Recognition and prevention of nosocomial invasive fungal infections in the intensive care unit

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Despite recent advances in antifungal treatments, the morbidity and mortality of fungal infections, especially invasive candidiasis, in patients in the intensive care unit setting remain high. Because of this, there has been a great interest in improving the evaluation, risk assessment, and prevention of fungal infections in the intensive care unit. Some important advances in the diagnosis of invasive candidiasis include rapid species identification and improvements in antigen testing. The introduction of several prediction rules has helped to guide clinicians in the use of prophylaxis or preemptive antifungal therapy in high-risk patients. However, the most immediate benefit has been realized with the introduction of new antifungal agents that have proved to be safer than those available in the past. (Crit Care Med 2010; 38[Suppl.]:S380–S387)

KEY WORDS: candidemia; invasive candidiasis; antifungal prophylaxis; empirical antifungal therapy; preemptive antifungal therapy; intensive care unit

Invasive fungal infections are an increasingly prevalent problem in hospitalized patients, especially those in the intensive care unit (ICU). There are a number of different types of fungal infections, including invasive mold infections, that occur in ICU patients; however, *Candida* species account for >85% of fungal infections in the ICU setting and will be the focus of this review (1–3).

Epidemiology of Candida *infections in the ICU*

Candidemia and invasive candidiasis rates seem to be increasing in the United States and elsewhere in the world (4–8). *Candida* is now the fourth leading cause of bloodstream infections in the United States (1) and is responsible for 10% of all nosocomial infections in European ICUs (4).

There have been numerous reasons postulated for this increase in invasive *Candida* infections, including the increasingly large population of patients with compromised immunity secondary to cancer, solid organ and stem cell transplantation, chemotherapy, and immunosuppressive therapy for a variety of different diseases. In addition, there has been an increase in survival of the sickest of patients; an increase in invasive procedures that disrupt the host's natural barriers to infection; and increased empirical use of broad-spectrum antimicrobial agents, which increases colonization with *Candida* species by changing the normal microbiota. All of these factors are postulated to have contributed to the increase in *Candida* infections and are particularly applicable to patients in the ICU.

Sources of Candida *spp. Causing Invasive Infections. Candida* spp. are part of the normal human commensal microbiota. The majority of invasive infections occur secondary to *Candida* strains that are colonizing the patient (9, 10). When there is disruption of the integrity of the normal barriers to infection, such as breech of the integument by central catheters, or a breakdown of the gastrointestinal (GI) mucosal barrier, the host's colonizing strain of *Candida* gains access to the bloodstream. When the route of infection is via a vascular access catheter, colonization of the patient's skin is the usual source of the yeast. However, outbreaks of candidemia secondary to transmission of *Candida* species colonizing healthcare worker's hands have been reported, and rarely, parenteral nutrition solutions have been contaminated with *Candida* (9–11). The GI tract can serve as the entry point for *Candida* because of breakdown of the mucosal barrier secondary to critical illness or to chemotherapeutic agents that destroy the mucosal barriers, and parenteral feeding also seems to impair the integrity of the mucosal barrier (10, 12). Uncommonly, candidemia can occur secondary to a local infection, such as pyelonephritis, or from an abscess.

Shifts in Candida *Species Causing Invasive Infection.* Although *Candida albicans* remains the most common species causing invasive infection in most ICUs, in others, *Candida glabrata* has become increasingly prevalent (5, 13–16). The prominent species in many neonatal ICUs is *Candida parapsilosis* (11), and this is the species most often implicated when transmission of *Candida* species has been traced to a healthcare worker's hands (9). In some tertiary care centers, nearly 50% of candidemias now are caused by non-*albicans Candida* spp. (17–20). It is postulated that the shift from the more fluconazole-susceptible *C. albicans* to several non-*albicans* species that have decreased susceptibility or resistance to fluconazole has occurred partly because of the widespread use of fluconazole (21). This is especially true among patients receiving therapy for hematologic malignancies. In at least one large cancer hospital, the most frequently isolated species were *C. glabrata*, which caused 31% of candidemias, and *Candida krusei*, which was implicated in 24% (22).

