Invasive candidiasis in the intensive care unit

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Objective: **To review epidemiologic trends, advances in diagnosis and susceptibility testing, therapeutic options and guidelines, and management strategies for invasive candidiasis as relevant to the intensive care unit physician.**

Data Sources, Study Selection, Data Extraction, Data Synthesis: **Nonstructured review of peer-reviewed original articles, review articles, abstracts, guidelines, and consensus statements appearing in Medline, major scientific journals, and conference proceedings.**

Conclusions: **Invasive candidiasis is a problem associated with substantial morbidity and mortality that is highly prevalent in the intensive care unit setting. Recent epidemiologic studies have shown a trend toward increasing numbers of infections and a shift toward infections caused by non-*albicans Candida* species. Guidelines for the management of these diseases have been published and recommend amphotericin B, fluconazole, or caspofungin as the primary therapeutic option. The choice of agent should depend on local epidemiology and patient factors. The role of newer antifungal agents for this population, such as the new azoles and echinocandins, remains to be determined. Priority areas of research include diagnostics, risk identification, and management strategy assessment such as prophylactic, preemptive, and empirical therapy. (Crit Care Med 2006; 34:857–863)**

KEY WORDS: invasive candidiasis; intensive care unit; review; therapy; prophylaxis; antifungals

Invasive candidiasis (IC) is a problem of increasing relevance in the healthcare setting and in particular for intensive care units (ICUs). Great advances in medical technology have allowed patients to survive complex diseases longer, at the cost of creating populations that are vulnerable to a wide variety of previously unrecognized or underestimated diseases. Until recent years, *Candida* was often regarded as little more than a contaminant or "normal flora" in laboratory results, instead of the highly prevalent and potentially aggressive pathogen we recognize today. The term *invasive candidiasis* encompasses a wide variety of severe or invasive diseases that include candidemia, disseminated candidiasis, deep organ involvement, endocarditis, and meningitis, excluding more superficial or less severe diseases such as oropharyngeal and esophageal candidiasis (1, 2). In terms of life loss and economic impact, invasive candidiasis is very costly. With an attributable mortality of as much as 40% to 50%, invasive candidiasis has an estimated cost of $40,000 (U.S.) per episode (3–7). This review focuses on recent epidemiologic trends, advances in diagnosis and susceptibility testing, therapeutic options and guidelines, and management strategies for IC, as relevant to the ICU physician.

Epidemiologic Trends. Recent surveys have shown that candidemia is now the fourth most common nosocomial bloodstream infection in the United States, with similar trends being reported worldwide (8–12). The overall population incidence of this disease is 10 cases per 100,000 in the United States, but institutions have reported increases in incidence as high as 487% in the past 2 decades. ICUs are known to have a tenfold higher incidence of this disease than medical and surgical wards (12–16).

Risk factors for this disease have been identified and extensively described (14, 17, 18) and are shown in Table 1. The single most important risk factor for IC in ICU patients is prolonged stay in the ICU. Most studies have shown that the incidence of IC in the ICU peaks around day 10 of the ICU stay, and studies have shown increased incidence of both *Candida* colonization and invasive disease after day 8 (17, 19–21). Other important risk factors for adult critically ill patients are central venous catheters, acute renal failure, broad-spectrum antibiotics, parenteral nutrition, high Acute Physiology and Chronic Health Evaluation (APACHE) II score, diabetes, immunosuppressive therapy, surgery (particularly abdominal and, even more so, of the upper gastrointestinal tract), transplantation, hemodialysis, and pancreatitis (22). In addition to these risk factors, infants in the neonatal ICU also have increased risk with low gestational age, low American Pediatric Gross Assessment Record (APGAR) scores, and congenital malformations (23, 24). Colonization with *Candida* has been identified as an important risk factor with high predictive value for development of invasive disease (particularly with increasing numbers of colonized sites) in single-center studies, but no significant association was found in one of the largest multicenter epidemiologic studies (18, 25). If anything, *Candida* colonization should be addressed as a risk factor and not as an infection itself. This is particularly true when the colonization index (an index based on the number of positive sites/cultured sites) increases. Risk factors for death or bad prognosis have also been extensively described, and frequently mentioned ones are age, failure to remove central lines, malnutrition, and non-*albicans* fungemia (26, 27).

