Surgical critical care: Fungal infections in surgical patients

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Objective: **To review the epidemiology, risk factors, diagnosis, treatment, and prevention of *Candida* infections in surgical intensive care unit patients.**

Design: **Selected review of the literature.**

Setting: **Critically ill patients either in an intensive care unit or having undergone a major surgical procedure.**

Interventions: **None.**

Main Results: ***Candida*** **infections are the third most common cause of bloodstream infection in the intensive care unit, with increasing numbers of infections due to nonalbicans species. The diagnosis of an invasive fungal infection is difficult, and the risk factors must be recognized and minimized. There is no general consensus about what signs, symptoms, and cultures define a fungal infection. A new 1,3 beta-glucan blood test may assist is the definition of invasive fungal infection. Treatment of fungal infections is now possible with a variety of antifungal agents, with different spectrums of activity, mechanisms of action, and adverse events. Prevention (prophylaxis) is a reasonable strategy in highly selected patients with a significant risk of fungal infection.**

Conclusion: **New antifungal agents and diagnostic tests may improve the outcome of surgical intensive care unit patients with invasive fungal infections. However, agreement about definitions of fungal infection makes study and conclusions of prevention and treatment trials difficult to interpret. (Crit Care Med 2006; 34[Suppl.]:S215–S224)**

KEY WORDS: *Candida*; fungus; epidemiology; risk factors; therapy; prevention; diagnosis

In the last 25 yrs, the proportion of nosocomial infections caused by fungi has dramatically increased (1–4). Clinicians have often considered fungal infections a problem of neutropenic patients, but today, at least half of all nosocomial fungal infections occur in critically ill surgical patients as deep-seated and bloodstream infections (1, 5). In addition, *Candida* infections have been increasingly described in the pediatric and neonatal patient populations (4). Thus, no matter what kind of patient population is located in the intensive care unit (ICU), fungal infections will be seen. This review will focus on the special patient population of patients who have critical illness related to surgery or a surgical problem and who develop a *Candida* infection.

Critically ill patients usually have many of the risk factors that are known to be associated with fungal infections (6–9). Typically, patients are treated with invasive devices or procedures, broad-spectrum antibiotics, and have either classic or unmeasured forms of immunosuppression. Certainly, patients with a longer length of ICU stay and patients with colonization with *Candida* seem to be at special risk for invasive fungal infection (1, 10–12). Although many of the risk factors for fungal infections are known, these factors have not been used in a clinically meaningful way to identify patients who will acquire a fungal infection (13). Moreover, this is confounded by the fact that there is no consensus about the definitions of fungal infections in nonneutropenic patients. Because there are no consensus definitions of fungal infections, the presentation and analysis of evidence-based guidelines for the prevention and treatment of fungal infections in critically ill surgical patients is more difficult (13). This review will focus on a series of clinical questions relevant to the care of critically ill or injured surgical patients.

What Are the Pathogens Involved in Fungal Infections in the ICU?

In surgical ICUs 20 yrs ago, fungal infections were fairly simple; they were caused by endemic fungi, or by the yeasts and molds, of *Candida* and *Aspergillus* (3). *Candida* exists in two separate forms, the yeast and the mycelial form. Although either form when isolated from tissue is pathognomonic of infection, usually, the mycelial form causes invasion. In a very large national report of fungal infections, *Candida* species accounted for >80% of all fungi isolates causing nosocomial infections (2–4). *Aspergillus* species and many of the emerging fungal pathogens such as *Fusarium* and *Rhizopus* species comprise about 10% of the remaining nosocomial infections. These infections are uncommon but do occur in surgical patients, especially those with classic immunosuppression, such as solid organ transplant patients or patients undergoing chemotherapy. Although *Candida albicans* remains the single most common yeast species isolated from hospitalized patients, in some units, only 50% of all *Candida* species isolated will be *C. albicans* (14–18). The remaining *Candida* infections are caused by nonalbicans species and include: *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. lusitaniae*.

When a single systemic antifungal (amphotericin B deoxycholate) with broad antifungal activity was available, knowledge about specific fungal species was of academic but not clinical importance. However, with increasing availability of a wide variety of antifungal agents in both intravenous and oral form, it is important to recognize that some of the agents at standard doses do not cover some common fungal species (19, 20). Clinicians should be particularly aware of three nonalbicans *Candida* species that can and do cause infection: *C. glabrata*, *C. krusei*, and *C. lusitaniae* (16, 20–22).

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When bacterial sensitivities are reported, we are used to seeing some notation that a pathogen is sensitive or resistant to a specific antibiotic. However, for fungal species, there is a new category—that of dose-dependent sensitivity (19, 23). Essentially, this category means that giving a higher than recommended dose of a particular drug can result in effective therapy without toxicity. *C. albicans* is a species generally very sensitive to fluconazole, with sensitivities in the range of 0.125–0.250 μg/mL. For *C. glabrata*, dose dependence for fluconazole is typically seen when a minimal inhibitory concentration of 16 μg/mL is present and resistance seen when the minimal inhibitory concentration is ≥32 μg/mL (19). Depending on your institution, *C. glabrata* may be sensitive, dose dependent, or resistant to fluconazole and itraconazole and may have variable sensitivity to amphotericin. Because *C. glabrata* may account for 20–25% of all infections and the sensitivity patterns may dictate therapy, the clinician should be aware of this pathogen and of how frequently it is present in your institution. Unlike *C . albicans* and *C. glabrata*, *C. krusei* is always resistant to fluconazole, dose dependent or resistant to itraconazole, often resistant to flucytosine, and of variable sensitivity to amphotericin. *C. lusitaniae* is also of variable sensitivity to amphotericin.

