Fungal Infections in the Intensive Care Unit

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Learning Objectives

1. Classify a critically ill patient's risk of invasive fungal infection.
2. Construct a reasonable prophylactic, preemptive, or empiric antifungal therapy regimen for a patient in the intensive care unit (ICU).
3. Develop an algorithm for routine surveillance of invasive fungal infections in the ICU.
4. Distinguish between each of the newer antifungal agents and their relative advantages and disadvantages in the ICU setting.
5. Justify antifungal treatment algorithms designed for the ICU based on current evidence regarding appropriateness.

Introduction

Invasive fungal infection is a well-documented complication of many conditions and procedures that result in immunosuppression, including transplantation, human immunodeficiency virus (HIV) infection, and treatment of malignancy. During the past several decades, opportunistic fungi have emerged as serious nosocomial threats, particularly among patients in the intensive care unit (ICU). According to national surveillance efforts coordinated through the Centers for Disease Control and Prevention and institutional reports, there has been a greater than 10-fold rise in invasive candidiasis among critically ill patients since the 1980s. About one-half of all candidemias occur in the ICU setting, making the management of this disease important for pharmacists caring for the critically ill. In patients with candidemia requiring ICU care, death rates are almost double those of patients on general hospital wards. Attributable mortality for candidemia is 20% to 40% depending on the patient population studied.

Mold infections are also increasingly common, particularly among transplant recipients and patients with hematologic malignancy. It is estimated that more than 10,000 hospitalizations per year are attributable to aspergillosis, totaling 0.03% of hospital discharges overall. This is a 20% increase compared with the previous 2 decades. If left untreated, the mortality associated with invasive aspergillosis is 100%. Unfortunately, despite recent advances in antifungal therapies such as the availability of extended-spectrum triazoles and the echinocandin class, response rates remain suboptimal.

Invasive fungal disease, independently of the causative pathogen, imposes a substantial financial burden, partly because of longer requirements for ICU care, expensive antifungal pharmacotherapy, and greater overall use of hospital resources. Estimates of the annual costs for inpatient management of candidemia range from $44 million to $320 million in the United States; a single hospitalization for aspergillosis generally costs more than $60,000.

Numerous advances during the past decade have changed the way invasive fungal disease is managed, and many have application in the ICU. The availability of new drugs and new drug classes has brought new therapies to the ICU.

Baseline Knowledge Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on fungal infections in the ICU include:

- Lewis RE, Rodgers PD. Invasive fungal infections. In: Chisholm-Burns MA, Wells BG, Schwinghammer TL, Malone PM, Kolesar JM, Rotschafer JC, et al, eds. Pharmacotherapy Principles and Practice. New York: McGraw-Hill, 2008:1211–30.
- Dodds Ashley ES, Lewis R, Lewis JS, Martin C, Andes D. Pharmacology of systemic antifungal agents. Clin Infect Dis 2006;43:S28–S39.

These drugs have improved outcomes and may have a role in preventing disease. Advances in fungal diagnostics and antifungal susceptibility testing have improved the identification of patients who require antifungal therapies and aid in drug selection. The ICU pharmacist is invaluable for providing safe and effective antifungal therapy to these patient populations.

EPIDEMIOLOGY OF INVASIVE FUNGAL INFECTIONS IN THE ICU

Candida spp.

Candidiasis encompasses a host of diseases caused by *Candida* spp. These pathogens infect most body systems, producing mild mucocutaneous disease and funguria to serious deep-seated infections such as meningitis, endocarditis, and intra-abdominal infections. *Candida* spp. represent the fourth most common cause of bloodstream infection acquired in the hospital, and the attack rate appears even higher among patients in the ICU, where up to 10% of nosocomial disease is attributed to these pathogens. It has been reported that invasive candidiasis rates in the ICU are more than 10-fold those on medical or surgical wards.

As the incidence of candidal infections among critically ill patients has grown, the specific pathogens causing disease have changed. *Candida albicans* is the most common species isolated, accounting for 40% to 60% of invasive candidiasis. However, there has been a distinct rise in the incidence of non-*albicans* candidal infections, particularly after second-generation azoles such as fluconazole became available in the late 1980s. Fluconazole exposure is a risk factor for subsequent infections with strains that are resistant to fluconazole, either inherently or through acquired resistance mechanisms.

Among non-*albicans* spp., *Candida glabrata* and *Candida tropicalis* are the most commonly isolated, each causing around 20% to 30% of disease cases. Although *C. tropicalis* is widely susceptible to the available antifungal agents, *C. glabrata* has decreased susceptibility to azole antifungals, particularly fluconazole. In addition, among patients in the

ICU, infection with *C. glabrata* is associated with higher mortality than other species of *Candida.*

Candida parapsilosis is becoming more common in nosocomial candidiasis. This organism is associated with the use of plastic devices; therefore, it is often observed in patients with infections secondary to intravenous catheters, particularly those receiving total parenteral nutrition. Fortunately, it appears to be less virulent than other fungal pathogens. Although reported to account for 10% to 20% of all candidal infections, at some centers, the incidence of *C. parapsilosis* is higher than that of *C. albicans.*

When combined, *Candida krusei* and *Candida lusitaniae* infections account for less than 15% of all candidal disease. However, the intrinsic resistance of *C. krusei* to fluconazole and of *C. lusitaniae* to amphotericin B makes it important to correctly identify and understand these pathogens, particularly in the ICU setting.

Knowledge of the local epidemiology of *Candida* spp. is paramount for appropriate empiric and preemptive therapy. This is true not only for the institution but also at the unit level because different ICUs within a medical center may experience considerable variation in the causes of invasive candidiasis. When specific data are unavailable to help predict the species, it is helpful to have a clinical prediction rule for infections caused by non-*albicans* pathogens. Although many factors have been investigated to predict the likely candidal species, including lack of prior antibiotic therapy, previous fluconazole treatment, history of solid tumors, and male sex, no risk stratification tool has proven adequate in prospective evaluations. Therefore, clinicians will continue to rely on the microbiology laboratory for speciation of these pathogens.

Mold Pathogens

Invasive mold infections, predominantly invasive aspergillosis, have become more common, primarily affecting transplant recipients and patients with hematologic malignancies and associated severe neutropenia. Although uncommon, invasive aspergillosis can also occur in ICU patients who are not immunosuppressed, such as patients with chronic lung disease and severe liver failure. Unfortunately, much of the available information on the epidemiology of invasive mold infections in the ICU population is from data obtained at autopsy.

Other mold pathogens that have been identified in this setting include *Fusarium* spp., *Scedosporium* spp., and the *Zygomycetes*, each of which poses therapeutic challenges and is associated with poor outcomes. Mold infections have been attributed to nosocomial outbreaks associated with the aerosolization of spores in the setting of construction, contaminated medical products including equipment, and even hand lotion. The most common manifestation of invasive aspergillosis and other mold pathogens is lung and/or sinus disease; however, infection of the skin and central nervous system can also occur. These pathogens rarely cause bloodstream infection.