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Table 1. Risk factors for invasive candidiasis

Host factors
Extremes of age
Neutropenia
Renal failure
Higher APACHE II score
Trauma/burns
Bowel perforation
Medical interventions
Chemotherapy
Dialysis
Central venous catheters
Antibiotic use (risk increases with each additional antibiotic)
Parenteral nutrition
Prior surgery (especially abdominal)
Length of ICU stay of >7 days
Nasogastric tubes
Gastric acid suppression
Candida colonization

APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

Risk Factors for Invasive Candidiasis. The risk factors for invasive candidiasis have been assessed in many different studies from multiple institutions from around the world. The factors found most often include extremes of age, trauma or burns, high Acute Physiology and Chronic Health Evaluation II score, recent abdominal surgery, GI perforation, central venous catheters, total parenteral nutrition, dialysis, broad-spectrum antiinfective therapy, and prior known *Candida* colonization (7, 11, 23–25) (Table 1). In one single-center study, independent risk factors included presence of a Hickman catheter (odds ratio [OR], 9.5), gastric acid suppression (OR, 6.4), ICU admission (OR, 6.4), nasogastric tube placement (OR, 3.7), and an OR of 1.5 for each antibiotic the patient received (26). The largest prospective cohort study of risks for candidemia evaluated 4,276 patients admitted to a surgical ICU for >48 hrs. Of these patients, 42 developed candidemia. Factors independently associated with candidemia on multivariate analysis included prior surgery (relative risk [RR] 7.3), acute renal failure (RR, 4.2), receipt of parenteral nutrition (RR, 3.6), and, in patients who had undergone surgery, presence of a triple lumen catheter (RR, 5.4) (11).

Several recent studies (20, 27, 28) identified risks of infection with non-*albicans Candida* species. In one study (27), the following risks were significant by multivariate analysis: prior fluconazole exposure (OR, 11.6), central venous catheter (OR, 1.95), and increased number of antibiotics given (OR, 2.31). In another study (29), recent GI surgery (OR, 2.87) and recent antifungal therapy (OR, 4.6) were risk factors for infection with non-*albicans Candida* species. One drawback of these analyses is that all non-*albicans Candida* infections were considered together. In a large, prospective, observational registry, the risks of candidemia by *Candida* species were evaluated (20). Patients with *Candida parapsilosis* candidemia were compared with patients infected with other *Candida* spp. and were less likely to have neutropenia or to have received steroids or other immunosuppressive drugs. Patients with *C. krusei* candidemia were more likely to have had exposure to other antifungal agents, have a hematologic malignancy, have received a stem cell transplant, have neutropenia, or have been treated with corticosteroids. Despite the association of certain findings with non-*albicans Candida* infections, it has not been possible to predict which patients who have candidemia have a non-*albicans* infection rather than a *C. albicans* infection (17).

Outcome of Invasive Candida *Infections.* Despite advances in antifungal therapy for invasive candidiasis, there remains an unacceptably high mortality rate (3, 11, 16, 30). Several studies have redemonstrated the high crude and attributable mortality of candidemia. Candidemia has been noted to have an associated mortality as high as 71% and an attributable mortality from 30% to 62% (3, 31). Early treatment of candidemia significantly decreases the attributable mortality, and, not surprisingly, untreated invasive candidiasis has a very high mortality rate (32, 33). A recent, prospective, observational study (34) in French ICUs found that independent factors associated with mortality from invasive candidiasis in the ICU included Type 1 diabetes mellitus (OR, 4.51; $p = .002$), immunosuppression (OR, 2.63; $p = .0045$), and mechanical ventilation (OR, 2.54; $p = .0045$). Other authors (13, 16, 35–38) have noted increased mortality rates associated with extremes of age, underlying comorbidities, duration of persistently positive blood cultures, failure to remove infected intravascular devices, higher Acute Physiology and Chronic Health Evaluation II scores, and delay in antifungal therapy for more than 48 hrs. Mortality seems to be higher in patients with candidemia due to some non-*albicans* species, specifically *C. krusei*, and in some series, *C. glabrata* (20, 39). However, other reports on *C. glabrata* infections do not find mortality rates to be higher than those normally noted with *C. albicans* (13, 16). Most centers (16) reported that candidemia with *C. parapsilosis* has a mortality rate lower than that seen with other species. The costs of an episode of candidemia in patients in the United States have been estimated to be $39,000 in adult patients and $92,000 in children; the difference in cost is primarily related to the longer mean length of stay, which was 21.1 days in children compared with 10.1 days in adults (3). Similar effects of *Candida* infections on hospital cost and length of stay have been described in China and Spain (40, 41). In the Spanish study (41), both *Candida* colonization and infection were associated with significant economic impact.

