Editorial

Nosocomial Candidemia: An Ounce of Prevention Is Better Than a Pound of Cure

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This issue of *Infection Control and Hospital Epidemiology* contains an article by Puzniak et al.[1] entitled "Has the Epidemiology of Nosocomial Candidemia Changed?" There is no short or simple answer to this question. A review of progress since the early 1980s (prior to the dawn of the "fluconazole era") reveals that several advances have been made in the diagnosis and management of candidemia. Modern, automated blood culture methods have improved our ability to detect candidemia, a thoughtful and rigorous effort has led to the development of standardized methods for susceptibility testing of *Candida* (and to the demonstration of clinical correlation between in vitro test results and outcome),[2-4] and several new antifungal agents provide equivalent therapeutic results with less toxicity than amphotericin B deoxycholate.[5] In addition, the introduction of fluconazole prophylaxis in selected high-risk patient populations (eg, patients receiving a bone marrow transplant and high-risk patients receiving a liver transplant) has resulted in decreased infection rates in these groups[6,7] and may be associated with an overall decline in mortality due to invasive candidiasis.[8] But in keeping with the maxim that "no good deed goes unpunished," widespread azole use may have facilitated a less encouraging change in the epidemiology of nosocomial candidemia: the emergence of *C. glabrata* as a more frequent nosocomial pathogen.[9] Although the decreased susceptibility of *C. glabrata* to azoles and amphotericin B makes this development disturbing, the other species commonly causing nosocomial candidemia (*C. albicans*, *C. tropicalis*, and *C. parapsilosis*) remain susceptible to fluconazole,[10] and the feared emergence of *C. krusei* as a more common cause of nosocomial candidemia has not occurred.

What has not changed is that hospital acquisition of *Candida* bloodstream infection (BSI) remains a devastating complication of healthcare delivery. The study by Puzniak et al. is the latest in a series of recent articles ascribing an extremely high crude (35% to 61%) and attributable (24% to 49%) mortality to nosocomial candidemia.[1,11-14] Acquiring candidemia in the hospital carries no less risk of death during hospitalization today than it did in the 1980s and early 1990s.[15-20] Could it be that this unchanging, high crude mortality means that nosocomial candidemia is merely a marker for severe underlying illness, but doesn't itself contribute significantly to mortality? Prospective clinical trials generally estimate attributable mortality to be much lower than do retrospective cohort designs,[21,22] and we have previously outlined reasons why a retrospective cohort design might overestimate attributable mortality.[14] However, we believe that estimates based on the presence of *Candida* in sterile sites within 48 hours of death or at autopsy[21,22] grossly underestimate attributable mortality by not including deaths among patients who, although they may clear their infection, die of downstream effects of the physiologic insult sustained during infection. There is evidence supporting a substantial contribution of nosocomial candidemia to mortality, including (1) the high attributable mortality estimates from several retrospective cohort studies,[13,14,20] (2) the independent association of *Candida* BSI with mortality in large studies using multivariate models to examine microbiologic risk factors for mortality among patients with BSI,[23,24] and (3) the mortality benefit documented in association with reduced rates of candidiasis in patients receiving a bone marrow transplant with the use of fluconazole prophylaxis.[6]

So will advances in treatment lead to reductions in *Candida*-associated mortality? As Puzniak et al. point out,

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https://doi.org/10.1086/502451 Published online by Cambridge University Press

their study and other recent studies predate the wide availability of the new agents caspofungin and voriconazole. Future studies may yet demonstrate that these agents are more efficacious than amphotericin and fluconazole; however, current data demonstrate only equivalent efficacy for caspofungin (although an important reduction in toxicity when compared with amphotericin B deoxycholate[21]), and published data comparing voriconazole with available agents for candidemia are not yet available. One study suggests that combination therapy may improve outcome in patients with nosocomial candidemia, but these data are complicated by an imbalance in severity of illness score between study arms and therefore require confirmation and extension to other agents and comparators.[25]

The risk factors for nosocomial candidemia have been well established and, as Puzniak et al. describe, have not changed significantly during the past two to three decades. Presence of a central venous catheter, intensive care unit (ICU) stay, renal failure, surgery, receipt of antibiotics (increasing risk with each additional antibiotic[26]), and receipt of total parenteral nutrition are all recognized to increase the risk for nosocomial candidemia.[1,26-28] One important risk factor that was not examined in the study by Puzniak et al. is preexisting colonization with *Candida* at other body sites. Intensity of *Candida* colonization is a well-known risk factor for subsequent infection,[26,28] and we suspect that the association they found between gastric acid suppression and candidemia reflects an associated increased risk for gastrointestinal colonization and overgrowth with *Candida*, previously described in the National Epidemiology of Mycoses Survey.[29] The gastrointestinal tract may not only serve as a source of candidemia (through translocation, particularly in critically ill patients receiving total parenteral nutrition or chemotherapeutic agents), but may also increase risk by serving as a reservoir for increased colonization density at other body sites.