How Common Are Fungal Infections in Surgical ICU Patients?

Data from a nationwide (United States) concurrent surveillance study (Surveillance and Control of Pathogens of Epidemiologic Importance [SCOPE]) found 24,179 cases of nosocomial bloodstream infections in 49 U.S. hospitals during a 7-yr period from March 1995 through September 2002 (60 cases per 10,000 hospital admissions) (24). In this large series, *Candida* species accounted for 4.6 bloodstream infections per 10,000 admissions and 9% of all bloodstream infections, with a slightly higher rate in ICU patients (10.1% of all) than on the ward (7.9%). In the ICU, *Candida* infection was the third most common bloodstream pathogen isolated behind coagulase-negative *Staphylococcus* and *Staphylococcus aureus* (24).

Although commonly thought of as a disease confined to neutropenic cancer patients, *Candida* is in fact either the third or fourth most common bloodstream isolate from the ICUs including surgical, cardiac surgical, and burn ICUs (2–4, 24–26). At the Johns Hopkins Hospital, yeast isolates accounted for 15% of bloodstream isolates from 1992 through 1995 (27). In a recent multiple-center, prospective study on risk factors for *Candida* bloodstream infections in surgical patients, the incidence of fungal infections overall was 0.98/1000 patient days and increased to 1.42/1000 surgical ICU days when a central venous catheter was in place (1). Whereas these studies present the prevalence of *Candida* in bloodstream infections, they are likely to substantially underestimate the importance of *Candida* because infection at other sites is not captured. Moreover, several autopsy studies have shown that *Candida* infections are often undiagnosed antemortem. One series found that antemortem blood cultures were positive for fungus in only 44% of autopsy-proven fungal infections (28).

Can a Normal Person Develop a Fungal Infection?

Candida species are part of the normal endogenous flora of humans, living in the gut lumen and more rarely on mucocutaneous surfaces. The question of whether a normal person, even one without a surgical stress, can develop a fungal infection was addressed in a seminal article by Krause et al (29). They demonstrated that a normal person ingesting 10^{12} of live *C. albicans* could develop symptoms lasting 9 hrs, with candidemia seen at 3 and 6 hrs and candiduria at 2.75 and 3.5 hrs. Signs and symptoms of fungemia cleared after ingesting epsom salts, nystatin, and with normal host defenses. In this experiment on himself, Krause proposed that the presence of *Candida* in the urine and blood after oral ingestion was clearly the result of transmigration across a normal intestinal barrier (29).

Can We Identify Patients Who Are at Risk for Fungal Infections?

Patients in the ICU often are not eating normally, and the size of the intestinal villi are substantially affected by lack of enteral nutrient intake, most likely allowing easier transmigration of pathogens across the intestinal barrier. In addition, the use of even short-duration antibiotics can cause an increase of *Candida* in excess of 10^9 organisms in the gut and, when combined with altered villous size, integrity, and motility, can explain some increased susceptibility of ICU patients to both systemic infections and to peritoneal infection (10, 11). Thus, antibiotic use, duration of use, and broad-spectrum antibiotics are all risk factors for fungal infections.

In the prospective trial examining risk factors for *Candida* bloodstream infections in 4,276 surgical patients, several risk factors were identified. In the multivariate analysis, the relative risk associated with an increased risk of a bloodstream infection with *Candida* included previous surgery (relative risk, 7.3), acute renal failure (relative risk, 4.2), receipt of parenteral nutrition (relative risk, 3.6), and for patients who had undergone surgery, a triple-lumen catheter (relative risk, 5.4) (1). These factors do not imply any specific pathogenesis of fungal infection but merely reflect identifiable risk factors in ill patients. Thus, surgeons and physicians caring for surgical patients, especially those patients in an ICU, must be aware of this problem and attempt to minimize these known risk factors.

Of course, patients with immunosuppression with defects in either T-cell dysfunction (prevention of colonization and superficial invasion) or in phagocytosis (prevention of deeper invasion and hematogenous dissemination) have an increased risk of fungal infection. Some authors have suggested that patients in the ICU and at high risk can be identified by the presence of more than three risk factors (8).

Candida colonization is one major risk factor, with both duration of colonization in time and intensity of colonization (colonization index = number of sites positive/number of sites cultured) recognized as important factors (8). Pittet et al. (8) attempted to refine the use of surveillance cultures by advocating the use of the "corrected colonization index," or ratio of body sites positive for fungus on a given day (the colonization index) corrected for the heaviness of fungal growth in the sample. Pittet et al. (8) reported that this corrected colonization index had a >66% positive predictive value for subsequent fungal infections.

