Echinocandins: Ask Not What They Can Do for Esophageal Candidiasis—Ask What Studies of Esophageal Candidiasis Can Do for Them

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(See the articles by Krause et al. on pages 770–5 and de Wet et al. on pages 842–9)

And so, my fellow Americans: ask not what your country can do for you—ask what you can do for your country.

President John F. Kennedy, 20 January 1961

Although much less common than bacterial infections, fungal diseases have attracted robust interest by both health care providers and pharmaceutical companies for developing newer, broadly active, more effective, safer, and more-tolerable antifungal drugs. The echinocandins belong to a relatively new class of fungicidal compounds that are uniquely able to inhibit the synthesis of 1,3-β-D-glucan, which constitutes a major component of the cell wall of many pathogenic fungi but is absent in mammalian cells. These antifungal compounds are highly active in vitro against Candida and Aspergillus species; are marginally active against dimorphic fungi, such as Histoplasma capsulatum and Coccidioides immitis; and have no effect against Cryptococcus neoformans and the zygomycetes.

Caspofungin, the only echinocandin that is currently available for use in the United States, was initially approved by the US Food and Drug Administration (FDA) for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other antifungal therapies and, more recently, was approved for treatment of esophageal, bloodstream, and invasive Candida infections. Two other echinocandins, micafungin and anidulafungin, are currently being reviewed for possible FDA approval and are the subject of the 2 clinical trials that are reported in this issue of Clinical Infectious Diseases [1, 2]. These 2 prospective, randomized, double-blind, multiple-center, international clinical trials demonstrated that a 14–21-day course of intravenous micafungin [1] or anidulafungin [2] is as effective and safe as intravenous [1] or oral [2] fluconazole for treatment of esophageal candidiasis in patients with HIV infection or other predisposing risk factors. One prospective, randomized, international clinical trial had previously demonstrated that caspofungin is as effective and well tolerated as intravenous fluconazole [3], and 2 other trials had concluded that caspofungin is as effective as and better tolerated than amphotericin B for the treatment of esophageal candidiasis [4, 5]. Although the trials of neither micafungin [1] nor anidulafungin [2] assessed the recurrence of esophageal infection more than 2 weeks after completion of therapy, the results of a previous study had shown no significant differences in the rates of recurrence at 4 weeks after completion of a course of caspofungin or fluconazole [3].

The collective results of the 5 prospective clinical trials that compared echinocandins to fluconazole [1–3] or amphotericin B [4, 5] support the following principles: (1) all 3 echinocandins (caspofungin, micafungin, and anidulafungin) are probably of equivalent efficacy in treating esophageal candidiasis; (2) although it is conceivable that a fungicidal agent (i.e., an echinocandin) may inherently be superior (in terms of adequacy of response and time to resolution of clinical and mi-
crobiologic indicators of disease) to a fungistatic drug (i.e., an azole) in treating certain fungal diseases, the potential advantage of killing over inhibiting the multiplication of fungal cells does not materialize in the scenario of esophageal candidiasis; and (3) the degree of immunosuppression is more influential than the type of therapeutic agent in determining the likelihood of recurrence of esophageal candidiasis.

Since the mid 1990s, oral fluconazole and itraconazole oral solution have been considered to be convenient, not-so-expensive standard treatment for most cases of esophageal candidiasis [6]. No parenteral class of antifungals, including the echinocandins, is likely to reverse this prevalent clinical opinion, particularly now that a generic version of fluconazole has become available. Echinocandins have been reported to be beneficial in patients with esophagitis who are either infected with a fluconazole-resistant Candida strain or who have not clinically responded to fluconazole [7]; however, oral voriconazole is a less expensive and more convenient treatment than echinocandins and is equally effective as oral fluconazole [8].

The wide implementation of HAART has already reduced the overall incidence of esophageal candidiasis in the United States and other countries that could afford to institute this expensive public health measure; this may help explain why all clinical trials of echinocandins involving patients with esophageal candidiasis were conducted in Latin American and African countries. The HAART-induced improvement in immunity has also resulted in less use of oral triazoles for primary and secondary prevention and has spearheaded the evolving practitioners’ perception that a lower proportion of esophageal infections are being caused byazole-resistant or -tolerant Candida strains.

And so, what is the purpose of studying echinocandins in the context of treating a disease with a decreasing incidence and a plethora of alternative therapies? From the industry perspective, the most important objective of studying echinocandins in patients with esophageal candidiasis is to secure approval by the FDA and other international regulatory authorities for using these drugs for primary treatment of infection. Clinical trials of antifungal agents for treatment of Candida infections that affect some other bodily sites, noncandidal fungal infections, or clinical syndromes without a documented fungal infection present peculiar problems that may be hard to overcome. For instance, the lack of a widely accepted strategy for distinguishing Candida infection from colonization of the urinary tract can disallow the proper inclusion of patients and the accurate assessment of outcomes in clinical trials. Despite the existence of guidelines for the diagnosis and management of invasive aspergillosis, it is practically impossible to complete prospective randomized trials that assess primary treatment of this infection; this helps explain why caspofungin was approved by the FDA for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other antifungal agents in the absence of randomized comparative data. Although it is standard clinical practice to administer antifungal agents to neutropenic patients who remain febrile despite receiving seemingly appropriate antibacterial therapy, most patients with the syndrome of febrile neutropenia do not have documented invasive fungal infection; this underscores the reason why the FDA did not regard the submitted results of a clinical trial of febrile neutropenia as sufficient for approving the clinical use of micafungin.

From the perspective of health care providers, clinical trials of echinocandins in the context of esophageal candidiasis may allow us to better predict the efficacy, safety, and tolerability of such drugs when considered as treatment for the following more serious and potentially lethal clinical scenarios: (1) candidemia and invasive candidiasis that do not favorably respond to therapy with fluconazole, amphotericin B, or a combination of these 2 drugs in approximately one-third to one-fourth of patients [9–11], thereby encouraging the potential use of caspofungin [12] and anidulafungin [13] on the basis of initially promising clinical data; (2) Candida infections associated with medical devices [14], particularly that echinocandins have been shown in vitro studies to be more potent than azoles or amphotericin B against Candida biofilms [15, 16]; (3) persistently febrile neutropenia or critical illness, despite antibacterial therapy; (4) invasive aspergillosis, either alone or in combination with other antifungals; and (5) receipt of a transplant or serious illness in persons who are receiving inducers, inhibitors, or metabolic substrates of the cytochrome P-450 system (including rifampin, phenytoin, barbiturates, calcium channel-blocking agents, antiretroviral agents, cyclosporine, sirolimus, tacrolimus, sulfonlyurea oral hypoglycemics, warfarin, and omeprazole) and in whom echinocandins, but not azoles, can be administered concomitantly without much concern for drug interactions or pharmacokinetic alterations [17]. More clinical experience is required to further assess whether the reported elevation of hepatic transaminase levels in patients receiving both caspofungin and cyclosporine is clinically relevant and whether such a phenomenon applies as well to the other 2 echinocandins, micafungin and anidulafungin.

In this era of uncontrolled increases in the cost of health care, a third, rather unspoken objective could materialize from studying a number of drugs that belong to a single class of antifungals. Should all 3 echinocandins prove to have similar efficacy, safety, and tolerability in the context of treating nonesophageal Candida infections (as in the case of esophageal candidiasis), it is theoretically possible that competition may drive their acquisition costs down and, therefore, allow even more patients to potentially benefit from their use. That, however, can be achieved...
only when the rules of a free marketplace genuinely apply to the health care system.

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References