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Shifting Patterns in the Epidemiology of Nosocomial Candida Infections*

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The incidence of candidemia—a common and potentially fatal nosocomial infection—has risen dramatically, and this increase has been accompanied by a shift in the infecting pathogen away from *Candida albicans* to treatment-resistant non-albicans species. Prophylactic azole antifungals, such as fluconazole, may play an important role not only in the management of candidemia but also in the proliferation of hard-to-treat Candida species. In a variety of acute nosocomial settings, IV fluconazole, 400 mg/d, has reduced Candida colonization and infection. A growing body of evidence supports the still controversial contention that the increasing use of azole antifungals is at least partially responsible for the proliferation of treatment-resistant, non-albicans isolates, especially *Candida glabrata*. Thus, selecting the most appropriate candidates for prophylactic antifungal intervention—*ie*, those with the highest risk for candidemia—may be indispensable, not only in preventing candidemia, but also in reducing antifungal overuse, which may contribute to the emergence of treatment-resistant Candida isolates.

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Candida species are the principal pathogens of a variety of infections in humans, including candidemia, a potentially lethal and increasingly common nosocomial bloodstream infection. Indeed, candidemia has been associated with an attributable mortality rate of almost 40% and, for survivors, a 30-day increase in the length of hospital stay.[1] Alarmingly, the incidence of nosocomial candidemia has risen sharply in recent years, particularly in critical care units.[2,3] At the same time, there has been an important shift in the type of Candida infections—away from *Candida albicans*—to more treatment-resistant, non-albicans varieties. In 1990, nearly 80% of all the cases of nosocomial candidemia could be attributed to *C albicans*[4]; however, in an epidemiologic study[5] that examined the distribution of bloodstream isolates from patients in the ICUs at six regional hospitals, *C albicans* was the causative pathogen in just 48% of Candida nosocomial bloodstream infections, with the remaining Candida infections attributed to *Candida glabrata* (24%), *Candida tropicalis* (19%), and *Candida parapsilosis* (7%). In the six neonatal ICUs in this study, the rank order of Candida species causing bloodstream infections was *C albicans* (63%), *C parapsilosis* (29%), and *C glabrata* (6%). A further analysis of the Candida species present in urine and stool revealed a broad spectrum of non-albicans colonization, although *C albicans* remained most common (Table 1). Many of the non-albicans species, especially *C glabrata* and *Candida krusei*, are less susceptible to commonly used azole antifungal agents, and thus their increasing prevalence may contribute to the steady increase in nosocomial bloodstream infections seen over the past several decades.[6] We will explore the role of azole antifungal prophylaxis in the management of candidemia and in the proliferation of non-albicans isolates.

Prophylactic Interventions in Candidemia

Several studies have examined the issue of whether early intervention with antifungal agents reduces the risk for Candida infection. In one prospective, double-blind, placebo-controlled study, Eggimann and colleagues[7] examined the role of IV fluconazole, 400 mg/d, in the prevention of intra-abdominal Candida infections in 49 high-risk patients with recurrent GI perforation or anastomotic leakages. Patients were evaluated daily, and specimens for culture were obtained three times weekly during the drug prophylaxis period, which continued until the underlying surgical condition resolved. The principal end points were the frequency and timing of intra-abdominal candidiasis, defined as the presence of an abscess or peritonitis or candidemia in at least one blood culture. Also evaluated were the frequency of extra-abdominal candidiasis and the emergence of persistent Candida colonization.

Peritonitis and catheter sepsis secondary to Candida infection were less common in the fluconazole group (Table 2). *C albicans* accounted for most of the Candida species isolated before and during prophylactic treatment, and all were susceptible to fluconazole. In addition, of the 13 patients in each group without detectable Candida colonization at the start of the study, subsequent colonization was seen in significantly fewer fluconazole-treated patients than in placebo-treated patients (15% vs 62%). Further, Candida infection developed in 8% and 31% of these fluconazole-treated and placebo-treated patients, respectively. Similarly, for the 10 fluconazole-treated and 7 placebo-treated patients who were colonized at study entry, the persistence of colonization or the emergence of new colonization was significantly less likely with fluconazole than with placebo treatment (30% vs 70%, respectively). It should be noted, however, that of the seven patients who acquired Candida infection in the placebo group, six patients had mixed fungal and bacterial infections, reducing their susceptibility to antifungal treatment. These results indicate that for high-risk, nonneutropenic patients, prophylaxis or early treatment with fluconazole may be effective in limiting intra-abdominal Candida infections.