Advances in Diagnosis of Fungal Infections

Limitations of Traditional Culture and Radiologic Methods

One of the most challenging aspects of treating invasive fungal infections involves appropriate diagnosis. Traditional methods of diagnosing fungal infection include clinical evaluation, culture, radiographic evidence, and histopathology. However, each method is problematic because of difficulties detecting the pathogens and underlying host factors in patients most at risk of fungal disease (Table 1-1).

Fortunately, culture is a reliable method of detecting fungemia, the most common invasive fungal infection in ICU patients; however, identification delays can prolong the time to appropriate antifungal treatment. Many patients are unable to tolerate the procedures required to obtain specimens from deep-seated sites of infection that would be required for culture or histopathologic diagnosis. Radiographic findings of fungal infections are related to changes caused by the host's immune response to the pathogen; thus, these conventional diagnostic methods may miss disease in immunocompromised patients.

New and Emerging Fungal Diagnostic Methods

Within the past 5 years, many advances have been made in fungal diagnostics. Most prominent among these is the development and release of two new diagnostic tests: the galactomannan assay and the beta-glucan assay. The galactomannan assay was a much-anticipated test for its ability to identify *Aspergillus* with a simple blood sample. It is approved for prospective screening for invasive aspergillosis in hematopoietic stem cell transplantation (HSCT) recipients.

Although practitioners may be tempted to use this test as a one-time diagnostic tool, data supporting its diagnostic use were obtained by serial sampling of at-risk patients. A common strategy is to routinely screen high-risk patients with the test as often as two times/week. A change in the optical density value in various body fluids, including serum, to an index value greater than 0.5 indicates disease up to 1 week before clinical symptoms of invasive aspergillosis develop. Sensitivity and specificity can be as high as 80% and 89%, respectively, in patients with malignancy; although these values appear to be much lower for ICU patients and transplant recipients.

There has been some success in expanding the use of this assay to other types of clinical specimens. Data are now available to support testing samples from the lung obtained by bronchoalveolar lavage, urine, and cerebrospinal fluid. Unfortunately, the galactomannan assay is associated with false-positive results when patients are receiving concomitant β-lactam antibiotics, most notably piperacillin/tazobactam. Using a higher cutoff value may address this issue. Prior antifungal use can cause false-negative results, making use of the assay difficult in patients who are receiving antifungal prophylaxis.

Table 1-1. Overview of Fungal Diagnostic Techniques

Method	Pathogen(s) Detected	Comments
Traditional Methods		
Culture	All	Replication time is longer for fungi than for bacteria; may take a long time to complete; may be negative for certain fungal pathogens in blood; unable to differentiate colonization from true infection; may require invasive specimen
Histopathology	All	Cannot confirm identification because many pathogens are morphologically similar; requires invasive specimen
Radiology	All	Cannot identify specific pathogen and may be difficult to distinguish from bacterial or other causes; lack of immune response in immunosuppressed patients results in false-negative results; delay in symptoms related to infection
Rapid Diagnostic Tools		
Galactomannan	*Aspergillus* only	False positive with β-lactam antibiotics; low sensitivity in solid-organ transplant recipients; controversy regarding positive test cutoff[a]
Beta-glucan	*Candida* spp. and *Aspergillus* only	False positive with dialysis filters, gauze, sponges, albumin, immune globulin; controversy regarding positive test cutoff[b]
Fungal PCR	All; test is specific to organism	Not commercially available
PNA FISH	*Candida albicans* and *Candida glabrata*	

[a]Controversy exists whether the cutoff for a positive test should be greater than 0.5 or 1.
[b]Controversy exists whether the cutoff for a positive test should be 60 pg/mL or 80 pg/mL.
PCR = polymerase chain reaction; PNA FISH = peptide nucleic acid fluorescence in situ hybridization.

The beta-glucan test is a nonspecific diagnostic test that detects the presence of many types of fungi by targeting a component of the fungal cell wall. The test can detect both *Candida* and *Aspergillus* but not *Cryptococcus* or *Zygomycetes*. Obvious limitations include the inability to identify the causative pathogen, but when used as part of a prospective monitoring program, the test may allow earlier initiation of antifungal therapy in patients who have not yet shown clinical symptoms. The test is very sensitive for detecting fungal pathogens, but because of other environmental sources of beta-glucan, specificity is greatly improved if more than one sample is tested. Specifically, in the ICU population, use of the beta-glucan test as a once- or twice-weekly serial monitoring tool may help identify patients who should receive further diagnostic work-up. Although false positives are common when only a single test is performed, persistent elevations over time can accurately identify patients with true invasive fungal infections.

A new rapid testing method is also available for identifying *Candida* isolates in patients with positive cultures for yeast. Peptide nucleic acid fluorescence in situ hybridization (PNA FISH) can differentiate between *C. albicans* and *C. glabrata* more rapidly than traditional testing methods (e.g., germ tube test). A positive culture is still required, however. There are costs to implement this testing, and because the benefit is derived from earlier pathogen identification, rapid turnaround is a key component of success but creates staffing demands within the laboratory. Because this test allows a determination of *Candida* spp. almost immediately after a culture becomes positive, it also allows earlier initiation of appropriate therapy. Many hospital pharmacy departments are interested in implementing such testing procedures to limit the use of more expensive, broader-spectrum antifungal drugs. Pharmacoeconomic analyses support pharmacy-based cost savings after implementing PNA FISH as part of a program to direct early antifungal treatment. Polymerase chain reaction techniques for fungi are also promising diagnostic prospects but require further development for clinical applications.

Antifungal Susceptibility Testing

Standards for susceptibility testing of antifungal agents against yeasts were introduced more than a decade ago and have recently been updated to include recommendations for the new azole antifungal agent voriconazole and the echinocandins caspofungin, micafungin, and anidulafungin. Interpretive criteria for posaconazole susceptibility are not yet available but are anticipated. Methods are available for both broth dilution and disk diffusion. Recently, commercially available systems, including Etest (AB BIODISK, Solna, Sweden), for antifungal susceptibility testing have been released.

The ability to determine antifungal drug susceptibility is invaluable in guiding antifungal drug selection and in deescalating in the same manner as applied to antibacterial therapy. Unlike testing for bacterial pathogens in which

breakpoints are defined as susceptible (S), intermediate (I), and resistant (R), antifungal susceptibility for the azole antifungal agents is defined as susceptible, susceptible-dose-dependent (S-DD), or resistant (Table 1-2).

At present, only a susceptible range for the echinocandins has been defined. This range has been set at 2 mcg/mL or less for all three agents in the class. Because no documented cases of clinical resistance exist, and because greater than 99% of candidal isolates have minimum inhibitory concentrations (MICs) less than 2 mcg/mL, no resistance breakpoints have been set, including for isolates of *C. parapsilosis*. Based on these data, isolates with an MIC greater than 2 mcg/mL can be considered clinically resistant; thus, this value has been proposed as a breakpoint for resistance.

