The End of an Era in Defining the Optimal Treatment of Invasive Candidiasis

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(See the Major Article by Andes et al, 1110–22.)

We are approaching the 20th anniversary of 3 publications that helped redefine management of invasive candidiasis. In reviewing candidemia at Barnes Hospital, Fraser et al [1] reported a 20-fold increase in incidence in 1988–1989 compared with a decade earlier and a 63% mortality rate among the significant minority of patients who did not receive antifungal therapy. In an accompanying editorial, Edwards endorsed the authors’ call for a change in the management paradigm for candidemia: all patients required antifungal treatment [2]. Within 2 years, Rex et al [3] reported that fluconazole was as effective as amphotericin B deoxycholate for the treatment of candidemia in nonneutropenic patients. Therefore, just as candidemia and other forms of invasive candidiasis were emerging as major problems, clinicians had a well-tolerated and effective alternative to amphotericin B, the highly toxic frontline agent.

Almost 2 decades later, it is hard not to feel disappointment at where we stand in treating invasive candidiasis. Despite the introduction of the echinocandin antifungal agents, which are safe and broadly fungicidal against Candida species (including fluconazole-resistant isolates), mortality rates remain as high as 40% or greater [4]. Indeed, the echinocandins have been equivalent, but not superior, to fluconazole and amphotericin B in clinical trials [5–7]. Moreover, basic questions about adjunctive management measures are still unanswered. Most notable among ongoing controversies is the need for routine central venous catheter removal among patients with candidemia, which has been a matter of particularly contentious debate [8–14]. Measured against successes in the treatment of invasive aspergillosis [15–16], progress against invasive candidiasis has been middling.

In this context, the study by Andes and colleagues in the current issue of Clinical Infectious Diseases is among the most notable on invasive candidiasis in recent years [17]. The authors conducted a patient-level review of 1915 patients from 7 randomized antifungal treatment trials. Their most important finding is that treatment with an echinocandin was associated with improved survival and greater clinical success than treatment with a triazole or amphotericin B. In subgroup analyses, the improved outcomes were evident among patients infected with Candida albicans and non–C. albicans species and patients with candidemia. There were no differences in outcomes among patients infected with C. parapsilosis, which is significant because echinocandin minimum inhibitory concentrations against this species are typically elevated [18]. Interestingly, the benefit of echinocandin therapy was observed among patients with APACHE II scores in the lowest 2 quartiles; for patients with scores ≥24, outcomes did not differ by drug class.

One must be cautious in interpreting this study. Patients were enrolled in trials with diverse study designs, conducted over an extended period of time during which many advances in care were introduced. Investigators were limited to available data, which were often incomplete and not originally collected for patient-level analysis. Nevertheless, it is reasonable that pooled data would show differences that were not apparent in individual studies, particularly since the latter were powered for non-inferiority. Indeed, strong trends toward improved outcomes for patients treated with echinocandins compared with fluconazole and amphotericin B deoxycholate were reported in 2 of the earlier trials [5–6]. Moreover, the data are biologically plausible. The fungicidal activity and antifungal spectrum of the echinocandins may afford advantages over triazoles, and improved tolerability compared with amphotericin B may lessen...
failures due to withdrawal of therapy or toxicity. It is also not surprising that the most severely ill patients were unlikely to benefit from a particular drug class, as anticipated mortality rates with APACHE II scores ≥24 are approximately 50%–85% [19–20]. Many patients with invasive candidiasis are beyond the help of antifungal therapy by the time of diagnosis.

The authors’ claim that their data support central venous catheter removal during candidemia is more problematic. Clearly, catheter removal was associated with better mortality and clinical success rates. The findings are limited, however, by the lack of standardized criteria for catheter removal or data on time to removal. Because patients had to be alive to have a catheter removed and removal could occur at any point during treatment, there is a bias toward better outcomes in this group. In the absence of a randomized trial of catheter management approaches, heated debate about this issue will continue. Likewise, limitations of the available data made it impossible to address other timely issues, such as the impact of prior antifungal exposure or time to institution of antifungal therapy, the performance of lipid formulations of amphotericin B, the role of transitioning patients from an echinocandin to fluconazole, or outcomes among neutropenic patients.

Taken together, the data either support or do not contradict most of the Infectious Diseases Society of America’s practice guidelines for invasive candidiasis, which recommend an echinocandin for more severe illnesses, infections due to *C. glabrata* or *C. krusei*, or in settings of recent triazole exposure or neutropenia [21]. The authors maintain that an echinocandin should now be considered the first-line choice for most patients with invasive candidiasis. In general, we agree with this conclusion, albeit with important caveats. If echinocandins are associated with better outcomes in patients with a wide range of APACHE II scores, regardless of species, it is hard to justify withholding these agents. At the same time, we believe it is reasonable to transition to fluconazole to complete therapy in patients who are clinically stable and infected with isolates that are likely to be fluconazole susceptible [21–23]. The results of this study cannot be extrapolated to invasive diseases like meningitis, endophthalmitis, and urosepsis, in which echinocandins are limited by pharmacokinetic considerations, or to uncommon entities like endocarditis or myocarditis, for which clinical experience with echinocandins is limited. Echinocandins also should be avoided in patients with breakthrough infections or extensive prior exposure because resistance has been documented [24]. Finally, we feel it is never inappropriate to consider lipid formulations of amphotericin B, which are reliably fungicidal and less toxic than amphotericin B deoxycholate. In the absence of clinical trial data to the contrary, we advocate central venous catheter removal within the first 48 hours, if feasible. If catheters are retained, in vitro data suggest that echinocandins and amphotericin B may treat *Candida* within biofilms more effectively than fluconazole [25].

In conclusion, the Andes et al study likely marks the end of an era. The 30-day mortality rate among patients randomized to receive an echinocandin was still 27%, compared with 36% for other regimens. In fact, the findings that increased APACHE II score, age, and immunosuppressive therapy were independent predictors of mortality highlight that the host is a major driver of outcomes. In patients as sick as those with invasive candidiasis, it is not surprising that rapid initiation of antifungal therapy may be more important than choice of specific agent [26–27]. In this regard, the major challenge facing the field is the development of improved diagnostic tests. The sensitivity of blood cultures, the current gold standard for candidemia, is only 50%, and blood cultures become positive late in the disease course [28–29]. Nonculture-based assays, such as β-D-glucan detection or polymerase chain reaction, have the promise to diagnose patients with invasive candidiasis earlier or identify high-risk patients who might benefit from preemptive antifungal therapy [30–31]. In the future, therefore, improved outcomes are most likely to result from development and validation of early intervention strategies. Andes et al may have brought us as far as we are going to get in defining the optimal treatment of invasive candidiasis with our present management approaches.

**Note**

Potential conflicts of interest. All authors: No reported conflicts.

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**References**