Diagnosis of suspected invasive candidiasis

The diagnosis of invasive candidiasis is challenging because of its protean manifestations and the inadequacy of the currently available diagnostic modalities. Further complicating the diagnosis of invasive candidiasis is the difficulty in differentiating *Candida* colonization from invasive infection. This nuance complicates clinical care of patients as well as design of studies to assess treatment and prevention of invasive candidiasis and may lead to overutilization of antifungal therapy.

Clinical Clues. Invasive candidiasis has a variable and nonspecific clinical presentation. Patients may have very few signs or symptoms. As many as one in five patients may not have fever, and, in some series, only half develop leukocytosis (35). On the other hand, candidemia may present as fulminant sepsis that is indistinguishable from that noted with bacteremia. Invasive candidiasis can cause abscesses in many organs in the absence of positive blood cultures. Clinical clues to invasive candidiasis and candidemia include the development of skin lesions and eye lesions. The skin lesions appear suddenly, can occur on any area of the body, are nontender and nonpruritic, and usually are manifested as pustules on an erythematous base. Biopsy of these lesions reveals budding yeast and sometimes hyphal forms typical of *Candida*. Endophthalmitis, manifested as chorioretinitis, with or without extension into the vitreous body, should be sought in every patient who has candidemia (42–44). Vitreal involvement seems to be less

commonly noted now than several decades ago, possibly because of earlier detection of chorioretinal lesions and recommendations to treat all patients who have candidemia (43).

Culture-Based Techniques. Blood cultures have been widely reported to have a low sensitivity for *Candida* species (50% to 60%). Most of the studies that demonstrated this were based on older culture techniques and were able to use autopsy evidence of invasive infection as the gold standard. Modern culture techniques, such as lysis centrifugation and the BACTEC and BacTAlert automated systems, show improved yields compared with older techniques; however, the sensitivity of these techniques is not known because autopsy-based studies have not been repeated (45, 46). Biopsy samples from skin lesions or other tissues should be submitted for culture when obtained. Generally, these samples are plated onto Sabouraud dextrose agar with and without antibiotics added, and the yield should be high.

A disadvantage of culture-based techniques is the time it takes for a blood culture to become positive and then the additional time for the organism to grow on subculture to determine the species of *Candida*. In most laboratories, it is 2–4 days until a final identification is reported to the clinician. If therapy is delayed for >48 hrs after the culture is taken, waiting until the culture results are known, mortality seems to increase (37, 38). A rapid fluorescence-based system, fluorescence in situ hybridization using peptide nucleic acid probes (PNA-FISH), can identify *C. albicans* and *C. glabrata* directly from a blood culture as soon as the culture bottle is noted to be positive and yeast are seen on smear of material taken from the bottle. Use of this system, which is gaining acceptance, has decreased the time needed for identification of specific *Candida* species from days to hours (47, 48).