In early clinical trials evaluating caspofungin for the treatment of invasive candidiasis, *C. parapsilosis* had higher MICs to caspofungin than other species of *Candida*. Since then, interest has focused on outcomes of patients with *C. parapsilosis* in clinical trials using the echinocandins for candidemia (Table 1-3). These higher MICs were not associated with increased clinical failures; therefore, breakpoints were established that classify most *C. parapsilosis* isolates as susceptible.

Perhaps one of the more difficult aspects of applying antifungal susceptibility testing to clinical care has been translating susceptible-dose-dependent activity into an appropriate treatment regimen. According to comments by members of the expert panel proposing the breakpoints, infections caused by fluconazole-susceptible, dose-dependent pathogens would be expected to require daily fluconazole doses of about 400 mg; however, these data were based on the treatment of patients with esophageal candidiasis, not on more invasive disease.

Recently, the pharmacodynamic target for fluconazole in treating candidemia has been identified as an area-under-the-curve/MIC ratio of 11.5. Taking the higher end of the susceptible-dose-dependent range (32 mcg/mL), a daily

Table 1-2. Antifungal Susceptibility Breakpoints for *Candida* spp.

Antifungal Agent	S (mcg/mL)	S-DD (mcg/mL)	R (mcg/mL)
Fluconazole	≤ 8	16–32	≥ 64
Itraconazole	≤ 0.12	0.25–0.5	≥ 1
Posaconazole	N/A	N/A	N/A
Voriconazole	≤ 1	2	≥ 4
Flucytosine	≤ 4	8–16	≥ 32
Amphotericin B	≤ 1	N/A	> 1
Anidulafungin	≤ 2	N/A	N/A
Caspofungin	≤ 2	N/A	N/A
Micafungin	≤ 2	N/A	N/A

N/A = not applicable; R = resistant; S = susceptible; S-DD = susceptible-dose-dependent.

Table 1-3. Clinical Efficacy of Echinocandins for Candidemia in Clinical Trials[a]

Agent	Success for All *Candida* spp. (%)	Success for *Candida parapsilosis* (%)
Caspofungin	73.4	70
Micafungin	89.6	89.2
Anidulafungin	75.6	64

[a]Data are from different clinical trials; therefore, results are not directly comparable.
Information from Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002;347:2020–9; Kuse E-R, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 2007;369:1519–27; and Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356:2472–82.

fluconazole dose of 400–800 mg would achieve this target in most adults with normal kidney function. Therefore, although many clinicians have avoided the use of azole agents in patients with isolates in the susceptible-dose-dependent range, emerging data suggest this practice is unnecessary.

At-Risk Patient Populations

Although invasive fungal infections are an increasingly common problem in the ICU setting, their incidence is still relatively low, with fewer than 1% of all patients admitted to an ICU ultimately developing fungal disease. Ideally, clinicians would be able to target patients at highest risk of these infections to focus prevention efforts. Several groups have attempted to identify patients with risk factors for invasive fungal infection. Possible risk factors that may be found in the ICU are listed in Table 1-4.

In many studies, certain risk factors clearly increase the chance of developing invasive candidiasis; these include known candidal colonization (e.g., sputum, stool), presence of a central venous catheter, and prolonged receipt of broad-spectrum antibacterial agents. In addition, patients with malignancy and solid-organ transplant recipients have their own set of risk factors beyond those associated with general ICU admission, which should be considered when determining an individual's risk of invasive fungal infections.

Although many risk factors have been identified, using these as a clinical prediction score has proved challenging. Many of the criteria are broad and encompass most of the ICU patient population. Prospective evaluations documenting the sensitivity and specificity of these scores, or the positive outcomes associated with their use, are lacking. Clinicians eagerly await the results of clinical trials targeting antifungal prophylaxis in high-risk ICU patients (e.g.,

NCT00520234), as well as trials trying to combine risk criteria with preemptive therapy approaches using newer diagnostic tools (e.g., NCT00672841).

Pediatric patients are also at risk of developing invasive fungal disease while in the ICU. For children with malignancy, many of the risks of developing disease are the same as in adults. In the neonatal ICU, candidemia and invasive candidiasis are the most commonly encountered invasive fungal infections. Neonatal disease is different from that seen in older children and adults because of its much more subtle presentation. Risk in this population is most closely linked to premature birth and day of life, with earlier gestational age at delivery and younger patients being more likely to develop disease.

Management of candidal infection is also different among these very young patients and is dictated in large part by the unique pharmacokinetic properties of many of the antifungal agents. The Infectious Diseases Society of America (IDSA) treatment recommendations reflect the differences in treating infants, with amphotericin B being the primary treatment recommended in the neonatal population, although data are emerging with the new echinocandins and extended-spectrum azole agents for this indication. Many of the available antifungal agents, such as fluconazole, voriconazole, and the echinocandins, require higher weight-based dosing than used in adults and older children, further differentiating neonatal candidiasis from other forms of the disease.

Prophylactic, Preemptive, and Empiric Strategies

Given the negative outcomes associated with the development of invasive fungal infections and the difficulty in obtaining a definitive diagnosis in many patients, early intervention either to prevent infection or to preempt severe fungal infection is desirable. Because they are the most common fungal pathogens in the ICU, most strategies focus on *Candida* spp.

Prophylactic therapy provides antifungal agents to a broad population of patients to prevent disease. This strategy has been employed in select ICU settings with positive outcomes and is endorsed by the IDSA for at-risk patients in ICUs with a high incidence of invasive candidiasis. Tools based on risk criteria are often applied to avoid unnecessary drug exposure in individuals unlikely to develop disease.

To date, three studies have evaluated the effectiveness of fluconazole as prophylaxis in various ICU patients. The most compelling data came from a surgical population with gastric perforation where *Candida* peritonitis was reduced by 50%. Other studies that showed differences targeted critically ill populations where the actual or anticipated length of ICU stay was more than 48–72 hours. Although these studies showed a decrease in the incidence of candidal infection, the effect on mortality was less clear. These

Table 1-4. Risk Factors for Invasive Fungal Infections in the ICU

Adult Patients	Solid Organ Transplant Recipients	Patients with Malignancy
Candida colonization	**All transplant recipients**	**All patients with malignancy**
Diabetes mellitus	Immunosuppressant medications	Neutropenia: duration and severity
Kidney failure	Corticosteroids	Mucosal damage
Hemodialysis	Receipt of more than one organ	Concomitant viral infection
Severe acute pancreatitis	Acute or chronic rejection	Recent chemotherapy
High APACHE II score	Advanced donor age	**HSCT recipients**
Prolonged mechanical ventilation	CMV infection	Graft vs. host disease
Central venous or urinary catheter	**Liver transplant recipients**	Prior invasive fungal infection
Prolonged stay in ICU	Intraoperative blood requirement > 40 units	Delayed engraftment
Broad-spectrum antibacterials	Choledochojejunostomy	Underlying malignancy
Parenteral nutrition	Retransplantation	Induction with cytarabine
Major surgery	Reexploration	
Burns	Length of transplant operation	
	Fulminant hepatic failure	
	Lung transplant recipients	
	Delayed chest closure	
	Bronchiolitis obliterans	
	Heart transplant recipients	
	Delayed chest closure	

APACHE II = Acute Physiological and Chronic Health Evaluation II Scale; CMV = cytomegalovirus; HSCT = hematopoietic stem cell transplantation; ICU = intensive care unit.

studies have supported, however, that prophylactic regimens, particularly with azole agents, do not result in drug safety concerns.