One of the very basic questions is whether colonizing species ultimately cause fungal infection. In nonneutropenic patients with candidemia, 84% of colonizing and infecting species were identical, and time from colonization to infection could be short (5 days) (30). Similarly, Petri et al. (31) have shown that 64% of patients in the ICU were colonized and that all patients who had invasive infection had been previously colonized. Maximal colonization occurred between days 10 and 15 of an ICU stay, but some patients had positive blood cultures at 5 days. However, in this study, colonization was not sufficient to predict infection

because the overall prevalence of invasive fungal infection was quite low (2%) compared with fungal colonization 64% (31).

In a 3-month prospective study, we identified 14 patients with a definite or probable fungal infection among 159 eligible patients in the medical ICU, surgical ICU, and Oncology Center at Johns Hopkins Hospital (32). In the multivariate model, the only factors that predicted fungal infection were fungal burden, gastrointestinal surgery, and increasing Acute Physiology and Chronic Health Evaluation score. These data demonstrate a significant and independent association between positive fungal surveillance cultures and infection. Because the overall prevalence of the disease is low, the positive predictive value of the presence of colonization in more than two sites or in more than half of all body sites cultured is low and therefore cannot be used in isolation in assessing the patient's risk of a fungal infection. However, the negative predictive value, and more importantly, the negative likelihood ratio of these indices, strongly suggests that in the absence of fungal colonization, infection is unlikely. Furthermore, the data suggest that one possible use of surveillance fungal cultures would be to be to target the highest-risk patient populations for further intervention (8, 32).

In a recent study of 92 medical ICU patients with a length of stay of >7 days, surveillance cultures were used to determine the colonization index at admission and at weekly intervals (33). At ICU admission, the mean colonization index was 0.26 ± 0.26, with 42.4% of patients having an index between 0.2 and 0.5 and 22.8% of patients with an index of >0.5. Every week the patient stayed in the ICU, the index on average increased 0.1 per week. Patients with heavy fungal colonization had a longer length of ICU stay, but other outcomes could not be clearly associated with this index.

Duration of ICU length of stay is certainly a risk factor and maybe a proxy for severity of illness, the use of invasive devices, and increased colonization. The prevalence of invasive candidiasis is relatively low in the first 5–7 days of ICU stay but, by day 7, dramatically increases, peaking around day 21 (33, 34).

Among surgical patients, solid organ transplant recipients, and in particular, liver, pancreas, and small-bowel transplant patients, seem to have a greater risk of developing invasive fungal infections. Rates of invasive *Candida* infection in liver transplant patients vary from 1.3% to 15% among those receiving antifungal prophylaxis (35–37) to 23% among patients not receiving prophylaxis (38). Among pancreas transplant recipients, the prevalence of invasive fungal infection has been estimated to be approximately 9% (39), and among small-bowel transplant recipients, the prevalence has been estimated to be as high as 59% (40).

In addition to the above, risk factors identified in the general surgical patient population include: duration of antibiotic use or use of anti-anaerobic agents (1, 8), parenteral hyperalimentation (1, 41), severity of illness (8, 34), gastrointestinal perforation (41–43), and hemodialysis (1). Risk factors associated with invasive fungal disease in organ transplant patients are somewhat different from those identified for heterogeneous surgical patient populations. Although factors such as renal insufficiency (44), multiple antibiotics (45), and fungal colonization (38, 44) are also associated with invasive fungal disease in liver transplant patients, factors related to the surgical procedure and posttransplant immunosuppression may confer additional risk. For example, multivariate regression analyses have shown that operation time of ≥11 hrs (44), retransplantation (38, 44), transfusion of cellular blood products (37), abdominal or thoracic reoperation (44), cytomegalovirus infection (37, 44), and choledochojejunostomy anastomosis (37) are significantly associated with an increased risk of invasive fungal infection. Risk factors for invasive fungal infection in other solid organ transplant populations are not as well defined. In a study of posttransplant intraabdominal fungal infections in pancreas transplant recipients, those with older donors, those whose transplants were drained into the gastrointestinal tract as compared with those drained via the bladder, those receiving living related donor organs, and those undergoing pancreas and renal transplantation (as compared with pancreas alone) were at higher risk of infection (39).

However, despite these known risk factors, it is extremely difficult to identify a uniform large group of high-risk patients. This remains one of the most important drawbacks to using prophylactic therapy.

What Does Isolation of a Fungus from a Culture Mean? How Are Fungal Infections Defined?

Fungal pathogens can be isolated under a number of clinical conditions. Isolation of a fungal pathogen without any signs or symptoms of clinical infection is termed colonization. After colonization, *Candida* are believed to gain access to the bloodstream by three major routes: through the gastrointestinal tract mucosal barrier, from an intravascular catheter, and from a localized source of fungal infection. As many as 50–80% of critically ill patients may become colonized at a single site with *Candida* species during prolonged ICU stay (25, 26, 31, 32). As noted previously, when multiple sites are tested and are negative, the absence of fungal colonization almost ensures that a fungal infection is not present (32).

Nosocomial exogenous transmission of *Candida* and *Aspergillus* is considered a less frequent but possible mechanism for infection (45–48). In a recent study of ICU patients and nurses, 6% of nurses' hand cultures contained fungal pathogens, from which 2 of 57 patients with candidemia could be linked with DNA fingerprinting (48). Cross-infection of *Candida* by hand transmission has been described in several studies (15, 16). Nail contamination in the operating room has been linked to an outbreak of *Candida tropicalis*—infected sternal wounds (46). Parenteral nutrition has also been identified as a potential source of contamination with infections described with *Candida parapsilosis* (47).