Another important epidemiologic trend is a fairly dramatic shift in the *Candida* species that are causing disease. Whereas *C. albicans* is still the most common species seen (currently accounting for 40%–60% of cases), since the

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Table 1. Risk factors for invasive candidiasis in the intensive care setting

Adult Intensive Care Patients	Neonatal and Pediatric Intensive Care Patients
Prolonged length of stay	In addition to the adult risk factors
High acuity	Prematurity
Diabetes	Low APGAR score
Renal failure	Congenital malformations
Hemodialysis	
Broad-spectrum antibiotics	
Central venous catheter	
Parenteral nutrition	
Immunosuppressive drugs	
Cancer and chemotherapy	
Severe acute pancreatitis	
Candida colonization at multiple sites	
Surgery	
Transplantation	

APGAR, American Pediatric Gross Assessment Record.
Table is adapted from Refs. 14, 17–25.

introduction and widespread use of the second-generation azoles in the 1980s, there has been a steady increase in the number and prevalence of non-*albicans* species, which collectively account for 40% to 60% of the species currently being reported as causes of invasive disease (6, 8, 10, 16, 28). This shift is relevant because some of these species have reduced susceptibility or intrinsic resistance to fluconazole, as is the case is for *Candida glabrata* and *Candida krusei*, respectively (29). A worrisome trend is the increasing number of reports of fluconazole resistance among species that are typically fluconazole-susceptible, such as *C. albicans*. There are many recent reports regarding this phenomenon, but larger epidemiologic studies have failed to show a definite geographic or temporal trend toward fluconazole resistance, despite heavy azole usage (6, 8, 10, 15, 16, 28, 30, 31). This epidemiologic shift has greatly impacted the therapeutic choices for initial and definite therapy for this disease (32). Table 2 shows the typical distribution of *Candida* species being reported in most centers in the United States and worldwide.

New Diagnostic Tools and Antifungal Susceptibility Testing. As with most infectious diseases, the current "gold standard" for the diagnosis of IC is either a positive culture specimen from a sterile site or characteristic histopathology. These two methods have limited sensitivity, often making the diagnosis of this disease rather difficult, forcing the clinician to rely largely on clinical presentation and risk factors to make empirical therapeutic choices. Blood cultures are known to be negative for ~50% of patients with candidemia or disseminated candidiasis, and improvements in blood culture technique have increased the sensitivity to only 70% at best (2, 33). Cultures of specimens from nonsterile sites are very difficult to interpret because in many cases it is difficult to discern between contamination, colonization, and a significant isolate. Moreover, procedures to obtain histopathological evidence of disease may be highly invasive and not always feasible in the critically ill population.

Exciting developments in the diagnostic arena allow clinicians to obtain earlier, more specific and clinically useful results (34). These developments include advances in culture/identification techniques, serological diagnostics, and genetic markers. Culture and identification techniques have significantly advanced, allowing for more rapid identification of *Candida* to the species level. The availability of special media (e.g., CHROMagar) and rapid *in situ* hybridization/immunofluorescent techniques have significantly shortened the time to identification to the species level (35–38). The importance of this in relationship to therapeutic decisions will be discussed below. Although serological testing has been disappointing in the past, current techniques measuring antigens and fungal cell-wall components have shown promising results (34, 39–41). The most notable example is the recently approved assay for β-D-glucan (42). These tests not only are for diagnosis as a single point test but also are being explored as surveillance tools for preemptive therapy strategies. There are many panfungal and *Candida*-specific primers in the genetic testing arena, but there is no agreement as to which the best primer pairs are and which technique should be implemented. Thus, there are no commercially available genetic testing methodologies at this time (34).