The development of azole-resistant *Candida* spp. or the emergence of disease with pathogens inherently resistant to fluconazole is a concern with prolonged azole prophylaxis. This problem was first documented in patients with HIV receiving prolonged fluconazole therapy for the prevention of thrush, and it has since been replicated in patients with cancer and in transplant recipients. To date, results have been mixed regarding the impact of azole exposure and emerging azole resistance in the ICU setting; some have documented breakthrough fungal infections in these patients, whereas other institutions have not detected a statistically significant rise in infections attributable to non-*albicans* species after implementing a prophylaxis protocol.

Given concerns regarding the widespread azole use required with prophylaxis, many clinicians instead rely on empiric therapy for patients in the ICU setting. This practice involves waiting for the patient to exhibit signs and symptoms of infection. In cases where fungal disease is a concern, antifungal agents are added to the empiric antibacterial regimen. The recent update of the aspergillosis and candidiasis guidelines by the IDSA, as well as guidelines for the treatment of fever in the setting of neutropenia by the National Comprehensive Cancer Network, include empiric treatment for invasive fungal infection. These recommendations are discussed in greater detail in the following section. However, given the available data that demonstrate increased mortality with each hour that a candidal bloodstream infection goes untreated, this approach may result in therapy being provided too late in the course of disease.

Preemptive antifungal therapy may be a more promising approach; it limits the number of patients exposed to antifungal treatment yet still allows intervention early in the course of disease. The key to preemptive therapy is the availability of a diagnostic marker that helps direct clinicians to the need for antifungal therapy in addition to signs and symptoms, which may be delayed in critically ill patients. By using routine surveillance with one of these diagnostic tools (e.g., radiographic evidence, fungal serologic testing), targeted antifungal therapy can be started in a patient with the earliest symptoms of disease.

Given that many patients at high risk of infection have minimal symptoms, it may also be reasonable to consider treating on the basis of the persistent presence of serologic evidence of disease even before symptoms develop. The advent of the new antifungal diagnostic technologies discussed previously may aid in implementing this strategy. In particular, beta-glucan testing is attractive for the prospective monitoring of high-risk patients. In at least one study, patients who subsequently developed candidemia

were more likely to have detectable concentrations of beta-glucan before positive cultures. Clinical trials are continuing in various ICU populations to investigate preemptive therapy strategies combining beta-glucan testing with the echinocandins (e.g., NCT00672841).

TREATMENT STRATEGIES FOR PATIENTS WITH INVASIVE FUNGAL DISEASE

Candida Infections
Candidemia

Treatment guidelines for patients with invasive candidiasis were updated by the IDSA in 2009. For moderately to severely ill patients with *Candida* spp. in the bloodstream, initial treatment with an echinocandin is recommended, and should also be used for any patient already receiving azole prophylaxis.

The echinocandins have all been proven effective for treating candidemia and invasive candidiasis. This drug class is not subject to the issues regarding resistance associated with the azole agents; therefore, these agents make excellent clinical options for the initial management of yeast in the blood. As previously discussed, early concerns regarding higher MICs with *C. parapsilosis* have not translated to clinical differences in success rates (see Table 1-3). The three agents in the echinocandin class are essentially interchangeable. The updated IDSA guidelines for treating invasive candidiasis do not differentiate between members of this class with the exception of empiric therapy for patients with neutropenia, for which caspofungin is the only agent with sufficient data in this setting and is thus endorsed as the preferred treatment.

Fluconazole could be considered for initial treatment in institutions with a low incidence of non-*albicans* or resistant *Candida* spp. in the ICU. The extended-spectrum azole antifungal agent voriconazole is an alternative to fluconazole based on documented efficacy in patients with candidemia. The designation as an alternative agent, as opposed to first-line therapy, is partly because of the drug's adverse effect profile, drug-drug interactions, and cost. An important clinical consideration is whether voriconazole should be considered empiric therapy for patients with a recent fluconazole exposure or documented fluconazole resistance. Not all fluconazole-resistant isolates of *Candida* are resistant to voriconazole, and experience from HSCT recipients suggests that voriconazole retains activity against fluconazole-resistant isolates between 50% and 60% of the time. Without the results of susceptibility testing, however, echinocandin therapy should be used for patients when azole resistance is a concern.

The decision regarding the selection of an appropriate empiric regimen for an individual patient depends largely on the local patterns of infection and severity of illness. Delays in antifungal therapy are directly associated with mortality. To avoid these delays and guide appropriate initial therapy,

many institutions approach the management of fungal bloodstream infection in the ICU with an algorithm. One example of such an algorithm is represented in Figure 1-1.

Equally as important as initial drug selection are alterations in therapy based on available culture and other diagnostic data. Often, these infections can be managed with a narrower-spectrum agent, and in some cases, even oral azole therapy can be used to complete the treatment course. In some instances, converting to the azole is not only possible but actually the preferred course of treatment. One example is the presence of ocular involvement, where echinocandin penetration is suboptimal and the azole agents become the treatment of choice. This situation is encountered more often given the recommendation in the current IDSA guidelines that all patients with candidemia receive a dilated funduscopic exam within the first week of diagnosis.

Some of the most important aspects of medically managing the patient with candidemia involve determining and addressing the source of infection, which is often an intravenous catheter. Data are insufficient to suggest removing all catheters in fungemic patients, but catheter removal should be considered, especially in ICU patients. Patients should begin to clinically respond to therapy within 48–72 hours. For patients with persistent symptoms beyond 72 hours, metastatic sites of infection should be considered, as well as other causes of treatment failure (e.g., drug resistance, suboptimal drug exposure). Therapy should be continued for 2 weeks after a documented negative blood culture as long as there are no metastatic complications.

Urinary Tract Infections

Isolation of *Candida* from the urinary tract, common in ICU patients, often creates clinical controversy regarding management. The initial decision is whether treatment is needed. Most patients who are asymptomatic and have no risk factors for complications require no therapy beyond removing the urinary catheter, if possible. Patients without urinary tract symptoms, including those in the ICU with sepsis of unknown origin, those with neutropenia, or those soon to be undergoing a urologic procedure, should receive pharmacologic treatment because they are at risk of systemic disease.