Although candidemia is usually deemed to arise endogenously (preceded by colonization with the infecting strain), two other studies in this issue of *Infection Control and Hospital Epidemiology* remind us that *Candida* species are also transmitted from patient to patient in the healthcare setting.[30,31] Although this is a well-described phenomenon for *C. parapsilosis*, a species of *Candida* for which exogenous acquisition from contaminated infusates, the hospital environment, or the hands of healthcare workers is often implicated,[29,32,33] other *Candida* species may also be transmitted between patients, probably on the hands of healthcare workers.[30,34,35] Nor does an "endogenous" source of candidemia exclude in-hospital transmission of *Candida* as an important factor in infection. *Candida* species are common colonizers of human hands (particularly subungual spaces[36]), so exposure to *Candida* in the hospital environment is undoubtedly a common event.[37] Established risk factors (eg, antibiotic and device use) then favor the establishment of colonization and subsequent infection. Understanding this sequence of events has important implications for preventing morbidity and mortality resulting from nosocomial candidemia.

We agree with Puzniak et al. that better prevention methods will decrease candidemia-associated mortality much more than will advances in therapy. In other words, prevention is primary. Prevention of nosocomial candidemia should involve five strategies. First, intensive programs to maximize adherence to current hand hygiene recommendations are essential. Both alcohol and chlorhexidine are effective in killing *Candida* species on the hands of healthcare workers[38] and will decrease the risk of patients acquiring *Candida* colonization and subsequent infection in the healthcare setting. Second, strategies to improve adherence to current recommendations for placement and care of central venous catheters are important.[39] An educational program emphasizing important components of these guidelines successfully reduced catheter-related BSIs in an ICU.[40] Of note, the authors of this study reported 9 *Candida* BSIs in the 18-month preintervention period (12% of all nosocomial BSIs in their ICU) and not a single episode of catheter-associated nosocomial candidemia during the 18 months after the educational program.[40] Third, the importance of antibiotic use as a risk factor for nosocomial candidemia suggests that control of antimicrobial use is an important component of candidemia prevention. These three strategies—improved hand hygiene, optimal catheter placement and care, and prudent antimicrobial use—should form the bedrock of our approach to prevent morbidity and mortality resulting from nosocomial candidemia. Of secondary importance are the uses of presumptive (empiric) and prophylactic antifungal agents to decrease morbidity and mortality resulting from nosocomial candidemia.

Early empiric antifungal therapy should be guided by an understanding of the most important risk factors for nosocomial candidemia. The ICU patient with a central venous catheter, heavy antimicrobial exposure, a fever without a clear source, and *Candida* colonization at any site has a high risk for candidemia and may benefit from early empiric therapy.[5] Further study should be undertaken to more precisely define risk—a generalizable "candidemia score" that can be applied in an ICU environment to assist in making decisions about empiric antifungal therapy.

Decisions about expanding prophylactic antifungal use to the non-neutropenic ICU patient are substantially more difficult. Although well-designed, placebo-controlled trials have demonstrated a reduction in invasive candidiasis among surgical ICU patients who receive fluconazole prophylaxis,[41,42] the study populations selected were at high risk for candidemia, and the generalizability of the results has been questioned.[43] The potentials for drug toxicity, drug interactions, and the emergence of antifungal-resistant *Candida* species are arguments against a blanket recommendation to use prophylactic antifungal agents for non-neutropenic ICU patients. In our view, any approach to prophylaxis in this population must be institution specific and can be justified only if (1) major and concerted efforts have been made to improve hand hygiene, catheter placement and care, and antimicrobial use practices; (2) the rate of nosocomial candidemia or invasive candidiasis remains

elevated despite these efforts; and (3) a local observational study can define (using a "prediction rule") a subpopulation within the ICU with a cumulative incidence of invasive candidiasis approaching or exceeding 10%. Using this approach, we suspect that few institutions will find the need to expand antifungal prophylaxis outside of the transplant populations for which it is already recommended.[5]

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