Antifungal susceptibility testing is a relatively new tool that offers important information to the clinician in particularly difficult cases (43). Standardized microdilution and disk-based methodologies are gradually penetrating clinical diagnostic laboratories in most major medical centers, and clinicians should learn to use these resources judiciously. It is important to consider that antifungal susceptibility of the *Candida* species is very predictable in most cases; thus, early identification to the species level should be given priority over susceptibility testing, because it will often provide the clinician with sufficient information to make an appropriate therapeutic decision. The typical susceptibility patterns for the most common *Candida* species are shown in Table 2. Antifungal susceptibility testing is particularly useful in cases when therapeutic choices are limited because of patient factors and drug interactions and when antifungal failures or breakthrough infections occur (44, 45).

Treatment and Management of Documented IC. The Infectious Diseases Society of America (IDSA) has created evidence-based guidelines for the management of this disease (46, 47). These guidelines provide general management and treatment recommendations. On the basis of these guidelines, the first-line drugs of choice include amphotericin B, fluconazole, and caspofungin. For all of these drugs, large randomized controlled trials have demonstrated efficacy and safety for this indication (48, 49). It is important to consider that since the guidelines were published, four other compounds have either been approved for treatment against *Candida* by United States and European agencies or are in late development, backed by published clinical trials with favorable results. These compounds include: micafungin, anidulafungin, posaconazole, and voriconazole (50–55). Their role within the next set of updated guidelines and, in particular, in the ICU setting remains to be determined. Table 3 shows current and late-development therapy options for invasive candidiasis, with recommended dosages. Continuous infusions of amphotericin B have been advocated by some investigators, but we discourage this approach because of the limited information on this subject, the pharmacodynamic information against it, and mainly the availability of many other therapeutic alternatives (56–60).

Table 2. Epidemiological distribution and common susceptibility patterns of *Candida* species

Species	Frequency (%)	Common Susceptibility Patterns				
		Amphotericin B	5-FC	Fluconazole and Itraconazole	Voriconazole and Posaconazole[a]	Echinocandins[b]
C. albicans	40–60	S	S	S	S	S
C. glabrata	20–30	S to I	S	S-DD to R	S to S-DD?	S
C. krusei	5–10	S to I	I to R	R	S to S-DD?	S
C. lusitaniae	0–5	R	S	S	S	S
C. parapsilosis	10–20	S	S	S	S	S to I?
C. tropicalis	20–30	S	S	S	S	S

5-FC, 5-fluorocytosine; S, susceptible; I, intermediate; S-DD, susceptible dose-dependent (dose needs to be increased to achieve therapeutic efficacy); R, resistant.

[a]Although voriconazole and posaconazole are active *in vitro*, *in vivo*, and in early clinical experience against *C. glabrata* and *C. krusei*, their efficacy against these classically azole-resistant organisms hasn't been clearly established; [b]minimum inhibitory concentrations of the echinocandins are higher for *C. parapsilosis* than for other *Candida* species. Clinical trials have shown similar response rates for *C. parapsilosis* as compared with other species, but the full clinical significance of these findings is unknown. Table is adapted from several sources (6, 13, 16, 28, 30, 47).

Table 3. Currently available and late development antifungals for the treatment of invasive candidiasis