The value of prophylactic azole antifungal treatment was examined in patients receiving liver transplants, a

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Table 1—*Incident Colonization of Candida Species in Stool or Urine

Species	Stool, %	Urine, %
C albicans	26.5	13.9
C glabrata	7.7	5.6
C parapsilosis	4.2	1.3
C tropicalis	4.0	2.9
C krusei	1.6	0.5
Candida lusitaniae	0.8	0.1
Other	1.5	0.6
Total	49.7	23.3

*Reprinted with permission from Rangel-Frausto et al.[5]

group with the highest incidence of fungal infections.[8] This randomized, double-blind, placebo-controlled trial included 212 liver transplant patients who received fluconazole, 400 mg/d, or placebo for 10 weeks after transplantation. The main measures included fungal colonization, superficial or invasive fungal infection, mortality, and drug-related side effects. Fungal colonization rates increased in the placebo group (from 60 to 90%) and decreased in the fluconazole group (from 70 to 28%). Further, both superficial and invasive fungal infections occurred significantly less frequently in the fluconazole-prophylaxis group (9%) than in the placebo group (51%) [Table 3]. Additionally, fluconazole prophylaxis prevented most Candida infections, except for *C glabrata*. As expected, fluconazole-treated patients had higher serum cyclosporin levels and a higher incidence of CNS side effects, including headaches, tremors, and seizures. Although the between-group mortality and overall survival rates were similar, significantly fewer deaths related to fungal infection were seen in the fluconazole group (2%) than in the placebo group (13%). Even though the use of fluconazole prophylaxis in liver transplant patients did not improve overall survival rates in this study, its use appeared to be of value in reducing the likelihood of fungal colonization and subsequent infection. In this setting, however, careful monitoring of serum cyclosporin levels is necessary in fluconazole-treated patients to manage neurologic toxicities.

The value of azoles, such as fluconazole, in reducing fungal colonization and infection has spurred the use of these agents in the critical care setting. Although controversial, the notion that the growing use of azole antifungals, especially fluconazole, is responsible—at least to some extent—for the increase in non-*C albicans* infections is gaining increasing support.

Fluconazole Use and the Candida Shift

In a retrospective study,[9] covering the period from the beginning of 1990 through 1995, data were gathered from the surgical ICUs at the University of Pennsylvania and the University of Virginia Medical Centers and analyzed to determine treatment patterns and fungal infection rates. A sharp increase in the use of fluconazole was noted at both centers in critically ill surgery patients. Although most patients treated with fluconazole tested negative for fungal infections, there was an increase in the proportion of *C glabrata* isolated at the University of Virginia Medical Center ICUs, but not the University of Pennsylvania. This was linked to a greater tendency to use fluconazole in the University of Virginia Medical Center (2.2% vs 1.8% in the University of Pennsylvania, $p < 0.05$). In another study, conducted at the University of Texas Anderson Cancer Center, fluconazole prophylaxis significantly decreased the frequency of *C albicans* and *C tropicalis* infections, yet its use was associated with an increase in *C glabrata* and *C krusei* isolates.[10]

These studies raise a concern that the increased use of azole antifungals in surgical ICUs may cause a shift in the prevalence of Candida species toward the difficult-to-treat pathogens, particularly *C glabrata* and *C krusei*. It is, therefore, increasingly important to identify those patients at highest risk for candidemia, so that prophylactic antifungal therapy can be targeted to those who will glean the most benefit, an important step in minimizing the proliferation of resistant Candida species that may result from the overuse of antifungal therapy.

Risk Factors for Candidemia

Certain underlying physical conditions such as acute leukemia, leukopenia, burns, GI disease, and premature birth have been reported to predispose patients to nosocomial candidemia.[11] Yet there are also other independent risk factors.