The isolation of *Candida* from the blood is now universally accepted as constituting a fungal infection (49, 50). The source of candidemia can be from hematogenous spread from a deep-seated infection, from a catheter-related infection, or from gastrointestinal translocation, to name a few. Thus, in a candidemic patient, the clinician must search carefully for potential sources. Common sources would include intravascular catheters, septic thrombophlebitis, and intraabdominal sites. In addition, patients may develop new sources that may have resulted from candidemia, such as endophthalmitis, infective endocarditis, hepatosplenic candidiasis, and arthritis.

Although isolation of *Candida* from sputum is common, pneumonia secondary to *Candida* infection is rare (50–52). The value of deep tracheal suction or even bronchoalveolar lavage in defining this disease should be questioned. Histopathologic confirmation is recommended (50). Laryngeal infection should be considered and can be rapidly progressive in some case reports.

The importance and meaning of candiduria has been hotly debated (53–55). Kauffman et al. (53) have suggested that candiduria in hospitalized patients is not an important clinical problem. Nassoura et al. (54), however, suggested that in ICU

trauma patients, candiduria, when treated with bladder irrigation, was associated with a high rate of dissemination and death, whereas treatment with fluconazole in a small group of similar patients had an improved outcome. Candiduria is very common in hospitalized patients with urinary catheters for >14 days. In most cases, this represents colonization and not infection. However, most of these studies have not included ICU patients. In patients with a urinary catheter for >7 days, 389 of 1,765 patients had candiduria (55). Invasive *Candida* infections were seen in 105 of the 1,765 patients (5.9%), 48 of whom had candiduria (55). These authors also described a severity-of-illness adjusted increase in mortality in patients with candiduria (odds ratio, 1.58; 95% confidence interval, 1.25–2.0) (55).

Invasion or infection is when a fungal pathogen is isolated from a patient with signs and symptoms of an infection. This definition is, however, too simple to be applied to fungal pathogens, and colonization would be frequently considered infection when it is not.

However, no consensus opinion exists for what constitutes a fungal infection in a nonimmunocompromised host (25, 26, 49, 50, 56). However, in neutropenic patients, consensus definitions have been established (57).

Fungal infections can be classified into definite and probable. In brief, definite fungal infections with deep-tissue invasion are present when tissue invasion via a biopsy or culture from a sterile site with clinical or radiologic abnormalities is demonstrated. A blood culture has traditionally been the gold standard for the diagnosis of candidemia. A positive blood culture is an indication to start antifungal therapy (49). However, systemic *Candida* infection may occur in the absence of positive blood cultures. A blood culture has a 50% false-negative rate and can take up to 4 days to yield results. The clinician, however, should not be led to believe that a fungal infection is *not* present in the absence of a positive blood culture, or tissue biopsy, because nearly 44% of patients with a negative blood culture at autopsy have evidence of disseminated fungal infection (28). No agreement exists as to what signs and symptoms constitute a probable or possible fungal infection in a nonneutropenic patient.

At the present time, auxiliary serologic tests such as of fungal wall elements (mannan), D-arabinitol (cell membrane metabolite), enolase (cell cytoplasm), or polymerase chain reaction assays are of limited value (26). These tests have mixed sensitivities and specificities. However, recently, the results of the 1,3 beta glucan measurement for the diagnosis of invasive fungal infection was completed at six centers (58). At a cutoff of 60 pg/mL, the sensitivity and specificity of the assay were 69.9% and 87.1%, respectively, with a positive predictive value of 83.8% and a negative predictive value of 75.1%. At a cutoff value of 80 pg/mL, the sensitivity and specificity were 64.4% and 92.4%, respectively, with a positive predictive value of 89% and an negative predictive value of 73%. Of the 107 patients with proven candidiasis, 81.3% had positive results at a cutoff value of 60 pg/mL, and 77.6% had positive results at a cutoff value of 80 pg/mL. Of the ten patients with aspergillosis, 80% had positive results at cutoff values of 60 and 80 pg/mL. Patients with more unusual fungal pathogens have a similar reasonable positive predictive value and negative predictive value. Active investigation in this area is ongoing, but these early results are promising.

What Are Currently Available Systemic Antifungal Agents for the Treatment of Candidemia?

Currently available agents for the treatment of *Candida* infections include amphotericin B, fluconazole, itraconazole, voriconazole, flucytosine, the lipid amphotericin products and the echinocandins—caspofungin, micafungin, and anidulafungin (Table 1) (49, 50). Most *C. albicans* isolates are sensitive to all of these agents (18, 23, 59–61). In some patients with chronic exposure to antifungal agents, especially at low doses, resistance to both fluconazole and amphotericin B has been described (21, 22, 61, 62). However, some of the nonalbicans species, such as *C. glabrata*, *C. krusei*, and *C. lusitaniae*, may have resistance to either primary agent or may require dose modification. Voriconazole is a second-generation azole with a very broad spectrum of activity, including *Aspergillus* and *C. krusei* (63). Voriconazole is currently first-line therapy for aspergillosis but has also been favorably studied in a clinical trial of candidemic patients (64). As a first drug in the echinocandin class, caspofungin had a different mechanism of action (1,3 beta-D-glucan inhibition) (65). Glucans are essential components of the fungal cell walls, and inhibition of 1,3 beta-D glucan results in depletion of cell wall glucan, osmotic instability, and cell lysis. Like voriconazole, it has a wide spectrum of activity.

