Editorial Commentary

Invasive candidiasis trial supports echinocandins for primary therapy

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Candida, the most prevalent hospital-associated fungal pathogen, causes a variety of mucosal and deep-seated infections (1). Candidemia and other invasive *Candida* infections are among the more difficult to treat infections and are associated with high mortality rates, near 40% (2). Neutropenia, often related to chemotherapy or hematologic malignancy, places patients at high risk for severe disseminated candidiasis (3). The current recommended therapy involves a combination of treatment with antifungals, debridement and/or drainage of intra-abdominal sources, and removal of infected devices, such as vascular catheters and implantable cardiac devices (2,4-7).

Available antifungal agents for the treatment of invasive candidiasis belong to three distinct drug classes, which consist of the azoles, echinocandins, and polyenes. The activity of these agents have been examined in numerous clinical trials, and no study has established a superior regimen (8-17). However, the similarity of the trial designs has prompted investigators to further assess the combined data by meta-analysis and by analysis of pooled primary data (2,18,19). Similar to the individual trials, meta-analyses have not revealed superiority of a single antifungal drug for the treatment of invasive candidiasis (18,19). However, analysis of pooled primary data allowed investigators to question the efficacy of antifungals by drug class (2). For this large patient cohort, initial treatment with an echinocandin drug was found to be associated with significantly lower mortality (odds ratio 0.65) and higher clinical success (odds ratio 2.33). In light of these data and the increasing rate of azole-resistant *Candida*, the Infectious Diseases Society of America (IDSA) currently recommends echinocandin drugs for initial treatment of candidemia and invasive candidiasis (7). The available echinocandin drugs (caspofungin, micafungin, and anidulafungin) are considered comparable (7).

The echinocandin drugs exhibit a favorable safety profile, but have the limitation of only parenteral administration. In contrast, oral formulations are available for fluconazole and voriconazole, two triazoles effective for the treatment of invasive candidiasis (4,12). These agents are recommended as step-down therapy (following echinocandin treatment) for patients with susceptible *Candida* isolates. The azole-based regimens are also used routinely as initial therapy for invasive candidiasis in resource-limited areas. A newer azole, isavuconazole, recently received approval for the treatment of invasive aspergillosis and zygomycosis (20,21). In addition to activity against many filamentous fungi, this oral agent exhibits broad-spectrum activity against *Candida* and recently completed phase 3 study for the treatment of candidemia and invasive candidiasis (22,23).

In the randomized, double-blind, multinational clinical trial, Kullberg *et al.* compared isavuconazole and caspofungin for treatment of candidemia and invasive candidiasis (23). Adult patients received either IV isavuconazole or IV caspofungin as initial therapy. Following 10 days of IV therapy, optional step-down treatment included oral isavuconazole or oral voriconazole, for the IV isavuconazole and IV caspofungin arms, respectively. Isavuconazole failed to meet non-inferiority for the primary endpoint of successful overall response at the end of IV therapy (60.3% for isavuconazole, 71.1% for caspofungin). Baseline characteristics were similar between

the arms, as were secondary outcome measures, including all-cause mortality, overall response 2 weeks following the end of treatment, and safety.

The authors noted lower clinical response for patients with invasive candidiasis who had received isavuconazole (overall response 34.5% for isavuconazole *vs.* 65.8% for caspofungin) (23). This difference was less pronounced for patients with candidemia only (64.7% for isavuconazole *vs.* 72.4% for caspofungin). The finding is consistent with the enhanced efficacy of echinocandins in clinical and animal models of candidiasis (2,8,24). Another interesting observation is the lower clinical response for the patients with a BMI >25 in the isavuconazole arm. This prompts the question of inadequate drug levels for obese patients, which could be considered in further study of the drug.

Oral isavuconazole performed well as the step-down therapy (23). Failure occurred in only 5.8% of those receiving isavuconazole, compared to 15% of voriconazole-treated patients. Metabolism of voriconazole varies considerably among patients, and drug levels are frequently monitored to assure adequate, safe levels (25). It is possible that lower levels may have contributed to the higher failure rate in the voriconazole arm. Metabolism of isavuconazole is comparable among individuals and therapeutic drug monitoring has not been routinely recommended (26). Given both the success as step-down therapy in this study and its favorable safety profile, isavuconazole may be of use as a future alternative for step-down treatment. However, the study currently supports the recommendation for echinocandins as first-line, initial therapy (7).

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Footnote

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