Non-Culture-Based Techniques. There has been intense interest in developing an antigen assay for the diagnosis of invasive candidiasis. The current antigen-based assays include those targeting the cell wall components mannans and glucans. Mannans are a major cell wall component of *C. albicans*, and testing of oligomannoses has been undertaken to identify ideal antigenic targets. Unfortunately, mannans are present in the serum for a very short period of time, making them difficult targets for clinical use (49).

A more promising target has been an assay for (1→3)-β-D-glucan, a component of the cell wall of many fungi (50–54). This assay is not specific for *Candida*, but its early increase and persistence in serum make it an attractive target for fungal antigen testing in a variety of patient groups, including patients in the ICU. In one multicenter study, approximately 80% of patients with proven candidiasis had a positive test (54). The β-D-glucan testing has also been studied in a catheter-based biofilm model of candidiasis. In this study, the β-D-glucan level was shown to be positive when a *Candida* biofilm was present on the catheter, suggesting that the catheter needed to be removed for eradication of the infection (55). Whether this will prove to be useful clinically has yet to be determined.

Recent interest in non-culture-based techniques has focused on polymerase chain reaction technology. In some preliminary studies, polymerase chain reaction seems to facilitate diagnosis by improving sensitivity, and, in the right setting, the time to diagnosis (56–58). Polymerase chain reaction may also be useful in rapid identification of the infecting *Candida* species, allowing improvement in treatment (59). However, polymerase chain reaction assays are not routinely available to aid in the diagnosis of invasive candidiasis in clinical practice.

Strategies for risk identification

Because of the high mortality rates and the difficulty in establishing a diagnosis of invasive candidiasis, several groups have developed strategies to determine which patients are at greatest risk for invasive candidiasis so that prophylaxis or definitive therapy can be better focused. A number of prediction rules have been formulated to identify these patients (60–63). Several of these rules require assessment of *Candida* colonization, which is routinely performed in many European ICUs but in only a few ICUs in the United States. Those ICUs that utilize colonization as part of risk assessment generally screen multiple body sites either daily or several times weekly while the patient is in the ICU.

The Candida Colonization Index is the ratio of the number of body sites that yield the same species of *Candida* divided by the number of sites tested. A modification of this index is the Corrected Candida Colonization Index, which takes into account the density and degree of colonization as determined by semiquantitative cultures of each body site. In the study by Pittet et al (23), colonization was assessed daily in patients admitted to the surgical ICU, and the calculated index was shown to identify those patients at greatest risk of invasive candidiasis. Of 650 patients tested, 29 developed colonization with *Candida* spp. at multiple sites. Of these colonized patients, 11 developed invasive candidiasis. The Candida Colonization Index for those patients who went on to develop invasive infection was significantly greater (0.70) than for those patients who remained colonized but did not become infected (0.47; $p < .01$). Therefore, a Candida Colonization Index threshold of 0.5 correctly identified all of the patients who developed invasive disease. The elevated ratio preceded the development of candidiasis by as much as 6 days in some patients, which suggested an important window to intervene and potentially prevent invasive candidiasis.

The Candida Colonization Index has been utilized to identify a subset of patients who may benefit from preemptive antifungal therapy (63). Piarroux et al (64) refined the use of the Candida Colonization Index by using a Corrected Candida Colonization Index of ≥0.4 to determine the need for preemptive antifungal therapy. In this large study of preemptive therapy, the Corrected Candida Colonization Index performed better than the Candida Colonization Index to identify patients at risk for invasive candidiasis. Although the sensitivity of these indices seems to be good, many ICUs do not embrace this concept because of the cost of performing multiple semiquantitative cultures in all ICU patients to identify <5% of patients who will develop invasive candidiasis.

Other prediction rules have sought to integrate colonization with other risk factors to enhance specificity. The Candida Score, a bedside scoring system that utilizes evidence of multifocal colonization with other risk factors for invasive candidiasis, is calculated using the following point system: total parenteral nutrition (1 point) plus surgery (1 point) plus multifocal *Candida* colonization (1 point) plus severe sepsis (2 points). It has been shown that each of those characteristics is significantly ($p < .001$) and independently associated with invasive candidiasis prior surgery (OR, 2.71), multifocal colonization (OR, 3.04), parenteral nutrition (OR, 2.48), and severe sepsis (OR, 7.68). Using a cutoff value for the Candida Score of 2.5, the sensitivity was 81% and the specificity was 74% (60). Recently,

the same authors proposed a cutoff value of 3.0 instead of 2.5 (65).

