Is the Debate About Treatment of Candida parapsilosis Complex Infections With Echinocandins Much Ado About Nothing?

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(See the Major Article by Fernández-Ruiz et al on pages 1413–21.)

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The development of the echinocandin class of antifungals represents an important advance in the treatment of candidemia and other forms of invasive candidiasis. The echinocandins demonstrate very good efficacy, a favorable safety profile, and very few drug interactions. They have significant fungicidal activity against all Candida species. They are emerging as the treatment of choice for candidemia—but are they a panacea? They are only available for parenteral administration, have poor penetration into cerebrospinal fluid, and some species, such as Candida parapsilosis complex, demonstrate less in vitro susceptibility to the echinocandins than do most other Candida species, which raises the concern that infections caused by C. parapsilosis complex may be less responsive clinically to echinocandin therapy. A recent study in a murine model of disseminated Candida infection evaluated the efficacy of caspofungin against strains of C. parapsilosis with a range of susceptibilities and revealed differences among isolates. Caspofungin reduced the tissue burden of mice infected with isolates with minimum inhibitory concentrations (MICs) ≤0.5 μg/mL but was less effective against those with MICs of 1 μg/mL [1]. This concern has not been definitively addressed by the published, randomized clinical trials of the 3 echinocandins. Clinical and microbiological response rates for the echinocandins vs comparators in C. parapsilosis complex infection were not statistically significantly different in clinical trials. However, there were numerically higher numbers of persistent candidemia due to C. parapsilosis complex in the caspofungin arm compared with the amphotericin B deoxycholate arm and during standard-dose caspofungin compared with high-dose caspofungin, and the eradication rate of C. parapsilosis complex infection was lower with anidulafungin than with fluconazole [2–4]. None of these trials had sufficient power to assess noninferiority of echinocandins for C. parapsilosis complex, however. In a recent patient-level quantitative review of the same clinical trials, the species for which an echinocandin appeared least effective in univariate analysis was C. parapsilosis complex, and for this species only disease severity predicted survival [5]. This finding is consistent with the higher MICs of echinocandins with C. parapsilosis complex. Higher mortality, however, has not been definitively demonstrated for C. parapsilosis complex when treated with an echinocandin in clinical trials. This may be explained by the species’ relatively lower virulence, and lower virulence may partially explain the response of most C. parapsilosis complex infections to echinocandin therapy, regardless of reduced susceptibility. There is an ongoing debate on whether echinocandins are appropriate for treating C. parapsilosis complex infection.

Candida parapsilosis complex has emerged as one of the most commonly isolated Candida species causing bloodstream infections in Asia, Latin America, and parts of Europe. The observational study by Fernández-Ruiz et al, a subanalysis of the CANDIPOP study (a prospective surveillance program of hospitals in Spain), focuses on a large cohort of patients with C. parapsilosis complex bloodstream infection [6]. This study examines the impact of initial treatment on outcome—specifically, whether the use of an echinocandin entails a worse outcome compared with an azole. The population-based approach of the study enhances the validity of the results. Studies such as this also give an indication of what is
happening with regard to routine clinical management in actual practice. It is unlikely that there will be a randomized clinical trial that is designed to show optimal therapy for *C. parapsilosis* complex infections; well-designed observational studies become important sources of data that complement results from clinical trials. The primary outcome of clinical failure was defined as all-cause mortality between days 3 and 30 or persistently positive blood cultures after 72 hours of treatment. Patients who died within the first 72 hours were excluded from the analysis. Predictors of clinical failure were assessed for the entire study population, including neonates. A second analysis that excluded neonates calculated the propensity to receive an echinocandin or an azole as initial treatment given observed pretreatment characteristics. Propensity scoring was used to adjust for baseline imbalances between the treatment groups and potential confounding factors associated with initial therapy. It is noteworthy that this method can only adjust for known variables that were measured. It cannot exclude the potential effect of other confounders. Because the rates of in vitro resistance to azoles and the echinocandins that were tested, miconafungin and anidulafungin, were very low in this study, further analyses exploring the relationship between clinical failure and MIC values could not be performed. All resistant isolates were *C. parapsilosis* sensu stricto. Initial use of an echinocandin had no impact on the risk of clinical failure; a finding that is especially striking in view of the fact that those who received an echinocandin were more severely ill. This study also affirms an important principle in the management of candidemia—the protective effect of early central venous catheter removal. *Candida parapsilosis* complex candidemia has been associated with vascular catheters and parenteral nutrition. The authors acknowledge that catheter removal may have obscured any differences in antifungal treatment choice and outcome, but this is a moot point as removal of intravascular catheters is important in the management of catheter-related candidemia; even if the catheters are removed, antifungal therapy must be administered. They also acknowledge a lack of consistency in performing follow-up blood cultures, which may have caused persistence to have been underestimated. In general, if follow-up cultures are not obtained, the response should either be scored as indeterminate or a failure if other signs of progressive or poorly controlled disease are noted. Last, could there be a center effect? The number of cases and treatment by site are not provided.

There are numerous host, disease state, and treatment-related variables that affect the outcome of candidemia and other forms of invasive candidiasis. The selection of a particular agent for the treatment of candidemia should take into account a number of factors, including recent exposure to an antifungal agent, a history of allergy or intolerance to an antifungal agent, potential drug interactions, local epidemiology and resistance patterns, and severity of illness. The 2009 update of the clinical practice guidelines for the management of candidiasis by the Infectious Diseases Society of America (IDSA) provides a safe and reasonable approach to treatment of infections caused by *C. parapsilosis* complex [7]. The guidelines state that “for patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable.” The recommendation is graded B for strength (moderate evidence) and III for quality of evidence (evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees).

The therapy of candidemia and other forms of invasive candidiasis remains a challenging problem. Crude mortality is high; optimization of therapy is crucial to success. This article provides further support of recommendations of the IDSA guidelines. It is not carte blanche to treat all patients with *C. parapsilosis* complex infection with an echinocandin.

**Note**

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