Table 1. Agents for the treatment of fungal infections

Polyenes[a]
Amphotericin B
Amphotericin B in lipid complex (ABLC, Abelcet, The Liposome Company, Princeton, NJ)
Amphotericin B colloidal dispersion (ABCD, Amphotec, Alza Corporation, Palo Alto, CA)
Amphotericin B liposome (L-Amph, AmBisome, Fujisawa Healthcare, Deerfield, IL)
Azoles
Imidazoles, nonsystemic
Ketoconazole
Miconazole
Imidazoles, systemic
Fluconazole
Voriconazole
Posaconazole[b]
Ravuconazole[b]
Triazoles
Itraconazole
Echinocandins
Caspofungin
Micafungin[b]
Anidulafungin[b]

[a]Generic and trade names are listed for lipid amphotericin B products because of common confusion in the nature and name of these agents; [b]not currently approved by the Food and Drug Administration—in development.

Today, the physician caring for an ICU patient with proven or suspected candidemia has a wide selection of antifungal agents. As is true in all clinical situations, the clinician must balance the advantages and disadvantages of each agent in a given clinical situation (Table 2). If one is unsure about the exact fungal species, an agent with a broad spectrum of activity (amphotericin-containing products, caspofungin, and voriconazole) may be selected. If an oral agent is desired, then fluconazole and voriconazole should be considered. Some of the disadvantages to consider in antifungal selection include; toxicity (amphotericin products, voriconazole, itraconazole [intravenous], flucytosine), drug interactions (voriconazole), and cost (all except fluconazole). Individual clinical trials in nonneutropenic patients and meta-analysis of those trials support that amphotericin deoxycholate and fluconazole seem to have similar outcomes in overall mortality, attributable mortality, and clinical and microbiological response but differ in toxicity, with fluconazole favored (66–68). Thus, it is reasonable to utilize fluconazole in patients with candidemia (49, 50). Selection of fluconazole as a primary treating agent should be done with caution in patients

Table 2. General susceptibility of common *Candida* species to selected antifungal agents

Candida Species	Fluconazole	Itraconazole	Flucytosine	Amphotericin B
C. albicans	+	+	+	+
C. glabrata	Dose + to −	Dose + to −	+	+ to ±
C. tropicalis	+	+	+	+
C. parapsilosis	+	+	+	+
C. krusei	−	Dose + to −	± to −	+ to ±
C. lusitaniae	+	+	+	± to −

+, susceptible minimum inhibitory concentrations (MICs): fluconazole, ≤8 μg/mL; itraconazole, ≤0.125 μg/mL; flucytosine, ≤4 μg/mL. ±, intermediate. Dose +, susceptible-dose-dependent (S-DD) MICs: fluconazole S-DD, 16–32 μg/mL; itraconazole S-DD, 0.25–0.5 μg/mL; flucytosine I, 8–16 μg/mL. −, resistant MICs: fluconazole, >32 μg/mL; itraconazole, >0.5 μg/mL; flucytosine, >16 μg/mL.

who are critically ill and have an unknown fungal species, especially when they have been exposed to previous azole use (49). Before the release of caspofungin and voriconazole, an international expert panel attempted to develop consensus on the treatment of common clinical problems with fungus. The panel was divided about whether amphotericin B deoxycholate or lipid-containing products should be used (50).

In the 2004 treatment guidelines published by the Infectious Disease Society of America, primary therapy for candidemia in nonneutropenic adult patients is a choice between amphotericin deoxycholate (0.6–1.0 $mg \cdot kg^{-1} \cdot day^{-1}$, or lipid products), or fluconazole (400–800 mg orally or intravenously), or caspofungin (49). Alternative therapy was suggested: amphotericin B (0.7 $mg \cdot kg^{-1} \cdot day^{-1}$) with fluconazole (800 mg/day) for 4–7 days, then oral fluconazole at 800 mg/day. Since the publication of these guidelines, clinical trials with caspofungin and voriconazole suggest that these agents could be used for the treatment of candidemia in selected clinical settings (64, 67). The duration of therapy should be ≥14 days after the last positive cultures and resolution of all signs and symptoms of infection. When possible, intravenous catheters should be removed (69). This excellent evidence-based review should be read in detail for further explanations, evidence-based results, and expert consensus for a variety of *Candida* therapies.

With the availability of agents that are less toxic than amphotericin B, the clinical assessment of the likelihood of infection and the risk-benefit assessment of treatment vs. a definitive diagnosis of infection before treatment may be changing (62). Depending on the level of evidence supporting the presence of a fungal infection, antifungal treatment can be divided into prophylaxis, early presumptive therapy, and systemic therapy (56). When the indication for use of an agent is deemed "prophylactic," it is generally applied to an entire patient population before there is any evidence that the disease or its early manifestations is present. Early presumptive therapy is usually considered in the setting of known colonization before the identification of definitive infection. The use of antifungal agents in this setting can be theoretically distinguished from empirical therapy in that likelihood of infection for empirical therapy should be high and in patients with clear signs of infection who have been extensively evaluated for infection, have multiple risk factors for fungal infections, and usually have failed antibacterial therapy. In reality, these indications overlap substantially.