A recent prospective multicenter study (65) compared the Candida Score to the Candida Colonization Index to identify the patients at greatest risk of invasive candidiasis. Of 1107 patients admitted to the ICU for >7 days, 892 were shown to have *Candida* colonization or invasive candidiasis. Of the 565 patients who had a Candida Score of <3, 13 developed invasive candidiasis (occurrence rate, 2.3%). Of 327 patients who had a Candida Score of ≥3, 45 developed invasive candidiasis (occurrence rate, 13.8%). In the same study population, of those who had a Candida Colonization Index of <0.5, the prevalence of invasive candidiasis was 3.9% (16 of 411 patients), and of those who had a Candida Colonization Index of ≥0.5, 8.7% (42 of 481 patients) developed invasive candidiasis. It was calculated that the RR of invasive candidiasis for a Candida Score of ≥3 was 5.98 (95% confidence interval, 3.28–10.92) compared with an RR of 2.24 (95% confidence interval, 1.28–3.93) for a Candida Colonization Index of ≥0.5. Thus, the Candida Score, which included clinical factors as well as colonization data, proved to be more sensitive than the Candida Colonization Index.

Ostrosky-Zeichner et al (62) proposed a clinical prediction rule that obviates the need for obtaining surveillance cultures to assess *Candida* colonization. This rule identified the presence of several factors as highly predictive of invasive candidiasis when they were present before or within a few days of ICU admission. These included systemic antibiotic therapy on days 1–3 or presence of a central venous catheter on days 1–3 and at least two of the following: parenteral nutrition on days 1–3, dialysis on days 1–3, major surgery within 7 days, pancreatitis within 7 days, corticosteroids within 7 days or up to day 3, and other immunosuppressive agents within 7 days. The rate of invasive candidiasis in patients meeting these criteria was 9.9%, and use of this prediction rule led to the early identification of 34% of patients who went on to develop invasive candidiasis (62).

The application of these various predictive rules to identify patients at greatest risk of invasive candidiasis has not yet been widely adopted, and further study is required to determine how they will perform in different ICU settings (66).

Table 2. Strategies for prevention of invasive fungal infections in patients in the intensive care unit

Prophylaxis	Antifungal therapy given based on risk factors without evidence for colonization
Preemptive therapy	Antifungal therapy given based on risk factors and colonization with *Candida* in the absence of symptoms
Empirical therapy	Antifungal therapy given based on symptoms suggesting sepsis and risk factors before the documentation of infection

Strategies for risk reduction

Several strategies have been developed to reduce the risk of development of invasive candidiasis and candidemia in patients in the ICU setting. These strategies include prophylaxis, preemptive therapy, and empirical therapy (Table 2).

Prophylaxis. Prophylaxis with an antifungal agent has been utilized in an attempt to decrease the development of *Candida* infection. The term refers to the use of antifungal agents in patients with risk factors for invasive candidiasis but without documented colonization. In some studies, prophylaxis was used broadly on admission to the ICU, whereas others used prophylaxis only for specific groups of patients who were felt to be at high risk for invasive candidiasis (36, 63, 66–73).

