CLINICAL THERAPEUTICS

Echinocandins for Candidemia in Adults without Neutropenia

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

A 62-year-old man was admitted to the intensive care unit (ICU) with severe community-acquired pneumonia. On the sixth hospital day, he remained intubated and was receiving broad-spectrum antibiotics for his pneumonia when an episode of hypotension occurred, requiring volume expansion and the administration of vasopressors. The patient had diffuse pulmonary infiltrates and a serum creatinine level of 3 mg per deciliter (265 μmol per liter) and required mechanical ventilation with an oxygen concentration of 50%. Three days later, a blood culture of a specimen obtained from his venous catheter was reported to be growing candida species other than *Candida albicans*. An infectious disease consultant recommended that the central venous catheter be removed and replaced in another site and that treatment with caspofungin be initiated.

THE CLINICAL PROBLEM

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N Engl J Med 2006;355:1154-9.

Candida is the fourth most common cause of nosocomial bloodstream infection in general hospital populations.[1] The incidence of positive blood cultures for candida species was found to range from 2 to 28 cases per 10,000 hospitalizations in a survey of the worldwide literature between 1995 and 2005 and appears to have been generally stable or increasing during that decade.[2] Risk factors for candidemia include neutropenia, prolonged hospitalization (especially in the ICU), antibiotic use, intravascular catheterization, parenteral nutrition, abdominal surgery, and renal failure.[3]

Over 50% of the candida species isolates in the bloodstream are *C. albicans*, but there is some evidence of an increase in the incidence of infection with species other than albicans, primarily *C. glabrata*.[2] The increase in *C. glabrata* infections has been attributed to the extensive use of azole antifungal agents (particularly fluconazole [Diflucan, Pfizer]) for prophylaxis and therapy in high-risk populations, because this species is less sensitive than *C. albicans* to these drugs.

The effect of candidemia on the public health is somewhat difficult to assess, since most patients with such infections have one or more important coexisting diseases. However, in one analysis using data from the Nationwide Inpatient Sample 2000, candidemia was estimated to have been diagnosed in 8949 adults admitted to hospitals.[4] Candidemia was associated with an increase in mortality of 14.5%, a mean increase in the hospital stay of 10.1 days, and a mean increase in hospital charges of $39,331 per patient.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Candida species are a component of normal human flora, being found primarily in the gastrointestinal tract but also on the mucous membranes of the mouth and vagina. Transient skin colonization occurs from these sites. However, invasive candidiasis in healthy persons is extremely rare. Conditions favoring the development of an invasive infection include the suppression of normal bacterial flora with antibiotic agents and the disruption of the barrier function of the skin (as a result of the placement of an intravenous catheter) or of the gastrointestinal mucosa (as a result of chemotherapy-induced mucositis, surgery, or perforation).

The echinocandins are a new class of antifungal agents. They are noncompetitive inhibitors of the synthesis of beta-1,3-glucan, which is an essential constituent of the candida cell wall[5] (Fig. 1). Inhibition of the synthesis of beta-1,3-glucan disrupts the structure of the growing cell wall, resulting in osmotic instability and the death of susceptible yeast cells.[6]

The echinocandins are highly active in vitro against *C. albicans* as well as against other species, including *C. glabrata*, *C. tropicalis*, and *C. krusei*.[7,8] The minimum inhibitory concentrations of echinocandins are higher for the treatment of *C. parapsilosis* than for the other common candida species.[9] This difference has raised concern that *C. parapsilosis* might respond less well than other candida species or require higher doses.

However, in clinical trials there has been no evidence of reduced responsiveness of *C. parapsilosis* infections to echinocandin therapy, although the numbers are small.[10] In an analysis of all candida species isolated from 114 patients with candidemia, the minimum inhibitory concentration of caspofungin did not correlate with the outcome.[11] On the basis of these limited data, the candida species and in vitro susceptibility may not be of central importance in determining the outcome of echinocandin therapy for candidemia.

Clinically significant echinocandin resistance has been reported to arise during therapy for infections due to *C. albicans*, *C. glabrata*, and *C. parapsilosis*, but so far such cases have been rare.[12-14] When resistance to one echinocandin occurs, cross-resistance with other echinocandins has usually been complete. Candida species isolates with reduced susceptibility to azoles typically remain susceptible to echinocandins.