Drug	Usual Dose for Invasive Candidiasis	Comments
Amphotericin B deoxycholate	0.6–1.0 mg/kg IV every 24 hrs	Infusion-related reactions common, as well as arrhythmias. Monitor for nephrotoxicity (~30%).
Amphotericin B lipid compounds	3–5 mg/kg IV every 24 hrs	Fewer infusion-related reactions and nephrotoxicity (~10%) than with deoxycholate. Expensive. Patients may have reactions to one compound but not to another.
5-FC	37.5 mg/kg PO every 6 hrs	Never to be used on its own. To be used in combination with polyenes in cases of severe disease. Monitor levels and CBC for signs of bone marrow toxicity, particularly in the setting of renal failure. Diarrhea also common.
Fluconazole	400–800 mg PO or IV every 24 hrs	PO to IV bioequivalence >90%, even in patients who have undergone GI surgery. Drug interactions uncommon but possible. Mild to moderate increases in transaminase levels.
Itraconazole	400 mg PO or IV every 24 hrs	Less active than fluconazole against *Candida*. Oral form is not well absorbed, and IV formulation must be used with caution in renal failure. Many drug interactions.
Voriconazole	6 mg/kg IV every 12 hrs loading (day 1), followed by 3 mg/kg IV every 12 hrs or 400 mg PO every 12 hrs loading (day 1), followed by 200 mg PO every 12 hrs	Many drug interactions that require careful review of concomitant medications. Visual and hepatic side effects common. Advantages over polyenes and fluconazole uncertain, except for possible activity against *C. glabrata* and *C. krusei*. IV formulation cannot be used in renal failure.
Caspofungin	70 mg loading (day 1), then 50 mg IV every 24 hrs	Mild increases in liver function tests common. Avoid in hepatic failure with Child-Pugh B or C. Interaction with rifampin may require dose increase. Interaction with cyclosporine A not fully characterized and may be less problematic than originally thought.
Micafungin	100–150 mg IV every 24 hrs	Not FDA-approved for this indication, but open-label and randomized, controlled data show efficacy at this dosing range.
Anidulafungin	100 mg IV every 24 hrs	Not yet FDA-approved. Open-label data show efficacy at this dosing range. Data presented in abstract form following comparative trial with fluconazole show possible superiority of anidulafungin and similar side-effect profile.

IV, intravenous; PO, by mouth; 5-FC, 5-fluorocytosine; CBC, complete blood cell count; GI, gastrointestinal; FDA, U.S. Food and Drug Administration.

Our approach for the treatment of IC in the ICU is shown in Figure 1. Although the guidelines do not clearly address which drug should be used for a particular scenario, most experts agree that the initial or empirical choice between a polyene, an echinocandin, or an azole depends on two critical parameters: the epidemiologic characteristics of the particular ICU and host factors such as severity of illness, infection site, neutropenia, and coexisting organ dysfunction. Knowledge of the local epidemiologic characteristics of the ICU is important. For example, fluconazole may be a poor choice for empirical therapy in units with a high incidence of *C. glabrata* and *C. krusei*, although it may be a good and economic choice for a stable patient or for ICUs where *C. albicans* is still the predominant organism. Host factors are particularly relevant in the ICU setting. Although it offers only a theoretical advantage, most experts recommend using a fungicidal agent that covers all the *Candida* species (such as the polyenes or echinocandins), rather than fungistatic agents (such as the azoles) that may not cover all species, for a critically ill patient—when timing and accuracy may be crucial (1). Nevertheless, no published clinical trials support this approach; all current antifungals have been shown to be either equivalent or noninferior to each other in trials that often include critically ill patients. Other factors to be considered in the initial or empirical choice of antifungal agents are organ dysfunction (avoiding polyenes for patients with renal fail-

