EDITORIAL

The Evolution of Resistant *Candida* Species in Cancer Centers

Implications for Treatment and Prophylaxis

James Riddell IV, MD[1]
Carol A. Kauffman, MD[1,2]

[1]Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Medical School Ann Arbor, Michigan.

[2]Division of Infectious Diseases, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan.

The incidence of invasive candidiasis caused by azole-resistant *Candida* species has increased in the U.S. over the past 10 years.[1] Candidemia is the fourth leading cause of blood stream infection and disproportionately affects those with serious illnesses, such as hematologic malignancies and solid tumors, those who have received an organ transplant, and those who require intensive care unit management.[2,3] With an estimated crude mortality rate of 40% in some studies,[4,5] invasive candidiasis is a significant problem. The management of this infection has been complicated by the emergence of infection with *Candida* species that are resistant to the most commonly used agent for initial treatment, fluconazole. In this issue of *Cancer*, Hachem et al.[6] seek to further define the incidence of infection with fluconazole-resistant *Candida* species in a cancer hospital and document risk factors for infection with these organisms.

The study by Hachem et al. is an extension of a surveillance study that occurred from 1988 to 1992 at the University of Texas M. D. Anderson Cancer Center[7] and, as such, reflects the current practices of prophylaxis and management of fungal infections in patients who have hematologic malignancies and solid tumors. In the prior study, there was a decrease in the incidence of invasive *C. albicans* infections beginning in 1990, after fluconazole prophylaxis became commonplace for patients with leukemia. From 1990 to 1992, the rate of infection with *C. glabrata* remained relatively constant, but the rate of invasive *C. krusei* infection increased to 7%.[7] In their current study, which encompasses 1993 to 2003, Hachem et al. report a continuation of this trend, demonstrating dramatic increases in the rates of *C. krusei* infection (from 7% to 24%) and *C. glabrata* infection (from 12% to 31%) in patients with hematologic malignancies. *C. albicans* accounted for only 14% of all candidemias in this population in their study.

It is interesting to note that patients with solid tumors who did not receive fluconazole prophylaxis routinely had significantly lower

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Address of reprints: James Riddell IV, MD, Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Medical School, 3120 Taubman Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5378; Fax: (734) 763-5793; E-mail: jriddell@umich.edu

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rates of candidemia with *C. glabrata* and *C. krusei* compared with patients who had hematologic malignancies. *C. albicans* accounted for 45% of the candidemias, and *C. glabrata* and *C. krusei* accounted for only 18% and 2%, respectively; these rates are similar to those noted in tertiary care general hospitals.

It is important to interpret these findings in the context in which they occurred. Experience in a cancer hospital likely does not apply to the experience of other hospitals. In the U.S., the overall incidence of candidemia varies widely, depending on the location, from 6 up to 24 cases per 100,000 population per year.[8] Geographic differences exist throughout the world, with a low incidence of candidemia reported from many medical centers in Europe and Central America.[8] These differences extend to the isolation of fluconazole-resistant *C. glabrata* and *C. krusei*. The Artemis Surveillance Program, a worldwide surveillance network, has demonstrated only small increases in *C. glabrata* isolates, from 11% in 1997 to 12% in 2003.[9] Similarly, *C. krusei* increased from 1.7% to 2.7% over the same period. These data obviously differ greatly from the experience at M. D. Anderson Cancer Center.

Hachem et al. observed that fluconazole prophylaxis was associated with *C. glabrata* and *C. krusei* infections and that the absence of fluconazole prophylaxis was associated with *C. albicans* infections. Marr et al. from the Fred Hutchinson Cancer Center reported similar findings in bone marrow transplantation recipients who received fluconazole prophylaxis.[10] It should be emphasized that the experiences in tertiary care general hospital settings differ from the experiences in cancer hospitals with regard to the epidemiology of candidemia. For example, during a period similar to that of the study by Hachem et al., Lin et al. at the University of Chicago observed no association of fungemia with *C. krusei* or *C. glabrata* with fluconazole exposure,[11] and Malani et al. did not identify fluconazole prophylaxis as a risk factor for *C. glabrata* fungemia at our institution.[12] Furthermore, in European countries where fluconazole use also has increased, no increase in the incidence of *C. glabrata* infection has been observed.[8] In both Iowa and Michigan, an increase in *C. glabrata* candidemia was associated strongly with advancing age.[12,13] Therefore, it is likely that there are multiple factors, including geography, age, antifungal exposure, and underlying disease state, that are important in the observed increase of infections with non-*albicans Candida* species.