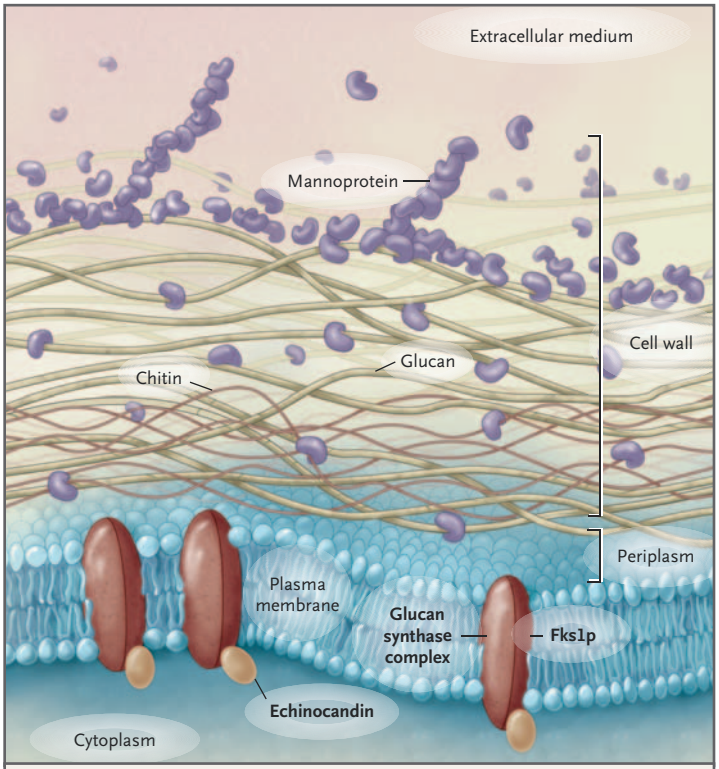

Figure 1. The Cell Wall of *Candida albicans*, Bounded by the Plasma Membrane and the Extracellular Medium.

The structural strength of the cell wall is maintained by fibrillar polysaccharides, largely beta-1,3-glucan, with lesser amounts of beta-1,6-glucan and chitin. Glucan and chitin are bound to each other and to proteins by covalent linkages. Mannoproteins are largely N-glycans that are attached to the fibrillar matrix by covalent and other bonds. The synthesis of beta-1,3-glucan is catalyzed by a glucan synthase complex in the plasma membrane; glucan is extruded into the periplasm and incorporated into the cell wall. The glucan synthase complex is inhibited by echinocandins, resulting in loss of the structural integrity of the cell wall. A subunit of glucan synthase designated Fks1p is thought to be the target of the echinocandin. Studies are under way to determine how the echinocandins inhibit Fks1p, the putative catalytic unit of the glucan synthase complex, and to identify the other proteins in the complex as well as topologic features of the complex within the cell.

CLINICAL EVIDENCE

Randomized clinical trials of echinocandins have included primarily patients with candidemia who did not have neutropenia, and candidemia was usually defined by a single positive blood culture with signs of infection. These trials have typically included 20% or fewer of patients who have other

forms of invasive candidiasis. The echinocandins that were evaluated in these trials, and that are currently available for clinical use, include caspofungin (Cancidas, Merck), micafungin (Mycamine, Funguard, Fujisawa), and anidulafungin (Eraxis, Pfizer).

Caspofungin and amphotericin B deoxycholate (conventional amphotericin B) (Fungizone, Bristol-Myers Squibb) were compared in a randomized, blind, noninferiority trial.[15] Among patients who had received at least 1 day of treatment, the rate of response after the completion of intravenous therapy was 73.4% among those assigned to receive caspofungin and 61.7% among those assigned to amphotericin B. Discontinuation because of toxic effects was an important reason for an inadequate response to amphotericin B. Caspofungin has not been studied in direct comparison with any of the azole antifungal agents in patients with candidemia.

Information on micafungin in invasive candidiasis is sparse.[16,17] The results of a randomized, double-blind comparison of 100 mg of intravenous micafungin daily with 3 mg of liposomal amphotericin B per kilogram of body weight daily are available only in abstract form.[17] Complete or partial responses were achieved in 89.6% of patients assigned to micafungin, as compared with 89.5% of those assigned to liposomal amphotericin B. Like caspofungin, micafungin has not been compared with any of the azole antifungal agents.

Anidulafungin (at an initial dose of 200 mg intravenously, followed by 100 mg intravenously daily) was compared with fluconazole (at an initial dose of 800 mg intravenously, followed by 400 mg intravenously) in a randomized, double-blind trial of candidemia and invasive candidiasis. The results have been described in an abstract and in the package insert for anidulafungin.[18,19] A complete or partial response was seen at the end of intravenous therapy in 75.6% of patients assigned to anidulafungin and 60.2% of those assigned to fluconazole. Survival was also improved with anidulafungin.