In patients with a localized fungal infection requiring drainage, there is no replacement for adequate drainage and debridement. Infections requiring debridement or drainage are often located in the abdomen, in the liver, biliary tree, pancreas, or peritoneal cavity. Although percutaneous drainage can play an important role in the management of these difficult problems, a recent retrospective review of percutaneous drainage of fungal collections in the abdomen or thorax suggested that clinical failures occur more often when complex fluid collections are present radiographically, when patients have a history of malignancy, and when patients are critically ill (70).

In addition, invasive skin infections involving burns or deep surgical site infections can also require debridement. Although there is some controversy, patients with central catheter–related infections most often will benefit from catheter removal in that blood cultures clear more quickly (69). Although it is not clear that mortality is reduced by removing a central catheter, mortality has been linked to the time it takes for blood cultures to clear (71). On the other hand, in some patients with limited venous access such as those dependent on total parenteral nutrition for life, successful treatment with the catheter *in situ* has been reported. The decision to retain a catheter should be weighed carefully against the mortality risk in a critically ill patient. Treatment duration should be ≥2 wks after the signs and symptoms of infection have resolved (50).

Should Combinations of Antifungal Agents Be Used?

Some experts are now using combination antifungal therapy for the treatment of complex fungal infections (72). The concepts supporting the use of a combination of agents are to maximize efficacy and minimize toxicity. In selecting agents that may have synergy, an understanding of the mechanisms of action of the agents must be considered. For example, selection of an agent that works on the cytoplasmic membrane (amphotericin B or azoles) plus an agent that works on DNA or protein synthesis (flucytosine) may allow more drug to get into the cell and cause killing. Alternatively, a cell wall–active agent (echinocandin) and a cytoplasmic agent (amphotericin B or azole) may be used in the hopes that more rapid killing would occur (72). Although there is considerable interest in combination therapy, definitive evidence supporting the routine use of combination therapy is lacking. In a randomized clinical trial comparing amphotericin B and flucytosine vs. fluconazole in nonneutropenic patients, the authors suggested that combination therapy was better for patients with peritonitis or for sterilizing tissues (73).

In a large randomized, double-blind, clinical trial involving 219 evaluable patients studying amphotericin B (0.6–0.7 mg/kg) plus fluconazole (800 mg daily for the first 5–7 days, followed by 800 mg of fluconazole daily) vs. fluconazole (800 mg daily) demonstrated a 69% vs. 59% ($p = .043$) efficacy, favoring combination therapy (74). However, the Kaplan-Meier analysis for time to failure did not reveal a significant difference ($p = .08$). In subgroup analysis, clearance of fungemia also favored the combination therapy (6 % vs. 17%, $p = .02$). However, the study overall cannot be used to definitely support the use of combination therapy or high-dose fluconazole therapy for the treatment of candidemia. For the treatment of invasive candidiasis, there are no clinical trials of the

combination of an echinocandin and either amphotericin or azoles.

Combination therapy for cryptococcal meningitis has been established for many years with the combination of amphotericin B and flucytosine in the pre-AIDS era, the gold standard based on a small clinical trial showing an improved outcome with combination therapy (72). Although several additional studies have been performed in the AIDS era, the studies are generally open-labeled, often with a second agent as optional. In the all-oral regimen of fluconazole and flucytosine, there were some microbiological benefits to the combined therapy.

Studies on the use of combined therapy for the treatment of *Aspergillus* currently are retrospective (72). Although they do not definitely show benefit, they also do not show antagonism. Currently, combined therapy for the treatment of fungal infections other than specifically described here should be done in consultation with local experts.

How Should You Treat Candiduria?

As stated previously, urinary candidiasis is an ill-defined group of clinical conditions, and there is no general consensus about how candiduria should be managed (53–55). Patients with parenchymal invasion of the urinary system, invasion, or candiduria as a sign of hematogenous dissemination, all require systemic treatment. Foley catheter change will result in clearance of *Candida* <20% of the time without additional treatment. However, removal of the catheter may result in clearance in as many as 40% of patients (49, 50, 56). In a candiduria-treatment trial, fluconazole (200 mg/day × 14 days vs. placebo) hastened the time to a negative urine culture (75). However, when patients were followed up at 2 wks, the number of patients with negative cultures in each group did not differ. However, only 48% of patients had follow-up (75). It is unclear if these poor results are secondary to follow-up selection bias or represent true drug failures.

Asymptomatic candiduria rarely requires therapy (50, 53). Candiduria should be treated in symptomatic patients, neutropenic patients, patients with renal allografts, and patients with urologic manipulation (50, 53). All urologic devices should be removed when possible. Some benefit to new material may be present when removal cannot be achieved. Treatment with fluconazole for a course of 7–14 days is preferred, but amphotericin B is also acceptable. Flucytosine may be effective but can lead to rapid resistance. Bladder irrigation may achieve clearance of funguria but is rarely indicated—certainly never when there is a concern about disseminated disease (49, 50, 54).

When Should Early Presumptive Therapy and Empirical Treatment Be Considered?