In 1997, a consensus conference—composed of 22

Table 2—*Candida Infections in High-Risk Surgical Patients

Variables	Fluconazole, No. (%)	Placebo, No. (%)	Relative Risk (95% CI)	p Value
Outcomes				
Candida peritonitis	1 (4)	7 (35)	0.12 (0.02–0.09)	0.02
Catheter sepsis	1 (4)	0 (0)		
All	2 (9)	7 (35)	0.25 (0.06–1.06)	0.06
Species				
C albicans	2	5		
C tropicalis	0	1		
C krusei	1	0		
C glabrata	0	1		

*Reprinted with permission from Eggimann et al.[7] CI = confidence interval.

Table 3—*Incidence of Proven Fungal Infections

Infection Type	Fluconazole (n = 108), No. (%)	Placebo (n = 104), No. (%)	p Value
Superficials	4 (3.7)	29 (27.9)	< 0.001
Invasive	6 (5.6)	24 (23.1)	< 0.001
Total	10 (9.3)	53 (51.0)	< 0.001

*Reprinted with permission from Winston et al.[8]

infectious disease experts from the United States, Europe, and Japan—identified several important independent risk factors for the development of nosocomial Candida infection in nonneutropenic patients. The highest-risk patients were identified as those with indwelling catheters, those undergoing complicated abdominal surgery, those receiving parenteral hyperalimentation, those receiving antibiotic treatment for > 14 days, and those with Candida isolated from at least two sites.[12] The panel of experts considered these patient groups as appropriate candidates for prophylactic antifungal therapy.

Similar risk factors for candidemia were identified in a separate matched case-control study by Wey and colleagues,[13] who examined the risk factors for hospital-acquired candidemia in 88 pairs of patients hospitalized between 1983 and 1986. The strongest single risk factor was prior antibiotic use, followed by prior hemodialysis, prior use of a Hickman catheter, and Candida species colonization from sites other than blood.

The role of Candida colonization in the development of subsequent candidemia was further examined in a 6-month prospective cohort study that included 29 patients at high risk for Candida infection.[14] Colonization was defined as the presence of Candida species in three or more samples from the same or different body sites on 2 consecutive days. A Candida colonization index—defined as the ratio of the number of distinct body sites colonized with identical strains divided by the total number of body sites tested—was determined daily. A corrected colonization index—determined by multiplying the sites with heavy Candida growth by the derived colonization index—was used to account for the extent of Candida growth at each site. Severity of the illness, as defined by APACHE (acute physiology and chronic health evaluation) II scores, and Candida colonization were found to be the only significant, independent risk factors for subsequent Candida infection. The specificity and predictive validity for subsequent infection were 69% and 66%, respectively, when using the colonization index (score ≥ 0.6), but rose to 100% for each measure with the corrected colonization index (score ≥ 0.4). Sensitivity was 100% for both methods. In this study, the intensity of the Candida colonization appeared to be of some value in predicting subsequent infection and in identifying high-risk patients; however, the results of this study suggest that satisfactorily measuring the extent of Candida colonization in clinical practice may be daunting. The corrected colonization index—the most difficult and least likely to be used in an actual clinical setting—was the only method to produce acceptable levels of predictive validity and specificity for subsequent infection.

Conclusion

It seems clear that early therapy or "prophylactic" intervention with azole antifungal agents can reduce the risk for subsequent candidemia. Although overall survival rates appear unaffected by this type of prophylactic intervention, reductions in infection rate and hospital stay offer potential benefits in terms of reduced morbidity and treatment costs. However, the growing use of these agents may be associated with unintended clinical consequences. As with the widespread use of antibiotics, the selective pressures exerted by the growing use of azole antifungals may encourage the proliferation of treatment-resistant Candida species, further challenging the effective management of nosocomial candidemia. Long-term repeated exposure of Candida species to a specific antifungal class may result in the preferential eradication of susceptible species like *C albicans* and promote the proliferation of resistant species, including *C glabrata*. Following the introduction of azole antifungal agents, several studies have detected an increase in the prevalence of non-*C albicans* species, often less susceptible to conventional azole antifungal treatment. Yet the relationship between azole antifungal treatment and non-*C albicans* proliferation remains controversial. Many of the studies supporting this relationship have been retrospective in design and included only a single treatment center, factors that may exaggerate the apparent increase in non-albicans isolates. Nonetheless, identifying and targeting the "best" candidates for prophylactic antifungal therapy—or those at highest risk for candidemia—may be an indispensable step not only in maintaining the effectiveness of antifungal prophylaxis but also in limiting the proliferation of treatment-resistant, non-*C albicans* isolates.

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