Among the studies using broad prophylaxis, the randomized, double-blind placebo-controlled trial of fluconazole, 400 mg daily, among surgical ICU patients reported by Pelz et al (70) showed benefit in regard to development of invasive candidiasis, but not in regard to overall survival. This study was performed at a single center in an ICU with a high baseline rate of candidiasis (16%) and used a broad definition of invasive infection that included *Candida* urinary tract infection, a diagnosis notably hard to prove. A single-center, randomized, double-blind, placebo-controlled study by Garbino et al (36) demonstrated that fluconazole, 100 mg daily, given to all mechanically ventilated patients, in addition to antibiotic selective digestive decolonization, resulted in a decrease in the rate of invasive candidiasis from 16% in the placebo group to 5.8% in the fluconazole group. This study also included in the end point the diagnoses of *Candida* urinary tract infection and pneumonia. In this study, as in the study by Pelz and colleagues, no survival benefit was shown.

With the increase in isolation of *C. glabrata* in ICU patients, several studies have looked at the benefit of prophylaxis with caspofungin compared with placebo. Two studies (61, 62) performed by the Mycoses Study Group at U.S. sites that had rates of invasive candidiasis of approximately 10% targeted only high-risk patients defined by the prediction rule of Ostrosky-Zeichner et al. The initial study proved difficult to enroll adequate patients and was stopped, but this study (62) did prove the benefit of the prediction rule. The second study just finished enrolling adequate numbers of high-risk patients; the data remain blinded. This study has the potential to establish the benefit of an echinocandin in a high-risk ICU population.

Further refinement of prophylaxis for very specific high-risk surgical ICU patients has been studied by the group from Switzerland (71, 72). The initial, randomized, double-blind study compared 400 mg of fluconazole to placebo in patients at high risk for intra-abdominal infection and showed that fluconazole was able to prevent both intra-abdominal *Candida* colonization and infection (71). A subsequent prospective, noncomparative, single-center study was performed in which caspofungin was given to surgical patients with recurrent GI perforation/anastomotic leakage or acute necrotizing pancreatitis. In this small study of very high-risk patients, caspofungin was effective in preventing invasive candidiasis in 18 of 19 patients (72).

Several meta-analyses and a Cochrane analysis (67–69, 74, 75) have attempted to establish whether there is benefit from prophylaxis in the ICU setting. In 2006, a meta-analysis of 12 clinical trials concluded that the use of prophylactic fluconazole or ketoconazole reduced total mortality by one quarter and invasive fungal infection rates by one half (67). Cruciani et al (68), in an analysis of nine studies including a total of 1,226 patients, concluded that prophylaxis was associated with a reduction in rates of candidemia (RR, 0.3), overall mortality (RR, 0.6), and attributable mortality (RR, 0.25). The meta-analysis by Shorr et al (69) noted a reduction in rates of fungal infection with prophylactic fluconazole; the pooled OR was 0.44 ($p < .001$). However, no change in the rate of development of candidemia, which was low in the placebo groups in all of the studies, or

in mortality rates could be detected. Finally, the meta-analysis by Vardakas et al (75) of six randomized controlled trials of high-risk surgical patients also concluded that prophylaxis was associated with a reduction in candidemia and in invasive and superficial *Candida* infections, but that there was no reduction in mortality. Thus, results from these meta-analyses varied depending on the trials included, the azoles and patient populations studied, and the different methodologies used. It does seem that invasive candidiasis can be decreased with prophylactic azole therapy, but issues of adverse effects and changes in the ecology of *Candida* species in a unit in which broad prophylaxis is given have not been adequately addressed.

It is clear that a beneficial effect of prophylaxis is strongest among patient groups with higher rates of invasive candidiasis. In the Cochrane analysis by Playford et al (67), 94 patients would need to be given fluconazole to prevent one invasive fungal infection, based on a prevalence of fungal infection of 2%. The number needed to treat was highly variable, from 9 in high-risk patients to 188 in low-risk patients. It has been proposed that a population should have at least 10% risk of invasive candidiasis to warrant use of prophylaxis (60, 62).

Use of a broad prophylactic strategy raises concern for the encouragement of colonization and infection by non-*albicans Candida* species, especially fluconazole-resistant *C. glabrata*, as noted in hematology and bone marrow transplant units (21). The exposure of many patients to the adverse effects of unnecessary medications also argues against the broad use of prophylaxis.