The treatment of choice for candiduria is limited by the pharmacokinetic properties of the available antifungal agents. With the exception of fluconazole and flucytosine, none of the available systemic antifungal agents achieve effective concentrations within the urine for treating infections of the lower urinary tract. Amphotericin B bladder irrigations are difficult to administer, and the role of these bladder irrigations remains controversial because there is insufficient evidence to support their use. Therefore, fluconazole for 2 weeks remains the drug of choice for patients requiring therapy.

Lung Infections

Candida is commonly isolated from the sputum of ICU patients. The role of this organism in causing lung disease
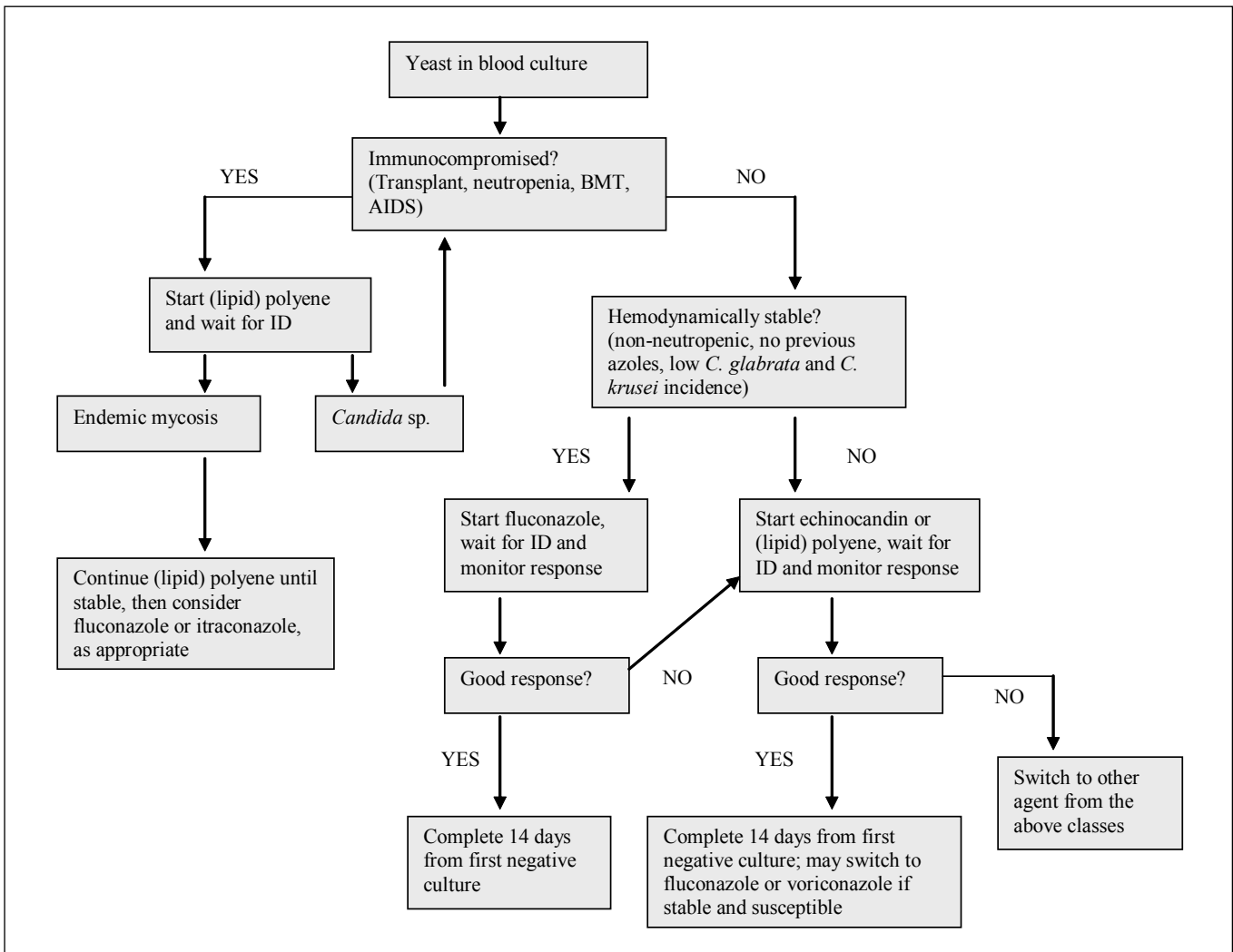
Figure 1-1. Suggested approach for the treatment of invasive candidiasis in the critical care setting. May need to treat longer if signs of dissemination such as endophthalmitis or liver, spleen, or skin involvement are found.

AIDS = acquired immunodeficiency syndrome; ID = identification; HSCT = hematopoietic stem cell transplantation.

among the critically ill is controversial. Studies have shown that fewer than 25% of ICU patients with a sputum culture positive for *Candida* spp. ultimately have pulmonary candidiasis. Lung disease in patients who are immunocompetent is rare. Furthermore, no firm definition exists for true candidal pneumonia, and diagnosis remains mainly clinical because radiographic evidence lags from the onset of disease, and rapid detection tests require further development.

The lack of firm diagnostic criteria makes decision-making regarding treatment even more difficult. True invasive candidal pneumonia is a severe disease that requires prompt treatment. Unfortunately, this diagnosis cannot be confirmed without a lung biopsy and histologic evidence of disease. At present, data are insufficient to warrant treating immunocompetent patients with *Candida* spp. cultured from respiratory tract specimens. However, the presence of *Candida* in the sputum of a patient with positive cultures at another site (e.g., blood, peritoneal fluid, pleural fluid) warrants the diagnosis of disseminated candidal disease.

Treatment should be considered for patients with evidence of disseminated disease or symptoms of pulmonary infection in the setting of positive sputum cultures for yeast, host factors suggesting a high risk of infection, and no other identified infection source. Host risk factors include recent neutropenia, HSCT, immunosuppressant therapies including corticosteroids, and severe immunodeficiency. Fortunately, all available anti-candidal antifungal agents have excellent lung penetration, and any would be appropriate.

Invasive Mold Infections
Empiric Treatment

Infections with molds are much less common in the ICU setting than disease caused by *Candida* spp. However, mold

infections do occur in ICU patients, and appropriate management is important. In the setting of an unidentified mold infection, amphotericin B, including the lipid formulations, remains the most broad-spectrum antifungal agent available and is an appropriate empiric option for managing critically ill patients with a suspected invasive mold infection. When *Aspergillus* is strongly suspected or has been confirmed, the newer triazole agent voriconazole is recommended as first-line treatment based on the 2008 IDSA guidelines (Table 1-5).

In many high-risk settings, including HSCT, leukemia treatment, and solid-organ transplantation, antifungal prophylaxis is routinely used. The primary agents used are voriconazole, posaconazole, and micafungin. Empiric treatment regimens should include a drug from a different class if the patient has a significant history of exposure to an antifungal agent. Breakthrough infections encountered during prophylactic antifungal therapy are more likely to be caused by an organism that shows either intrinsic or acquired resistance to the antifungal class being used as prophylaxis.