CLINICAL USE

Candidemia is typically diagnosed in the presence of a single positive blood culture for candida species. Positive cultures in specimens of blood obtained through an intravascular catheter are more likely to contain contaminants from skin flora on the catheter hub than are positive cultures of specimens obtained by venipuncture, but it is rarely safe to ignore the presence of candida in a blood culture, regardless of the source. In contrast, a positive culture of the catheter tip in the absence of a positive blood culture should not be used as the basis of a decision to begin treatment. Serologic testing, assays for glucan or antigen, and DNA testing have not been sufficiently promising to justify their use as guides to the initiation of therapy.

The considerations governing the choice of an echinocandin, as opposed to an azole, for initial treatment of candidemia in a patient who does not have neutropenia are not well established. The echinocandins have a broad spectrum of activity against a variety of candida species and thus may be especially preferred when *C. glabrata* or *C. krusei* is identified or suspected. In addition, fluconazole interacts with cytochrome P450 3A4, resulting in interactions with numerous agents; such interactions may dictate a preference for treatment with one of the echinocandins when other substrates of this enzyme complex are in use.

Data on which to base a choice among the three available echinocandins are even more limited. There has been more experience with caspofungin than with the other two agents. Micafungin has not been approved by the Food and Drug Administration (FDA) for invasive candidiasis, although it is approved for candida prophylaxis in patients undergoing hematopoietic stem-cell transplantation, and dosing for candidemia is not well established.

Before the initiation of therapy, it is helpful to obtain some assurance from the microbiology laboratory that the yeast seen on Gram's staining of a freshly positive blood culture is a candida species, because activity against other yeast is either poor or unknown. *Cryptococcus neoformans* and trichosporon species are known to be resistant to echinocandins. *C. albicans* can be distinguished from other candida species within hours by a variety of methods, but the final identification of species other than albicans takes several days. When an echinocandin is used, the determination of the candida species is probably irrelevant. Neither candida species nor antifungal susceptibility has proved to be predictive of therapeutic success with these drugs.

The echinocandins are not well absorbed orally and must be administered intravenously. Caspo-

fungin is given at an initial dose of 70 mg on the first day of treatment, followed by 50 mg daily; anidulafungin is given at an initial dose of 200 mg on the first day, followed by 100 mg daily. A recommended regimen has not been established for micafungin in the treatment of candidemia, although a dose of 100 mg daily was used in the European randomized clinical trial.[17] The presence of liver disease affects the metabolism of caspofungin to a limited extent, and a dose reduction is suggested, from 50 mg to 35 mg daily in the presence of moderate hepatic dysfunction (Child–Pugh score, 7 to 9, on a scale from 5 to 15, with higher scores indicating worse liver function).[20] Dose reduction in the presence of moderate hepatic dysfunction is not required for micafungin or anidulafungin.[21,22] Renal insufficiency does not require dose adjustment.

Echinocandin infusion should be given over a period of approximately 1 hour to minimize the risk of histamine-like symptoms. The patient should be observed closely during and after the initial infusion for such symptoms, including rash, urticaria, flushing, pruritus, bronchospasm, facial swelling, and hypotension; these symptoms are infrequent with slow infusion.

Removal or replacement of the central venous catheter is strongly recommended in patients with candidemia. A retrospective analysis of one clinical trial suggested that the duration of candidemia was shortened by prompt removal of the catheter.[23]

Some agents that greatly increase hepatic metabolism, such as rifampin (Rifadin, Aventis; Rimactane, Novartis), phenytoin (Dilantin, Parke-Davis), carbamazepine (Tegretol, Novartis), efavirenz (Sustiva, Bristol-Myers Squibb), and nevirapine (Viramune, Boehringer Ingelheim), may cause a small reduction in the blood concentrations of caspofungin and merit an increase in the dose, from 50 mg to 70 mg daily.[5] Caspofungin can decrease the area under the curve (AUC) for tacrolimus by 20%. Cyclosporine was reported to cause a 35% rise in the AUC for caspofungin, but two small subsequent studies failed to confirm this finding. Micafungin increased the AUC for sirolimus by 21%, and for nifedipine by 18%.[21] No interactions have yet been found with anidulafungin.[22]

Early during therapy, a complete ophthalmologic examination should be performed to detect endophthalmitis. Blood cultures should be obtained to document the resolution of fungemia. An intravascular focus of infection should be suspected when the blood cultures remain positive, including an intravascular catheter, endocarditis, or septic thrombophlebitis. In patients with blood cultures that clear but whose condition does not respond clinically, an undrained focus of infection should be suspected. If the response to one echinocandin is not adequate, the use of another drug in the same class is not likely to be effective.

If the clinical response appears to be satisfactory, and if no new signs or symptoms develop, treatment should be continued for at least 2 weeks. If the patient is able to receive oral medication, the regimen may be changed to oral fluconazole after 10 days of intravenous echinocandin therapy and a negative blood culture.