After weighing the evidence and noting the problems with each of the prophylaxis studies, the Infectious Diseases Society of America Guidelines Panel concluded that fluconazole, 6 mg/kg daily, could be recommended for high-risk patients in adult ICUs that have high rates (>10%) of invasive candidiasis (43). The Panel did not recommend broad use of fluconazole in all ICU patients.

Special Populations in the ICU. Antifungal prophylaxis is standard care for patients who have hematologic disorders and are neutropenic or have received a stem cell transplant. When these patients are admitted to the ICU, prophylaxis, usually with an azole, should be continued, following established local protocols for these populations. Another group of patients cared for in the ICU setting and at high risk for invasive fungal infections are those who have received a liver transplant. Several studies have demonstrated a benefit of prophylaxis with fluconazole (76–78) or lipid formulations of amphotericin B (78, 79). In the largest study, only 6% of patients given fluconazole for at least 4 wks postoperatively developed fungal infections compared with 23% of placebo recipients (77). Two meta-analyses that have evaluated the results of studies using itraconazole, as well as fluconazole or lipid formulation amphotericin B, have verified the benefit of prophylaxis in the immediate posttransplant period for high-risk liver transplant recipients (80, 81). Colonization, the development of invasive candidiasis, and mortality from *Candida* infection were reduced, but overall mortality was not changed. Cruciani et al (80) noted an increase in infections with *C. glabrata* in patients given fluconazole prophylaxis, but this effect was not noted by Playford et al (81). The Infectious Diseases Society of America guidelines (43) recommend fluconazole, 200–400 mg daily, or liposomal amphotericin B, 1–2 mg/kg daily, for 7–14 days posttransplantation. Individual transplant units need to establish which liver transplant recipients are at high risk for invasive fungal infections and would benefit from prophylaxis.

Prophylaxis with fluconazole for 7–14 days also is recommended for recipients of pancreas transplants and small bowel transplants. Both groups are cared for in the ICU setting posttransplantation and both are at high risk for invasive candidiasis (43, 82, 83).

Preemptive Therapy. A second strategy that can be used to prevent invasive candidiasis in the ICU setting is the use of preemptive antifungal therapy. In preemptive therapy, patients who are colonized with *Candida* and who have other risk factors for invasive infection are treated with an antifungal agent before invasive disease occurs. The Candida Colonization Index and the Candida Score have both been used to identify the population most likely to benefit from preemptive antifungal therapy (64). Leon et al (60) devised the Candida Score to determine which patients might benefit from early (preemptive) therapy for *Candida* infection. Piarroux et al (64) prospectively studied 478 patients, of whom 96 had a Candida Colonization Index of >0.4 and were treated with 400 mg fluconazole for 2 wks. The rate of invasive candidiasis in this group, 18 (3.8%) of 96, was significantly less than the 7% rate (32 of 455) in a historical control group that had received no preemptive therapy. These study results are weakened by the use of the historical control design; other studies, using a randomized, controlled, blinded approach are clearly needed to evaluate the usefulness of this approach.

Empirical Therapy. The use of empirical antifungal therapy is common practice in some ICUs that have high rates of invasive candidiasis. In this situation, antifungal therapy is given when patients have signs of systemic infection but before definitive laboratory studies identify the causative organism as *Candida* spp. In one study (84), 270 adult ICU patients who had fever despite administration of broad-spectrum antibiotics, central venous catheters in place, and an Acute Physiology and Chronic Health Evaluation II score of >16 were randomly assigned to receive either fluconazole, 800 mg daily, or placebo for 2 wks. A total of 11 (9%) patients who received placebo developed an invasive fungal infection compared with six (5%) patients in the fluconazole group; this difference was not statistically significant. There were only two patients with candidemia in the placebo arm and none in the fluconazole arm. Overall, too few patients had invasive candidiasis to be able to show a benefit from empirical fluconazole therapy. The outcomes of this study emphasize the importance of targeting the use of preventive antifungal therapy only for those ICUs that have a high prevalence of invasive candidiasis.

