culture is associated with higher hospital mortality than earlier initiation of treatment.<sup>12</sup> Positive blood cultures typically are not obtained until after 4-5 days have elapsed, with speciation and susceptibility testing requiring an additional 1-2 days. Antifungal susceptibility testing is not the standard of care or widely available. Knowledge of the independent risk factors for *C. glabrata* bloodstream infection can be used to promptly identify the need for an echinocandin and initiate empiric therapy in critically-ill patients.

## ***C. parapsilosis***

The preference for fluconazole instead of an echinocandin in non-neutropenic patients with invasive *C. parapsilosis* infections in the IDSA guidelines is based on the higher MICs of echinocandins for *C. parapsilosis* than for other common *Candida* species, although echinocandin use may be continued for patients who initially received the drug, are clinically improved, and have negative follow-up blood cultures.<sup>3</sup> However, the results of a meta-analysis published in late December 2010 raised questions about the validity of the IDSA preference for fluconazole over echinocandins in non-neutropenic patients with invasive *C. parapsilosis* infections. The meta-analysis involved five randomized, blinded trials comparing echinocandins with other antifungal agents (including fluconazole) in such patients.<sup>13</sup> The success rate in treating candidemia or invasive candidiasis due to *C. parapsilosis* was similar with echinocandins (76.5%) and other antifungal agents (73%).

“ Early appropriate antifungal therapy for invasive fungal infections is imperative to optimize patient outcomes. Difficulty making a diagnosis, identifying the infecting species, and resolving controversies in the management of these infections may make it difficult for clinicians to optimize treatment and outcomes. ”

—Peggy L. Carver, Pharm.D., FCCP



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