The importance of the study by Hachem et al. is the demonstration of high rates of invasive infections with non-*albicans Candida* species in patients with hematologic malignancies, emphasizing the value of ongoing surveillance within individual institutions. It is vital to have knowledge of local epidemiologic trends when selecting initial therapy for *Candida* bloodstream infections. It usually takes days for *Candida* to be identified to the species level and longer for an assessment of antifungal susceptibility. In an institution that has high rates of infection from fluconazole-resistant *Candida* species, an echinocandin or an amphotericin B formulation should be the initial treatment of choice. The echinocandins are considered equivalent to amphotericin B and fluconazole for candidemia.[14,15] In institutions that have lower rates of infection with *C. glabrata* and *C. krusei*, fluconazole remains appropriate as initial therapy for patients who are not critically ill and do not have specific risk factors for the acquisition of fluconazole-resistant *Candida* species.[16]

There are 2 major issues with regard to the data presented and the conclusions that were reached in the study by Hachem et al. First, they stated that their antifungal susceptibility studies are "in strict accordance with recommendations from the Clinical and Laboratory Standards Institute," yet no data are presented regarding susceptibilities. It would be extremely important to know how many of the *C. glabrata* isolates were resistant to fluconazole and how many fell in the dose-dependent susceptible or susceptible range. Equally important are susceptibilities of this species to voriconazole and posaconazole, especially in light of increasing use of both of these agents among patients with hematologic malignancies and increasing reports of cross-resistance among all triazoles.[17,18]

Second, the conclusions regarding outcomes drawn by Hachem et al. in their discussion need to be interpreted with caution. Although there are details listed regarding how outcomes were evaluated for these 635 patients, no specific data are reported with the exception of the last line in Table 2, which is headed "Clinical and microbiologic response to antifungals." Furthermore, there is no in-depth analysis of outcomes in their Results section. Data on the specifics of how patients were managed with regard to choice of antifungal agent, duration of therapy, and removal of central venous catheters are not presented. Despite these findings, the abstract states that response to antifungal therapy was worse in patients who had hematologic malignancies compared with patients who had solid tumors. It would be interesting to have an evaluation of the effects of isolating *C. glabrata* and *C. krusei* from blood cultures with regard to out-

comes. We still are left wondering about the clinical implications of the epidemiologic observation that these 2 species are increasing in frequency. We hope that this is a topic for a subsequent report from this group.

Finally, Hachem et al. raise the question of how to prevent candidemia, especially that caused by azole-resistant species, in high-risk populations. Two studies that were published last year demonstrated the benefit of the extended-spectrum triazole posaconazole in preventing invasive infections with both *Candida* and moulds in high-risk patients with chemotherapy-associated neutropenia subsequent to treatment for acute myelogenous leukemia or myelodysplastic syndrome[19] and stem cell transplantation recipients who had graft-versus-host disease.[20] In both of those studies, the incidence of breakthrough invasive candidiasis among all groups was extremely low, 0.7% and 1.4%, respectively, and was predominantly *C. glabrata* or *C. krusei*. Another multicenter, randomized study comparing fluconazole with voriconazole for prophylaxis in allogeneic stem cell transplantation recipients indicated that there was no difference in invasive fungal infections and very low rates of candidemia in each group.[21] The impact that the use of prophylactic antifungal agents, such as posaconazole and voriconazole, will have on the epidemiology of invasive candidiasis over time remains unclear. Not all patients may benefit from such therapy because of poor oral absorption of posaconazole, the myriad drug interactions with voriconazole, and the risk of hepatotoxicity, which can occur with both drugs.

The epidemiology of invasive *Candida* infections in high-risk cancer patients needs to be revisited frequently, particularly at institutions in which azole-resistant *Candida* species seem to be increasing, to provide guidance for the physicians who care for these patients. Correct initial treatment in patients with candidemia is a crucial factor for a successful outcome.[22,23] The selection of initial treatment should be based on factors that include prior antifungal exposure, the clinical status of the patient, and the epidemiology of candidemia at individual institutions. It is hoped that the group at M. D. Anderson Cancer Center will continue to share their experiences to help define the epidemiology of invasive *Candida* infections among cancer patients.

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