Combination Therapy

Combination antifungal therapy has been proposed as a possible way to improve outcomes for invasive fungal infections like aspergillosis. The availability of new antifungal agents that target not only the fungal cell membrane (e.g., amphotericin B, azoles) but also the fungal cell wall (e.g., echinocandins) has made combination therapy possible. The ability to administer agents with differing sites of activity bypasses the theoretical concern of antagonism between amphotericin B and azoles.

Studies in both in vitro and animal models of infection have produced conflicting data regarding the use of amphotericin B in combination with azoles. The only randomized clinical trial of amphotericin B and fluconazole in candidemia did not provide meaningful clarification because of underlying differences in the two treatment arms. Many centers have published their experiences with combination antifungal therapy for the treatment of mold infections, but these reports are limited by their retrospective design and small sample size. Unfortunately, clinical data showing the benefit of such a strategy are unavailable.

In the 2008 updated IDSA guidelines on invasive aspergillosis, combination antifungal therapy is recommended as an option for patients not responding to traditional agents, highlighting the positive data from reports using the echinocandins in combination with agents from other antifungal classes. Prospective evaluations of combination therapy for invasive aspergillosis are continuing.

Table 1-5. Summary of IDSA Guidelines for Treating Invasive Candidiasis and Aspergillosis

Disease State	First-Line Treatment	Alternative Regimen(s)
Invasive aspergillosis	Voriconazole 6 mg/kg IV q12h for 2 doses; then 4 mg/kg IV q12h or 200 mg PO q12h	Lipid amphotericin B 3–5 mg/kg IV q24h Caspofungin 70-mg IV loading dose; then 50 mg/day IV Micafungin 100–150 mg/day IV Posaconazole 800 mg/day PO in 2–4 divided doses Itraconazole dose depends on formulation
Candidemia (non-neutropenic patient; moderate-severe illness)	Caspofungin 70-mg IV loading dose; then 50 mg/day IV Micafungin 100 mg/day IV Anidulafungin 200-mg IV loading dose; then 100 mg/day IV	Fluconazole 800-mg IV loading dose; then 400 mg/day IV or PO
Candidemia (neutropenic patient)	Caspofungin 70-mg IV loading dose; then 50 mg/day IV Micafungin 100-mg IV daily Anidulafungin 200-mg IV loading dose; then 100 mg/day IV	Fluconazole 800-mg IV loading dose; then 400 mg/day IV/PO Voriconazole, if mold coverage desired Voriconazole 6 mg/kg IV q12h for 2 doses; then 4 mg/kg IV q12h or 200 mg PO q12h
Candida glabrata	Echinocandin (see above)	Fluconazole or voriconazole with susceptibility testing
Candida parapsilosis	Fluconazole	Echinocandin, if already responding to therapy
Solid-organ transplant recipient (prophylaxis)	Fluconazole 200–400 mg/day IV/ PO for 7–14 days	Liposomal amphotericin B 1–2 mg/kg/day IV for 7–14 days
ICU prophylaxis (high-risk patients only)	Fluconazole 400 mg/day IV/PO	

ICU = intensive care unit; IDSA = Infectious Diseases Society of America; IV = intravenous; PO = by mouth; q12h = every 12 hours; q24h = every 24 hours.

Antifungal Pharmacotherapy

In the past decade, five novel antifungal agents, including three from a new therapeutic class, have been marketed in the United States. With expanded therapeutic options, determining where best to employ each agent to optimize patient outcomes is imperative. Having a knowledge of the pharmacology of each of the new drugs, as well as an understanding of how best to administer more traditional therapies, will help optimize and individualize treatment.

Amphotericin B

Amphotericin B has been clinically used to treat fungal infections for more than 50 years and remains the treatment of choice for many invasive fungal infections. Its potent activity against many pathogens maintains its role as the cornerstone for treating many fungal diseases.

The conventional deoxycholate formulation of amphotericin B is associated with considerable toxicities, primarily kidney dysfunction and infusion-related reactions; these limit its use in many patients with severe disease. To ameliorate these adverse effects, three lipid-based formulations—amphotericin B lipid complex, liposomal amphotericin B, and amphotericin B colloidal dispersion—were marketed in the 1990s. These newer preparations have largely replaced amphotericin B deoxycholate in most clinical settings.

All lipid formulations have a lower incidence of nephrotoxicity than the conventional preparation. Unfortunately, infusion-related reactions with amphotericin B colloidal dispersion are at least as common as seen with the conventional amphotericin B formulation; therefore, this product is seldom used. To date, there is no conclusive evidence suggesting superior efficacy with any lipid formulation over the deoxycholate preparation.

Whether either of the two commonly used lipid formulations (i.e., amphotericin B lipid complex or liposomal amphotericin B) offers any substantial advantage over the other is debatable. Despite limited data suggesting that the liposomal product causes less nephrotoxicity, there appears to be no clinically significant difference. The liposomal product is associated with a unique cardiopulmonary toxicity that can present as chest pain and hypoxia with or without flank pain. The pharmacist should be aware of this rare reaction because it can mimic symptoms of a myocardial infarction and lead to unnecessary ICU transfer or further treatments.

Simple strategies can be employed to minimize toxicities with conventional amphotericin B that also benefit patients receiving the lipid preparations. For infusion-related toxicities, premedication with diphenhydramine and acetaminophen can prevent or minimize reactions in most patients. It is now considered standard of care to provide these drugs even with the first amphotericin B dose. Nephrotoxicity with each of the amphotericin B products can be minimized with the maintenance of appropriate hydration and sodium loading. A bolus infusion of normal saline (250–500 mL) immediately before the amphotericin B dose can be renal protective. Another strategy used to minimize amphotericin B toxicity has been to administer the drug by continuous infusion. Although this technique can prevent nephrotoxicity, it does not optimize the concentration-dependent pharmacodynamic properties of amphotericin B and should be avoided.

Echinocandins

The three available echinocandins are similar with respect to spectrums of activity, efficacy in clinical use, and adverse effect profiles. For most centers, the selection of an individual agent is based on small differences in drug formulation, institutional preference, cost, and approved indications.

These drugs represent some of the safest antifungal therapies available. Each of the agents has been associated with rare cases of significant liver toxicity warrenting appropriate monitoring strategies. One unique adverse effect of the class is a histamine-mediated infusion-related reaction similar to the red man syndrome observed with vancomycin. This reaction is related to the infusion rate and rapidly subsides when the infusion is discontinued; it will typically not recur if the infusion is resumed at a slower rate.