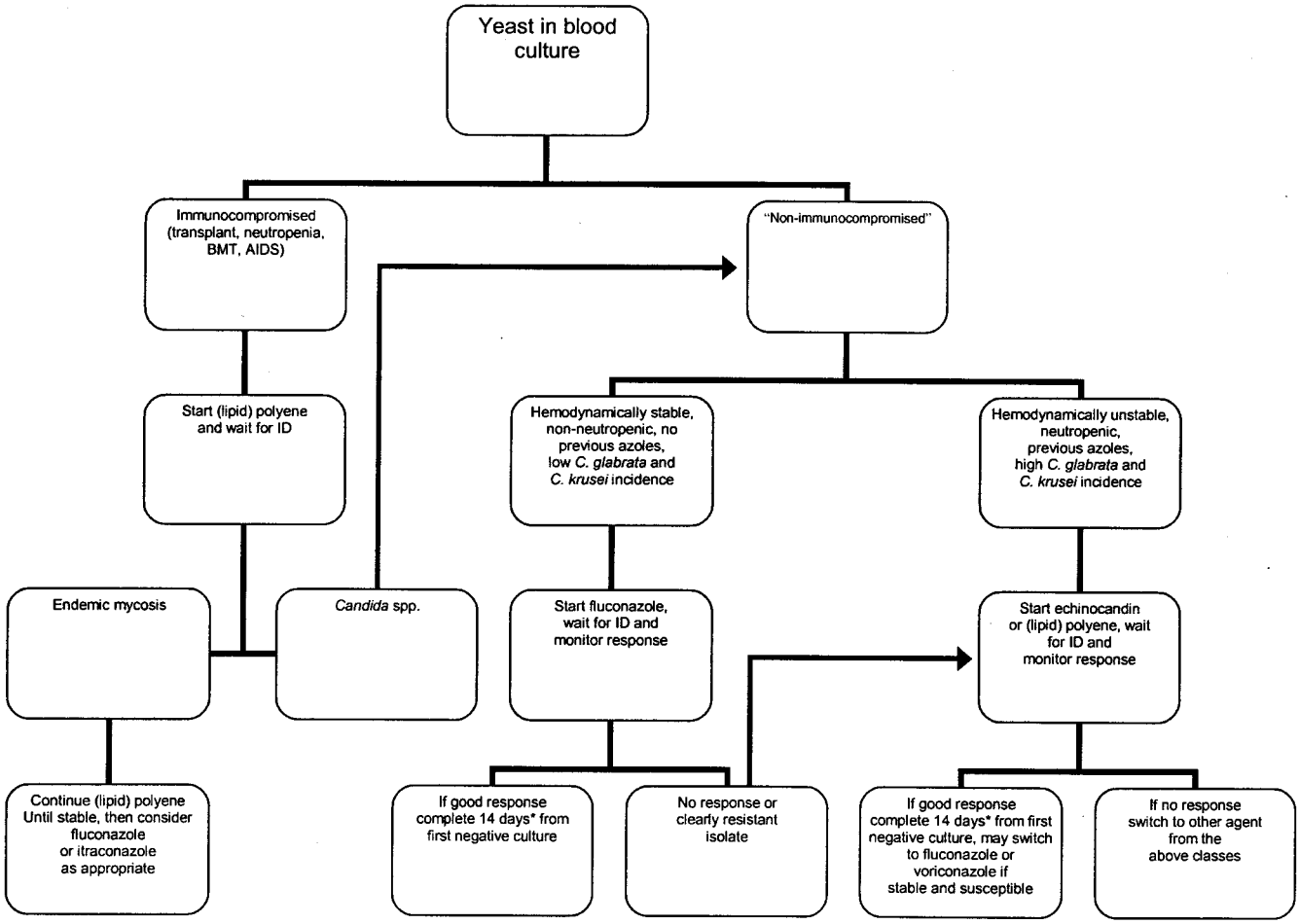

Figure 1. Suggested approach for the treatment of invasive candidiasis in the critical care setting. *May need to treat longer if signs of dissemination (such as endophthalmitis or liver/spleen/skin) are found. *BMT*, bone marrow transplantation; *AIDS*, acquired immune deficiency syndrome.

ure and possibly avoiding echinocandins and azoles in severe hepatic dysfunction) and drug interactions, because patients hospitalized in ICUs often have complex poly-pharmacies. Finally, an important factor to be considered is the cost of a specific antifungal agent. Antifungals have been recognized as significant "cost drivers" within the antimicrobial budget of most institutions. Although efficacy and safety should never be compromised, clinicians should be mindful of costs and utilize less-expensive antifungals or an oral formulation whenever appropriate. The concept of "de-escalation" is particularly important. One may start with a broad-spectrum (and often more expensive) antifungal, but when the patient stabilizes and/or organism identification or susceptibilities are available, one may switch to a more-specific agent or an oral formulation. Duration of antifungal therapy per the IDSA guidelines is 14 days from the first negative blood culture for candidemia (if disseminated disease is excluded) or until clinical, microbiological, or radiologic resolution of the infection (for other forms of IC, particularly disseminated disease).