Choice of Agents. Fluconazole has been used most often for prevention or empirical treatment of invasive candidiasis in the ICU. This agent is safe, can be given orally or intravenously, is well tolerated, and has excellent activity against *C. albicans*, *C. parapsilosis*, and *C. tropicalis*. Although not significantly metabolized by the cytochrome P450 (CYP450) system, fluconazole does inhibit CYP2C19, CYP2C9, and CYP3A4, and this inhibition can increase serum levels of warfarin, phenytoin, and agents that cause QT prolongation (Table 3). The major drawback, however, is the association with increased prevalence of *C. glabrata*, a species that often has decreased susceptibility or resistance to fluconazole. Fluconazole susceptibility testing, performed either by disk diffusion assay or by automated methods, such as the Vitek system, can be useful in determining

Table 3. Azole and echinocandin agents used in the treatment of invasive candidiasis

Antifungal Agent	Typical Dosing and Common Dose Adjustments for Candidal Infection	Route	Common and Important Adverse Effects
Fluconazole	100–800 mg daily Reduce dose by 50% for creatinine clearance of <50 mL/min	PO or IV	Drug interactions Hepatotoxicity Nausea Headache
Voriconazole	6 mg/kg IV every 12 hr for two doses, followed by 3 to 4 mg/kg IV twice daily or 400 mg PO every 12 hrs for two doses, followed by 200 mg PO twice daily Do not use IV if CrCl <50 mL/min because of cyclodextrin vehicle	PO or IV	Drug interactions Photopsia and other visual changes Hepatotoxicity Mental status changes
Caspofungin	70 mg IV loading dose, followed by 50 mg IV daily Decrease to 35 mg daily after 70 mg IV loading dose for Child-Pugh scores of 7–9	IV only	Hepatotoxicity (rare)
Micafungin	100 mg/day IV No dose adjustments	IV only	Hepatotoxicity (rare)
Anidulafungin	200 mg IV loading dose, then 100 mg IV daily No dose adjustments	IV only	Hepatotoxicity (rare)

PO, per os; IV, intravenous; CrCl, creatinine clearance.

whether an azole can be used or whether an echinocandin is required. Two newer-generation azoles, voriconazole and posaconazole, although used frequently for prophylaxis in high-risk populations, such as those with hematologic malignancies and neutropenia and those who have received a stem cell transplant, have not been studied as preventive agents in the ICU setting. Absorption issues with posaconazole make it less suitable for use in an ICU population, and increased drug-drug interactions with voriconazole make it less safe in this setting than fluconazole (Table 3). Amphotericin B has been used for the prevention of invasive fungal infections only for special populations in the ICU, such as high-risk liver transplant recipients. The toxicity of this agent precludes its use for most critically ill patients in the ICU setting.

Echinocandins are very safe and well tolerated, and they have excellent activity against most *Candida* species (Table 3). Several trials have used caspofungin as prophylaxis for high-risk patients in the ICU, but the studies (62, 72) reported to date were unable to establish benefit because the numbers of patients enrolled in the trials was too small. The echinocandins have decreased activity against *C. parapsilosis* compared with other antifungal agents, and this may preclude the use of these agents in a preventive role in those ICUs in which *C. parapsilosis* is a prominent pathogen.

Echinocandins are extensively metabolized and do not have significant excretion unto the urine as active drug. For this reason, they may not be useful in cases of urinary tract infection due to *Candida* spp. Candiduria is beyond the scope of discussion in this review of invasive infection. Readers are referred to other reviews (43, 85) for useful information on this topic.

Of concern with the use of widespread prophylaxis is the development of resistance to the antifungal agent used. Resistance has already been documented with fluconazole and is increasingly reported with the echinocandins (86). The preemptive and empirical strategies are appealing because they limit the use of antifungal agents to those patients who are most likely to benefit from the drug. Hopefully, appropriate criteria for their use will be established with future studies.

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