Echinocandin-Based Initial Therapy in Fungemic Patients with Cancer: A Focus on Recent Guidelines of the Infectious Diseases Society of America

To the Editor—I read with interest the recently published Infectious Diseases Society of America guidelines regarding treatment of candidiasis, the most common fungal infection in humans [1]. This long-awaited document is an important contribution in summarizing the best available evidence as derived from a series of recent prospective, multicentered candidemia industry-sponsored trials. On the basis of these studies, echinocandins are recommended as one of the preferred primary options for treatment of documented candidiasis and/or candidemia. The authors are cautious not to endorse the indiscriminate empirical use of echinocandins for high-risk patients with immunosuppression. For these patients, a lipid formulation of amphotericin B (3–5 mg/kg/day; A-I), an echinocandin (caspofungin; A-I), or voriconazole (B-I) are suggested [1]. I would like expand on 2 points that put these recommendations in perspective as they relate to empirical and early (“preemptive”) therapy for fungemic patients with cancer.

First, highly immunocompromised patients, especially ones with hematologic malignancies and/or who underwent stem cell transplantation were not included in the trials of all classes of modern antifungal agents (polyenes, triazoles, and echinocandins). These patients could be highly immunosuppressed (eg, because of a high dose of systemic corticosteroids) but not myelosuppressed, making the distinction of recommendation between neutropenic and nonneutropenic patients somewhat artificial. The lack of representation of highly compromised patients in modern candidemia trials is hardly surprising, because multiple comorbidities and frequent empirical or preemptive prior use of antifungals are common among this complex patient population and preclude enrollment. For example, in my institution for the last 6 months (July 2008–January 2009), we screened candidemic adult patients with cancer for enrollment in a candidemia trial. Of these 28 patients, only 3 were evaluable for enrollment according to the study’s restrictive eligibility criteria (1 was finally enrolled, because 2 patients declined to participate because they were not ill enough and wanted oral outpatient therapy). Thus, of the 28 patients screened initially, only 1 (4%) entered in the trial! The reasons for nonevaluable of the remaining 25 patients were prior systemic antifungal therapy given for >4 days at diagnosis of candidemia (13 patients), outpatient status (8 patients), advanced terminal cancer (2 patients), and other reasons (2 patients). Caution needs to be exercised for all these agents; polyenes have poor activity in neutropenic patients with candidiasis [2], and voriconazole might not be immune to problems of cross-resistance or tolerance (at least for some relatively common Candida species, such as Candida glabrata) in a patient population that is typically heavily preexposed to another azole, fluconazole, as prophylaxis [3]. Special vigilance is needed to assess large-scale experience in outcomes of highly compromised patients with fungemia who receive echinocandins, given the narrower spectrum of these agents. Although emerging data regarding the efficacy and tolerability of echinocandins in cancer patients are reassuring, these are derived from ad hoc analysis of randomized studies [2, 4] or single-institution experiences [5], in which patient selection bias is unquestionably high. More data are needed regarding the efficacy of echinocandin monotherapy, especially for neutropenic patients with active leukemia. Because coinfections in these patients are quite common [6], special emphasis needs to be given to whether the treatment of concomitant infections was appropriate, to decrease confounders for evaluation of response.

Second, although Candida infections comprise the vast majority of yeasts growing in blood cultures [7], clinicians should not always assume this to be the case, especially for high-risk hematology patients. To complicate things further, sporadic cases of Candida species exhibiting nonsusceptibility to echinocandins has been recently reported in this patient population [8]. We looked at our experience (2003–2007) at the M. D. Anderson Cancer Center in 275 episodes of fungemia in cancer patients. Of the 268 patients, 245 had Candida species grow in blood cultures, whereas the remaining 23 had fungemia due to non-Candida yeasts (Cryptococcus species, Trichosporon species, Saccharomyces cerevisiae, Rhodotorula species, and other rare yeasts in 11, 4, 4, 4, and 3 patients, respectively). These non-Candida yeasts were generally considered to be nonsusceptible to echinocandins [9]. In addition, 7 patients had pseudofungemia due to the phaeohyphomycetes Aurobasidium. Of the 245 bloodstream Candida isolates that had in vitro susceptibility testing (by the Clinical and Laboratory Standards Institute method), 5 had a minimum inhibitory concentration for echinocandins >2 µg/mL, which is defined as “nonsusceptible” [10]. Most of these patients had hematologic malignancy and/or underwent stem cell transplantation, had significant immunosuppression, and had antifungal exposure (data not shown).
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 patients 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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References


epidemiology of a still frequently lethal infection. Cancer (in press).

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 two 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 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-

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