The utility of combination therapy for most antifungal combinations is largely unknown (61). Early studies concentrated on amphotericin B and flucytosine for particularly severe disease, such as meningitis, endocarditis, or osteomyelitis, and support the current guidelines for use in these types of situations (47). Flucytosine should never be used alone for the treatment of IC, because organisms become resistant to it within a few days (62). More recently, a multicenter, randomized, double-blind, placebo-controlled trial of high-dose fluconazole vs. high-dose fluconazole plus amphotericin B showed that the combination was not significantly different when compared with fluconazole alone on the basis of the primary end points, but there was more rapid blood culture sterilization and perhaps an advantage for patients in the intermediate range of APACHE II scores (63). This study also dispelled concerns about clinically relevant antagonism between the two agents.

Aside from antifungal treatment, general principles of therapy include removing all compromised vascular lines, devices, and implants when possible, because the removal of these foreign objects actually correlates with better patient outcomes (47, 64, 65). Nevertheless, one may be less aggressive in pursuing central line removal in patients with tunneled catheters (because these are lower risk (66)) and patients with neutropenia or mucositis (because gut translocation may be the source rather than the intravascular catheter in this patient population (67)). Biofilms appear to play a major role in the persistence and proliferation of these infections, and there are interesting experimental data for echinocandins and polyenes demonstrating biofilm penetration and activity (68, 69). Although the frequency of endophthalmitis

is relatively low (3%–10%), it is recommended that all candidemic patients (particularly those with prolonged fungemia) have a dilated-eye examination (preferably performed by an ophthalmologist) to exclude disseminated disease and endophthalmitis, which are characterized by retinal infiltrates and vitreous abnormalities, because these two conditions require prolonged antifungal therapy and endophthalmitis may require vitrectomy and direct intravitreal antifungal instillation (47, 70). Failure to perform this examination can often result in partial courses of treatment for disseminated disease and subsequent relapse, deterioration, or deep organ involvement.

On the Edge of Evidence: Prophylactic, Preemptive, and Empirical Therapy. Because of the prevalence of invasive candidiasis, the poor performance of the available diagnostic methods, the high attributable mortality and increased morbidity, and the availability of safe and effective drugs for the management of these infections, more aggressive approaches have been advocated (71). Three strategies have received increasing attention in the past decade and are defined as follows: *prophylaxis* entails administering a drug to prevent disease in a high-risk population; *preemptive therapy* entails early treatment of the infection with use of clinical, laboratory, or radiologic surrogate markers of disease in high-risk hosts before clinical signs and symptoms or full-blown disease develops; and *empirical therapy* entails treatment of high-risk hosts who exhibit signs and symptoms of the disease, even in the absence of positive cultures or other evidence of disease (72, 73). Unfortunately, definitive evidence in the literature that supports the use of these strategies in the ICU is limited at this time. Nevertheless, there are a few studies, particularly in the area of prophylaxis, that are encouraging.

There have been three randomized clinical trials of antifungal prophylaxis with fluconazole in the ICU, but unfortunately all of them either had limited numbers or were conducted in a single center. Thus, none of these studies were definitely conclusive or have caused a paradigm shift regarding this issue. Eggiman et al. (21). conducted a prospective, randomized, placebo-controlled trial of fluconazole as prophylaxis for abdominal candidiasis in surgical ICU patients at two university hospitals in Switzerland. The study enrolled 43 patients, and the primary end point was development of intra-abdominal candidiasis. Frequency of candidal peritonitis was reduced from 35% to 4% in the fluconazole group, and the investigators also demonstrated that *Candida* colonization occurred in 62% of the placebo vs. 15% of the fluconazole recipients, reaching statistical significance.

