

Hence, in 275 episodes of fungemia initially reported as caused by a yeast, 30 (11%) involved either *Candida* species with a high minimum inhibitory concentration for echinocandins (5), a non-*Candida* opportunistic yeast (23), or pseudoyeast (7). We need prospective, multi-institutional studies to capture the prevalence of echinocandin-nonsusceptible *Candida* species and non-*Candida* yeasts. Finally, although it is unclear whether starting with an echinocandin for treatment of these patient is associated with inferior outcomes, further studies are needed to evaluate the impact of echinocandin-based preemptive therapy for that subset of patients.

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Reply to Kontoyiannis

TO THE EDITOR—We appreciate the comments of Dr. Kontoyiannis [1] relating to the recently updated Infectious Diseases Society of America treatment guidelines for invasive candidiasis [2]. It is easy to understand his perspective, which represents that of someone who almost exclusively treats severely immunosuppressed individuals. Let us briefly comment on the 2 issues that he raises: (1) the applicability of findings from large, randomized candidemia treatment studies to highly immunosuppressed patients, including those with neutropenia, and (2) the initial approach to antifungal therapy in this patient population with yeast in the bloodstream.

To address the first point, we agree that the numerous prospective, randomized trials for the treatment of candidemia have generally not enrolled significant numbers of neutropenic patients, stem cell transplant recipients, or other severely immunocompromised patients. In the earliest of

these studies, neutropenic patients were specifically excluded from enrollment into these trials because it was believed that their outcomes might not necessarily reflect those of nonneutropenic patients and that adding this element of heterogeneity might further confound the interpretation of study results [3, 4]. Subsequent studies have allowed enrollment of neutropenic patients, but these patients still constitute a very small proportion of the total enrollment [5–7]. As an example, in the largest of these recent studies, only ~10% of eligible patients were neutropenic at baseline [7]. Interestingly, the overall success seen in the neutropenic patients was similar to that seen in nonneutropenic patients. Still, these data do not sufficiently address the issue of optimal therapy for invasive candidiasis in the highly immunosuppressed patient. The obvious answer to this conundrum is to design and conduct a properly powered randomized trial comparing different therapies for an exclusively immunosuppressed and/or neutropenic population. Unfortunately, this has proven quite challenging. Large epidemiological surveys of candidemia in the United States demonstrate that only ~10% of all patients with candidemia are neutropenic [8]. Because of this reality, to conduct a candidemia treatment trial involving exclusively neutropenic patients has been considered unfeasible if one uses conventional methods of determining eligibility (ie, positive culture of blood or specimen from an ordinarily sterile site). For the moment, we are left to make the best of the limited data that are available from small numbers of these patients in randomized clinical trials, nonrandomized studies, and our collective clinical experience.

The second issue is equally difficult to address: how does one approach the neutropenic or severely immunosuppressed patient with fungemia due to non-*Candida* yeasts? Kontoyiannis correctly points out that non-*Candida* yeasts may account for up to 10% of all bloodstream yeast isolates in selected centers, but how com-

monly does this occur in the most centers? We simply do not have these data. From our perspective, this most important point emphasizes the need for constant vigilance in this area. We agree that less common yeasts can be important pathogens in these highly vulnerable patients and that any empirical choice for antifungal therapy may prove to be inadequate (eg, giving an echinocandin to treat *Cryptococcus neoformans* infection) for a particular heavily immunosuppressed patient with yeast in the bloodstream. Unfortunately, no single choice of an antifungal agent adequately addresses each of the possible pathogens. Fortunately, the recent development of early diagnostic techniques (eg, fluorescence in situ hybridization using peptide nucleic acid probes) that are able to reliably identify organisms as *Candida* species could soon make antifungal selection more targeted.

Finally, it is important to recognize the limitations of treatment guidelines in general. They are never intended to address every clinical situation, nor can they. Their main intent is to espouse the most reasonable and accepted treatment approaches, based on available data, for the more common and easily defined manifestations of a particular infectious process. With this in mind, we greatly value the perspective of those whose opinions differ from those offered in these guidelines.

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Cefepime and All-Cause Mortality

TO THE EDITOR—We are grateful to

Nguyen et al [1] for rising to the challenge and tackling the question of whether we should continue using cefepime. The primary outcome in our meta-analysis was all-cause mortality [2]. We did not use infection-related mortality as did Sanz et al [3]. When all-cause mortality data were not given in a published trial, we contacted the authors of that trial and asked for 30-day all-cause mortality data by intention to treat, as in Gomez et al [4]. Of note, copies of these letters were always sent to the pharmaceutical companies that funded these trials, but they were not answered, even after presentation of preliminary results [5]. Correspondence is available on request.

Prevention of death is the main goal of treating patients with sepsis. Assigning the direct cause of death for patients with sepsis is difficult or impossible, even with postmortem examinations [6–9]. Thus, infection-related mortality may not be reliable and can be biased. We wanted to capture all deaths, including those related to adverse events, superinfections, and *Clostridium difficile* infection. Completely unrelated causes should have been equally distributed between trial arms. Clinical and microbiological success may not be reliable; these are nonrandomized comparisons applied to a subgroup of assessable patients, using a poorly defined outcome.

Nguyen et al [1] raised the issue of confounders, both during a trial and between trials. Bow et al [10] used adequate randomization methods (central randomization and computer-generated sequencing), resulting in equal distribution of the risk factors related to mortality between the study groups. In our meta-analysis, in which we combined effects (not individuals), the main confounder considered was the comparator antibiotic. Visually and statistically, there was no heterogeneity between trials in the analysis for mortality (risk ratio, 1.26; 95% confidence interval, 1.08–1.49; $I^2 = 0\%$).

Three explanations for the difference in all-cause mortality might be examined.