In a patient who has a febrile illness that is consistent with infection, prophylactic therapy must be distinguished from empirical or preemptive therapy (49, 56). In a high-risk critically ill surgical patient with a long length of stay, multiple sites of fungal colonization, and a suspected infectious disease unresponsive to broad-spectrum antibiotics, the time for prophylaxis is long past (56). This patient is a candidate for empirical or preemptive therapy with the antifungals, as discussed in the invasive disease section above. This patient may have been a candidate for prophylaxis at an earlier time point in the illness. How does one make a decision for presumptive fungal therapy when there is little or no evidence that is randomized and controlled? Criteria that may be reasonable to consider in this assessment include: 1) a clinical impression that a fungal infection is present but not proven, 2) the fact that fungal cultures, including blood, may be negative even though a fungal infection is present, and 3) the morbidity and mortality associated with fungal infection. As suggested above, some additional consideration that might favor presumptive therapy include: 1) multiple risk factors for candidemia, 2) persistent fever despite broad-spectrum antibiotics, 3) colonization of *Candida* at multiple body sites, and 4) sudden development of high-grade candiduria.

Piarroux et al. (57) conducted a before (historical, 2 yrs) and after (prospective, 2 yrs) study of risk-adjusted administration of fluconazole prophylaxis based on the corrected colonization index of ≥0.4. Most importantly, surgical ICU–acquired *Candida* infections decreased from 2.2% to 0%, and overall *Candida* infection decreased from 7.2% to 3.8% ($p = .03$). Interestingly, the authors suggest that the colonization index should not be used for this risk stratification, only the corrected index.

Which Surgical Patients, If Any, Should Receive Antifungal Prophylaxis?

As is true of any therapy, the risks, benefits, costs, and efficacy of any therapy must be considered before this therapy should be recommended (13, 56). One of the most important considerations is whether fungal infections are seen in a particular patient population (i.e., what is the overall prevalence of fungal infections in a particular patient population and can patients who have a high prevalence be identified?). Eight major studies are applicable to the critically ill surgical patient population (12, 34, 38, 57, 76–78). In a study examining four treatment arms, Savino et al. (77) did not find any benefit to antifungal prophylaxis. However, the study had a fungal infection rate of only 3% (including multiply colonized patients). Thus, this study was underpowered to find a difference, even if one were to exist. In an encouraging, small clinical trial involving surgical patients, Slotman et al. (12) showed a decrease in fungal infections among patients receiving prophylactic ketoconazole.

In a trial of 43 high-risk, highly selected, recurrent gastrointestinal surgery patients, patients were randomized to fluconazole (400 mg intravenously) vs. placebo for the prevention of disseminated fungal infection (78). Fungal infection was found in 35% of patients in the placebo group vs. 4% in the fluconazole group, a finding even more significant in a Kaplan-Meier analysis ($p = .002$) (78). This is a well-conducted, convincing study demonstrating that highly selected patients can benefit from antifungal therapy immediately postoperatively. Based on this study, one should consider similar high-risk gastrointestinal surgery patients for antifungal prophylaxis.

In trauma/surgical ICU patients with an anticipated length of stay of ≥2 days, Ables et al. (79) conducted a study of prophylaxis with fluconazole (400 mg/day) vs. placebo. Fungal infection was broadly defined and included a syndrome of systemic inflammatory response without another infectious explanation. Although a trend toward increased failures was present in the placebo arm (19% vs. 13%), the case definitions and small sample size of this study makes the results difficult to generally apply.

Although a few small studies have been done on liver transplant patients and are not included here, Winston et al. (38) enrolled a large number of liver transplant recipients into a placebo vs. fluconazole

treatment arm for 10 wks (intravenous to oral). Although the definitions of fungal infection were broad, the authors demonstrated a significant decrease in all end points, fungal colonization, and fungal infections, both superficial and deep in the fluconazole-treated arm (38). As is true in all published antifungal prophylaxis studies in surgical patients, no significant difference in mortality was seen. However, this study was not powered for this end point. Notably, neurologic toxicity was higher in the fluconazole-treated group, presumably due to higher cyclosporine levels, which must be adjusted in patients with fluconazole treatment (38).

In a large, well-done study that enrolled 220 patients in the medical/surgical ICU on or after their third day in the ICU, 100 mg of intravenous fluconazole vs. placebo was given to patients who were observed for the development of a fungal infection (80). These patients were critically ill, mechanically ventilated, and also undergoing selective decontamination of the gastrointestinal tract. Candidemia was virtually eliminated, with nine patients in the placebo group and a single patient in the fluconazole group acquiring candidemia during the clinical trial. Invasive candidal infection was decreased from 8.9% to 3.9% ($p = .03$), and a decrease in the frequency and intensity of fungal colonization was noted (80).