Pelz and colleagues (20) studied the surgical ICU at The Johns Hopkins Hospital in a prospective, randomized, placebo-controlled trial. Patients whose potential length of stay was >3 days were randomly assigned to either full-dose fluconazole or placebo. The main end point was time to development of fungal infection in the intent-to-treat population. The definitions of fungal infection were compatible with the currently used European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria for diagnosis of fungal infection (74). The trial enrolled 260 patients, and the overall incidence of proven fungal infections was 15.4% for placebo vs. 8.5% for fluconazole. At ICU day 14, these authors showed a 0.4 probability of infection with placebo, vs. 0.13 with fluconazole ($p < .01$). In an open-label follow-up study, the investigators continued to show a sustained benefit to this strategy without demonstrating a significant shift to non-*albicans Candida* species, but they failed to show any differences in mortality (75).

Garbino et al. (19). studied a medical and a surgical unit in an academic center in Switzerland. This was a prospective, randomized, placebo-controlled trial examining the utility of fluconazole as part of a selective gastrointestinal decontamination strategy for 204 patients who were on mechanical ventilation for at least 48 hrs and who had an expected duration of stay in the ICU of at least 3 days. The main outcome was incidence of candidal infection according to nonstandardized definitions. The incidence of IC was 16% among placebo recipients, vs. 5.8% among fluconazole recipients. *Candida* colonization was significantly decreased over time in the patients who received fluconazole, and this study also failed to show a difference in mortality.

These three trials have shown that fluconazole prophylaxis may be considered effective in reducing the incidence of candidal infections and *Candida* colonization in selected critically ill patients, in both the medical and the surgical ICU setting. The studies have also shown that the concerns regarding an "epidemiologic shift" to fluconazole-resistant *Candida* species in the ICUs are unfounded, because none of these studies showed this concern. The major drawbacks of these studies are the lack of standardized disease definitions and the geographic limitation to one or two hospitals, as well as the lack of power to show a difference in mortality.

Perhaps the key issue for prophylaxis or preemptive or empirical therapy is identifying patients who are truly at the highest risk of the disease, because it is only in this population that the risk-benefit and cost-benefit equations for these interventions will work. Research is ongoing to explore risk factors such as colonization and to create risk factor–based clinical prediction rules (76–80).

One of the most common clinical issues in intensive care is the use of empirical antifungal therapy for febrile high-risk patients whose fungal cultures are negative. Knowing the poor performance of current diagnostic techniques and confronted with a highly prevalent and treatable disease, physicians understandably feel compelled to act empirically. The typical patient is critically ill, has at least one central venous catheter, is receiving broad-spectrum antibiotics, has at least one or multiple sites of *Candida* colonization (e.g., urine, sputum, and/or stool), and is febrile or hemodynamically unstable, and other sources of fever have been excluded. There is no literature to address this situation, but we believe that empirically treating carefully selected ICU patients at high risk is usually justifiable (1). Again, colonization (particularly of many sites) should be regarded as nothing more than a risk factor, not as a disease that requires treatment on its own, because studies have shown there is no benefit to treating forms of colonization such as asymptomatic funguria in nonimmunocompromised patients. Yet, in the correct context of a high-risk host with other risk factors (in which other causes of decompensation have been excluded), empirical treatment may be of value. Research in this area must focus on identifying these patients by means of risk factor–based clinical prediction rules and determining whether this strategy is more effective than prophylaxis, antifungal preemptive therapy, or specific therapy for documented fungal disease.

SUMMARY

Invasive candidiasis is a problem with substantial morbidity and mortality that is

Colonization (particularly of many sites) should be regarded as nothing more than a risk factor, not as a disease that requires treatment on its own, because studies have shown there is no benefit to treating forms of colonization such as asymptomatic funguria in nonimmunocompromised patients.

highly prevalent in the ICU setting. Recent epidemiologic studies have shown a trend toward increasing numbers of infections caused by non-*albicans Candida* species. Guidelines for the management of these diseases have been published and recommend amphotericin B, fluconazole, and caspofungin as primary therapeutic options. The role of newer agents in the ICU remains to be determined. The choice of agent should depend on local epidemiology and patient factors. Priority areas of research include diagnostics, risk identification, and assessment of management strategy, such as prophylaxis or preemptive or empirical therapy.

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