Data on average wholesale prices suggest that the average cost of a 20-day course of caspofungin in the United States is approximately $7,000 to $8,000, as compared with approximately $3,000 to $4,000 for anidulafungin and approximately $2,000 to $5,000 for generic intravenous fluconazole, depending on the dose.[24] The average wholesale price of micafungin, which, as noted, has not been approved for the treatment of candidemia, is approximately $4,000 to $5,000 for a dose of 100 mg daily for 20 days.

ADVERSE EFFECTS

The most extensive data on the safety of the echinocandins concern caspofungin, although no important differences in safety have been reported with micafungin and anidulafungin. Histamine-like reactions have occurred with rapid infusion of echinocandins. Anaphylaxis has been reported rarely.

The most common side effects reported in clinical trials of caspofungin have included fever (in 16% of patients), thrombophlebitis at the infusion site (14%), headache (8%), and elevation of levels of liver enzymes (alanine aminotransferase, 11%; aspartate aminotransferase, 12%; and alkaline phosphatase, 10%).[20,25] Isolated cases of clinically significant hepatic dysfunction, hepatitis, or worsening hepatic failure have occurred, although it is not clear whether they were drug-related.[26] All three echinocandins are classified by the FDA as pregnancy category C because of fetal abnormalities in studies in animals.

AREAS OF UNCERTAINTY

Because the echinocandins have been available for clinical use only since January 2001, the risk of uncommon or idiosyncratic side effects is not clear. The efficacy of the echinocandins in the treatment of candida endocarditis, meningitis, osteomyelitis, endophthalmitis, and brain abscesses remains to be determined, and drugs in this class should not be used alone for such infections until more data are available. The role of the echinocandins in the treatment of patients who have neutropenia likewise remains uncertain.

It is not known whether echinocandins can clear candida from contaminated intravascular catheters, particularly those that are difficult to replace, such as implanted catheters in patients with thrombocytopenia. Candida species (like many other microorganisms) tend to form biofilms (adherent layers of cells protected from immunologic access) on catheters; these biofilms are characteristically resistant to antifungal agents.[27] However, encouraging results have been obtained with echinocandins in studies in animals and in biofilms produced ex vivo,[28] suggesting that these drugs may be effective in sterilizing implanted devices.

GUIDELINES

The Infectious Diseases Society of America (IDSA) updated its guidelines for the treatment of candidiasis in 2004.[29] According to these guidelines, the primary recommendation for the treatment of candidemia in adults who do not have neutropenia is intravenous administration of conventional amphotericin B, at a dose of 0.6 mg to 1.0 mg per kilogram daily; oral or intravenous administration of fluconazole, at a dose of 400 mg to 800 mg daily; or intravenous administration of caspofungin, at an initial dose of 70 mg, followed by 50 mg daily. It is recommended that treatment be continued for 2 weeks after the last positive blood culture and the resolution of signs and symptoms of infection. Removal of all existing central venous catheters, if feasible, is also recommended. An ophthalmologic examination is recommended to rule out retinal involvement.

In 2003, four other societies published guidelines that included recommendations for the treatment of candidemia. In contrast to the IDSA, none of these societies recommend caspofungin for the treatment of candidemia with a fluconazole-susceptible species.[30-33]

RECOMMENDATIONS

The patient described in the vignette is similar to the majority of patients who have candidemia without neutropenia, who tend to be adults with serious coexisting diseases in medical and surgical ICUs. Conventional amphotericin B is poorly tolerated by such patients and is often stopped prematurely because of toxic effects. This patient has significant renal dysfunction and is thus a particularly poor candidate for treatment with conventional amphotericin B. Three equally appropriate options are available: intravenous fluconazole, caspofungin, or anidulafungin. Identification of the isolate as other than albicans increases the probability that it might be *C. glabrata* or *C. krusei*. In a gravely ill patient such as this one, starting with an echinocandin might be preferred, and caspofungin might be preferable to anidulafungin, given the longer experience with caspofungin.

We therefore recommend for this particular patient caspofungin at the standard dose of 70 mg given intravenously as an initial dose, followed by 50 mg given intravenously each day. If the patient has candidemia after more than a few days without an identified cause, switching to a daily intravenous infusion of liposomal amphotericin B at a dose of 3 mg to 5 mg per kilogram or amphotericin B lipid complex at a dose of 5 mg per kilogram would be reasonable. After there is a clear response to the therapy and the patient can receive medications orally, changing to oral fluconazole will save money and may allow the removal of all vascular catheters. Therapy should be continued for 2 weeks after blood cultures have become negative and clinical improvement has occurred.

No potential conflict of interest relevant to this article was reported.

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