The echinocandins are also relatively free of significant drug-drug interactions. Both caspofungin and micafungin interact with cyclosporine and tacrolimus, but these interactions are minor, do not require empiric dose adjustment, and can be managed with close clinical monitoring. Despite early warnings of possible additive liver toxicity, the use of cyclosporine and caspofungin in combination appears to be safe with careful clinical and laboratory monitoring.

Extended-Spectrum Triazoles

Voriconazole and posaconazole provide new treatment options for patients with invasive mold infections. These agents have distinct properties that differentiate them from each other and from other members of the azole class. Each of these agents has a broad spectrum of activity, including a wide range of yeasts and molds. One notable difference is the coverage against *Zygomycetes* offered by posaconazole but not voriconazole.

Oral administration is an advantage for both these agents, but it is not always feasible in the ICU setting. Currently, posaconazole is only available as an oral suspension, which requires administration with a high-fat meal. Substituting a high-fat nutritional supplement or a dosing regimen of 200 mg given orally every 6 hours in the fasting state achieves serum concentrations similar to 400 mg given orally every 12 hours administered with high-fat nutrition. Thus, the former regimen provides an option for ICU patients unable to receive oral intake. Posaconazole may be administered by a nasogastric tube. Of interest, total drug exposure is decreased when given by this route; however, the need for dosing adjustments has not yet been determined, and practitioners should be cautious when giving posaconazole by

this route. Initial data suggested that gastric pH was not a significant factor in the absorption of either agent; however, recent data and anecdotes from centers that routinely monitor posaconazole serum concentrations indicate that proton pump inhibitor therapy inhibits posaconazole absorption. Caution should be used when administering these agents together. In contrast to posaconazole, oral voriconazole should be given on an empty stomach because administration with concomitant food can decrease serum drug concentrations by about 20%. Voriconazole can be administered intravenously, but because of an excipient in the preparation, cyclodextrin, it should be used with caution in patients with decreased kidney function.

All azoles have been associated with liver toxicity and some degree of adrenal suppression, and both of these adverse effects are observed with voriconazole and posaconazole. Voriconazole also has two unique adverse events that are important to discuss with patients before initiating therapy. The first is a phototoxicity reaction that occurs when the patient is exposed to sunlight. Applying sunscreen does not protect against this reaction, which manifests as a bright red rash on any part of the skin exposed to the sun. The other reaction is transient visual disturbances, including hallucinations, which are temporally related to drug administration. Patients report bright flashing lights and have experienced visual hallucinations, particularly around the time of voriconazole initiation. Many patients adjust to these visual reactions after 1–2 weeks of treatment.

Like all azole antifungals, voriconazole and posaconazole inhibit drug metabolism by the cytochrome P450 (CYP) enzyme system. These agents each markedly increase cyclosporine, tacrolimus, and sirolimus concentrations. Because the interaction with sirolimus is unpredictable, concurrent administration of this immunosuppressant agent with voriconazole and posaconazole should occur only with careful serum concentration monitoring.

Azole drugs can prolong the half-life of many other agents used in the ICU, and notable on the list is the benzodiazepine class of drugs. Routine assessment for the presence of these drug-drug interactions should occur in all patients requiring azole therapy. As an important reminder, although not implicated as often in azole-induced drug-drug interactions, fluconazole at doses greater than 200 mg/day can result in substantial inhibition of CYP3A4. Voriconazole is metabolized by CYP2C19; therefore, it is subject to alterations in metabolism when administered with inhibitors and inducers of this isoenzyme, such as rifampin.

Because oral dosing is the primary method of administration for the two newest azoles, even in critically ill patients, the achievement of adequate serum drug concentrations is a concern. Fortunately, assays for serum drug concentration monitoring for both voriconazole and posaconazole are commercially available and have reasonable processing times; however, appropriate interpretation of these serum concentrations is not well defined. Serum concentration monitoring can verify drug absorption, and data are emerging to suggest efficacy targets for both posaconazole and voriconazole. Monitoring voriconazole concentrations can also be useful in the setting of suspected drug toxicity because voriconazole adverse effects have been correlated with elevated drug concentrations. When serum concentration monitoring is performed, a trough concentration should be obtained once steady-state concentrations have been achieved (i.e., after 5–7 days of uninterrupted therapy).

Role of the Pharmacist

No other member of the health care team is in a better position to oversee the development, implementation, and assessment of protocols to identify and appropriately manage fungal infections in the ICU than the clinical pharmacist. The pharmacist should be an active participant in designing these unit-based approaches to patient care, particularly given the need for routine, prospective monitoring with newer diagnostic technologies.

The available antifungal armamentarium provides limited options for clinicians. Recent advances have certainly expanded options, but tracking the unique spectrums of activity and data on efficacy with each fungal disease can make drug selection difficult and best conducted under the guidance of a pharmacotherapy expert. To optimize outcomes for patients receiving these medications, it is imperative that the drugs be administered with careful attention to appropriate dosing, drug-drug interaction management, and, when appropriate, therapeutic drug monitoring. The pharmacist is the most qualified member of the team to ensure the appropriate administration of these therapies.

Conclusion

Invasive fungal infections in the ICU are associated with considerable morbidity and mortality even under optimal treatment conditions. Delays in appropriate therapy can negatively affect patient outcomes. In addition to being difficult to diagnose and treat, these infections are costly and consume substantial institutional resources.

The available antifungal pharmacotherapies are very complex, are costly in some instances, are involved in numerous potential drug-drug interactions, and are associated with toxicity. Optimal management of invasive fungal infections involves careful coordination of appropriate patient risk factor identification, diagnostic testing, and early effective pharmacotherapy. To address this, many critical care practitioners have adopted protocols and algorithms to address the prevention and treatment of these infections in their patients.

ANNOTATED BIBLIOGRAPHY

1. Alexander BD, Pfaller MA. Contemporary tools for the diagnosis and management of invasive mycoses. Clin Infect Dis 2006;43(suppl 1):S15–S27.

   This review article summarizes the tools available from the microbiology laboratory related to diagnosis of fungal infections. The authors begin with a review of conventional testing methods (culture and histopathology) and discuss the relative merits and weaknesses of these more traditional technologies. There is a comprehensive discussion of newer testing methodologies for diagnosing fungal infection (beta-glucan and galactomannan) as well as tools to aid in fungal identification (PNA FISH). Finally, antifungal susceptibility testing is reviewed, including available testing methods and guidance on interpretation. The authors provide a critique of the available data on applying these methods, which will aid clinicians in determining how these tests may be useful in their own practices. In addition, the authors give a careful critique of clinical trials, highlighting areas that clinicians unfamiliar with the clinical microbiology laboratory may have overlooked.

2. Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Disease Society of America. Clin Infect Dis 2009;48:503–35.

