Systemic *Candida* Infection in the ICU

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## Introduction

Invasive fungal infections are a growing problem in the intensive care unit (ICU), with *Candida* species being the most common cause of these infections. *Candida* is now the forth or fifth most frequent pathogen isolated from bloodstream infections [1, 2]. In 2004, in order to summarize current knowledge about treatment of the different forms of invasive candidiasis, new guidelines for the treatment of candidiasis were published by experts on behalf of the Infectious Diseases Society of America (IDSA) [3]. The application of these guidelines to the treatment of systemic candidiasis in the ICU will be discussed, as well as new combination approaches to therapy, involving use of more than one antifungal agent.

## Candida species and Candidiasis

*Candida* can cause not only usually mild, mucocutaneous infection, but also much more dangerous invasive candidiasis, also known as systemic or deep-seated candidiasis. Invasive candidiasis is associated with significant morbidity and high mortality [4–7]. It is a life-threatening infection, usually involving multiple organs, the *Candida* having disseminated via the bloodstream to organs such as the liver, spleen and kidney (‘disseminated candidiasis’). Acute disseminated candidiasis is characterized by the rapid onset of fever, sometimes shock, and other signs of sepsis. Occasionally clinical signs such as the presence of retinal deposits or cutaneous nodules provide clues to the correct diagnosis but much more commonly the diagnosis is made on the basis of general signs or symptoms of active infection plus growth of *Candida* from the blood or another specimen taken from a normally sterile site. In immunocompromised patients, a presumptive diagnosis may be made based on multiple positive cultures from non-sterile sites. Because culture-confirmation is relatively slow compared to that achieved with bacterial infections, and may be negative even in the presence of subsequent proven fungal sepsis [8], antifungal therapy is sometimes given on an empiric basis, because early, aggressive administration has been associated with a lower mortality [9, 10].

*Candida albicans* is the commonest species associated with deep infection but other (“non-albicans”) species are becoming increasingly common, of which *Candida glabrata* now dominates [11, 12]. This shift in the epidemiology of *Candida* species is probably a direct result of a significant increase in the use of fluconazole over the last decade, both as prophylaxis or long term suppressive therapy in high-risk patients and as first-line and empiric therapy in non-neutropenic patients. Flu-
conazole is used because it is less toxic than amphotericin B, but some non-\textit{albicans} species, such as \textit{C. krusei} and some strains of \textit{C. glabrata}, are intrinsically resistant [11, 13]. Consequently, while fluconazole may reduce the incidence of candidiasis, its use has been associated with the emergence of fluconazole-resistance among strains of \textit{C. albicans} [14, 15] and an increase generally in the incidence of azole-resistant infections [16]. Multiple \textit{Candida} infections (with more than one species of \textit{Candida}) may also now be more common. In a survey conducted in the USA among patients with candidemia between 1995–97 [12] multiple fungal infections occurred with a frequency of 5%. These had the highest \textit{Candida}-attributable mortality (15%).

Because patients who succumb to this infection are already critically ill, the overall mortality is inevitably high. However, methods for distinguishing deaths due to \textit{Candida} from other causes of death are well described in the published literature. Thus while, for example, in a large prospective survey of candidemia involving 1447 patients in the USA, the overall mortality was 47%, the \textit{Candida}-attributable mortality was 10–15% [3]. The species associated with the highest \textit{Candida}-attributable mortality was \textit{C. albicans} (14%), rising to 15% when the infection was due to more than one species [12]. Most deaths from invasive candidiasis occur within 10–14 days of cultures from the blood or other clinically significant site becoming positive. The duration of a course of treatment in adults with candidemia, recommended by the IDSA guidelines, is 14 days after the last positive blood culture and resolution of signs and symptoms [3, 17, 18].

### Existing Treatments

A number of antifungal products are available but the mortality and morbidity of invasive candidiasis is still high despite current best therapy. The frequency of persistent candidemia is 12–17%, while \textit{Candida}-attributable mortality is 10–19% [3, 19, 20]. Antifungal drugs currently recommended for the treatment of invasive candidiasis by the IDSA are amphotericin B, fluconazole or caspofungin [3]. In each case these are given as monotherapy.

The IDSA makes an important point: extensive data from randomized trials are only available for acute blood-culture positive candidiasis and well-controlled trial-based data are lacking for other forms of invasive candidiasis (including intra-abdominal and urinary candidiasis, which are common in ICU patients).

Amphotericin B deoxycholate (Fungizone) has been the mainstay of treatment for systemic fungal infections since its introduction into clinical practice in 1959 [21]. It is a fungicidal drug with a broad spectrum of activity. However, clinical benefit can be limited by infusion-related toxic reactions (such as fever, rigors, chills and hypotension) and dose-limiting toxicity, especially to the kidney and liver. This toxicity limits the intravenous dose of amphotericin B deoxycholate, with the usual dose being 0.6 mg/kg, but doses can be increased to a maximum of 1 mg/kg of body weight per day if tolerated. Resistance to amphotericin B is rare (it is seen in some \textit{C. lusitaniae} isolates), but some isolates of \textit{C. glabrata} or \textit{C. krusei} show reduced susceptibility, suggesting a need for the higher dose.

The toxicity of amphotericin B has been considerably reduced by the development of lipid-associated formulations, of which the most commonly used are Ambisome and Abelcet. The manufacturer’s recommended dosage of these lipid-asso-