One of the largest studies conducted in surgical patients is the single-institution, randomized, double-blind, placebo-controlled trial of enteral fluconazole (800 mg load followed by 400 mg/day) vs. placebo for the prevention of fungal infections in high-risk critically ill surgical patients (34). The 260 patients were all expected to stay in the ICU for ≥3 days and accounted for only one third of all of the ICU patients. Using a strict case definition that did not include fungal colonization, the intent-to-treat analysis demonstrated 20 patients with fungal infections (15.3%) in the placebo group and 11 infections (8.5%) in the fluconazole group. However, four patients were included in the intent-to-treat analysis who, at study enrollment, were later found to have infections. These four patients were all randomized to the fluconazole group. Thus, the use of enteral fluconazole in this very select and high-risk patient population had a two- to threefold reduction in fungal infection (34, 80). The number needed to treat with prophylaxis to prevent a single fungal infection was 14.5, a low number suggesting a very significant effect (34). It should be noted that this study is a single-institution study with a high basal rate of fungal infection and with fungal infection definitions that are not universally accepted. This study (34) and the studies by Garbino et al. (80), Pelz et al. (81), and Piarroux et al. (57) all have similar findings. In highly selected surgical critically ill patients, antifungal preemptive or prophylactic therapy will reduce fungal infections. However, there were no effects noted on mortality.

So which patients should receive antifungal prophylaxis? It is reasonable to consider antifungal prophylaxis in patients similar to those studied in the above clinical trials. However, due to the cost of these agents and the increasing reports of resistance, the use of fluconazole as a prophylactic agent should *not* be extended to additional patient populations, especially those less ill and surely those at less risk (13). Critical elements in the decision making should be whether the patient population being considered for prophylaxis is significant enough to incur the cost and risk of eventual (and expedited) resistance that will develop with excessive use.

What Are the Outcomes and Costs of a Fungal Infection?

Patients who are critically ill and develop a fungal infection have a high basal mortality from their underlying critical illness (25, 26, 82–86). In studies, the crude mortality associated with nosocomial fungal infection has been reported to be between 30% and 75%, without significant changes in mortality during the last decade (25, 26, 82–86). In addition, when a bloodstream or pancreatic infection is present, the mortality rate among patients when fungal pathogens are present is higher than the rate among patients with bloodstream infections due to other pathogens (5, 85, 86). In a classic study by Wey et al. (6), patients with a fungal infection had an attributable mortality estimated at 38%; that is the mortality above the basal mortality. Mortality has not been a primary end point in clinical trials of antifungal treatment or prophylaxis principally because these critically ill patients are a diffuse group of patients with many additional reasons to explain a fatal outcome. Some experts have suggested that preventing or treating fungal infections is of a lesser importance because mortality benefit cannot be demonstrated directly.

Are There Any Favorable Data on Outcome and Fungal Infections?

As noted previously, removal of an intravascular catheter early on may have a survival benefit (70). In an older study of critically ill surgical patients with fungal peritonitis or endophthalmitis, the mortality rate among patients treated before the first positive blood culture was 42% (28). This lower mortality was compared with a mortality of 83% when treatment was deferred until after the first positive blood culture (28). These data suggest but do not prove that early intervention may be life saving. In our ICU, targeted prophylaxis has resulted in a dramatic decrease in the prevalence of fungal infections (82).

In addition to the known high mortality associated with fungal infections, the economic burden of fungal infections is substantial (83, 84, 87, 88). Goff et al. (87) demonstrated an increased cost of $41,000 (1993 U.S. dollars) when comparing high- and low-risk ICU patients. In a recent large European study of *Candida* colonization and infection, patients with evidence of colonization had both a prolonged ICU stay of 6.2 days (odds ratio, 1.69; 95% confidence interval, 1.53–1.87; $p < .001$) and a hospital stay of 8.6 days (odds ratio, 1.27; 95% confidence interval, 1.16–1.40; $p < .001$). Similarly, patients with *Candida* infection had an increased ICU stay of 12.7 days (odds ratio, 2.13; 95% confidence interval, 1.72–2.64; $p < .001$) and hospital stay of 15.5 days (odds ratio, 1.23; 95% confidence interval, 0.99–1.52; $p = .060$). In the terms of added costs (in Euros) *Candida* colonization resulted in an additional 8,000 EUR in direct costs and *Candida* infection almost 16,000 EUR (88). At the Johns Hopkins Hospital, we previously have reported that the attributable increase in the cost of ICU care for patients with fungal infections is $21,590 (83). Based on this pilot study, a preventive strategy that incurred a total cost per patient while in the ICU of less than $230 U.S./day would be cost-effective (83).

Summary

In certain high-risk critically ill surgical patient populations, such as patients with gastrointestinal surgery, central venous catheters, multiple antibiotics, and multiple sites of fungal colonization, a high index of suspicion should be developed for the assessment of the need for early pre-

sumptive therapy. Given the apparent benefit of early therapy, prompt and accurate diagnosis is critical. Because current techniques for the diagnosis of fungal infections are imperfect, diagnosis of these infections often is made on clinical grounds, based on assessment of these risk factors, and the status of fungal colonization. Early reports of 1,3 beta-glucan measurement are encouraging for the diagnosis of invasive fungal infection. The development of consensus definitions of what constitutes a fungal infection should have a high priority and is mandatory for the conduct of future investigation of the effect of fungal prophylaxis or treatment. The need for randomized controlled trials in this area is mandatory to balance the "costs" of early presumptive antifungal therapy vs. the benefits. Included in the analysis of clinical trials should be an assessment of the costs of therapy and of infection but also some measurement of the possibility of increased resistance to that therapy. On the other hand, the current burdens of a fungal infection include the attendant high attributable mortality and increased cost of a fungal infection, and in selected high-risk patient populations, targeted prophylaxis has been effective.

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