   Guidelines from the IDSA are the cornerstone for many pathways and algorithms for managing infectious diseases. In 2009, the society updated treatment recommendations for candidiasis, expanding on the previous version (2004). Changes in this version include expanded recommendations for using echinocandin antifungal agents. Additional data regarding the use of this antifungal class for candidemia have become available since the previous guideline release, and these agents have become primary treatment options for many forms of invasive candidal infections. The guideline is organized to respond to key areas of clinical controversy. Discussion particularly relevant to ICU patients includes management of candidemia and empiric treatment of suspected invasive candidiasis in patients with and without neutropenia. The critically ill patient is specifically addressed in treatment recommendations for candidemia. An approach to managing *Candida* in the urine is proposed that includes targeting patients at high risk of complications and managing azole-resistant infections. The consensus panel also provides recommendations for using antifungal prophylaxis in ICU patients.

3. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008;46:327–60.

   Although a less common infection in the ICU patient population, invasive aspergillosis is still an important fungal pathogen in the critically ill. The latest guidelines from the IDSA expert panel summarize the current standard of care for treating these life-threatening infections. This document solidifies the role of voriconazole as the first-line agent for treating invasive aspergillosis based on data showing superior efficacy compared with conventional amphotericin B. Potential approaches for treating refractory disease, including the use of different drug classes (e.g., amphotericin B or the echinocandins) and combination antifungal therapy, are reviewed, highlighting the limited availability of clinical data. Detailed discussion of surgical management and approaches to disease in uncommon sites is included. Finally, suggestions are made for prophylaxis in high-risk patient populations such as HSCT recipients and patients with hematologic malignancy.

4. Barkauskas CE, Perfect JR. *Candida* pneumonia: what we know and what we don't. Curr Fungal Infect Rep 2009;3:21–31.

   A common challenge in the ICU is managing questionable or presumed lung infection in a patient with sputum cultures positive for yeast. This article, a comprehensive discussion of lung diseases caused by *Candida* spp., reviews the available information regarding the epidemiology of these infections. Every aspect of medically managing immunocompetent and immunocompromised patient populations from diagnosis, differentiating between disease and colonization, pharmacologic therapy, and management of empyema, is discussed. An important concept in this article is when to withhold antifungal therapy for these patients. The authors also discuss optimal treatment strategies including appropriate agent selection.

5. Ostrosky-Zeichner L, Pappas PG. Invasive candidiasis in the intensive care unit. Crit Care Med 2006;34:857–63.

   The most common fungal infection in the ICU is invasive candidiasis, and this review provides a thorough overview of the topic. The authors discuss the epidemiology of infection, risk factors for disease, and appropriate management, specifically for the critically ill patient. Data regarding pharmacotherapy are reviewed, and recommendations are presented on agent, dosing, and key monitoring components. The authors also propose a management approach for the ICU patient with invasive candidiasis, including pathways for both immunocompetent and immunosuppressed patients. Commentary is also provided on current approaches to mitigating disease, including prophylactic, empiric, and preemptive therapies.

6. Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356:2472–82.

   This prospective, randomized study showed the superior efficacy of the echinocandin anidulafungin to fluconazole in patients with invasive candidiasis. Superiority was not maintained by the 6-week follow-up visit, but anidulafungin was deemed non-inferior to fluconazole at that time. The primary outcome of combined clinical and microbiologic efficacy determined at the end of intravenous therapy was 75.6% for anidulafungin and 60.2% for fluconazole. The protocol allowed conversion to oral fluconazole in both treatment arms after 10 days of intravenous therapy. Treatment duration was 2 weeks after the last positive blood culture. Around 20% of patients in each arm (anidulafungin, 21%; fluconazole, 17%) had Acute Physiological and

Chronic Health Evaluation II Scale (APACHE II) scores greater than 20, making this study applicable to critically ill ICU patients. However, given that fluconazole was one of the treatment options, the possibility of selection bias has been raised because clinicians may have hesitated to enroll patients when fluconazole resistance was a concern. In addition, the study included few neutropenic patients.

7. Kuse E-R, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 2007;369:1519–27.

The echinocandins are attractive agents for managing invasive candidiasis. Caspofungin was the first member of this class to be studied for candidemia and was as effective as conventional amphotericin B in a randomized, controlled trial. This double-blind, randomized study was the first to assess the use of micafungin for the same indication. Use of conventional amphotericin B as the comparator in the prior caspofungin study raised concerns over enrollment bias. In this study, the liposomal polyene amphotericin B product was administered at a dose of 3 mg/kg/day. Although this dose is included in the package labeling, it is lower than some clinicians suggest for treatment of disease. The dose of micafungin was 100 mg/day. Although dose escalations were allowed in both treatment arms during the study, dose escalation occurred in only about 10% of patients in each group. This study enrolled 537 patients with sterile site cultures (including blood) positive for *Candida* spp. The two treatments were deemed non-inferior with success rates of 89.6% (micafungin) and 89.5% (liposomal amphotericin B) at the end of all treatment. Efficacy data were also presented for the almost 20% of patients with APACHE II scores greater than 20 at baseline. Success was comparable between groups, with 92.3% of micafungin-treated patients and 88.5% of liposomal amphotericin B recipients responding. Overall, success rates appear higher compared with those reported in other clinical trials of candidemia and invasive candidiasis, largely because patients not surviving the first 5 days of infection were excluded from this analysis (the study population had to have received at least five doses of the study drug).

8. Pappas PG, Rotstein CMF, Betts RF, Nucci M, Talwar D, De Waele JJ, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 2007;45:883–93.

This study provides a comparison between two different echinocandins (caspofungin and micafungin) as well as insight into different micafungin dosages (100 mg/day and 150 mg/day) for treating invasive candidiasis. Similar to other studies involving patients with invasive candidiasis, about 20% of patients in each treatment arm had baseline APACHE II scores greater than 20, representing the critically ill population. Both dosing regimens of micafungin were non-inferior to caspofungin given at traditional doses. Response rates in the micafungin 150-mg dose arm were slightly lower than the 100-mg dose arm (76.4% and 71.4%, respectively), but this difference was not statistically signif-

icant. However, this result suggests there is no additional benefit to be gained from using a higher micafungin dosage.

9. Betts RF, Nucci M, Talwar D, Gareca M, Queiroz-Telles F, Bedimo RJ, et al. A multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. Clin Infect Dis 2009;48:1676–84.

This study of the treatment of invasive candidiasis addressed whether higher caspofungin dosages would improve outcomes. Caspofungin was the first echinocandin commercially available in the United States, and when initially released, concerns about toxicity resulted in conservative dosing regimens. The primary outcome of this study was the safety of caspofungin 150 mg/day compared with a traditional dosing strategy, a 70-mg loading dose followed by 50 mg/day. No safety concerns were identified with the higher dosing regimen, including subjects with APACHE II scores greater than 20 (25% and 27% of the patients in the traditional and high-dose groups, respectively). Although not designed to look at overall response, clinical outcomes were also similar between groups, suggesting that even though no acute toxicities are associated with the higher caspofungin dosage, there also may not be additional clinical benefit.

10. Kullberg BJ, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Rex JH, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. Lancet 2005;366:1435–42.

The use of voriconazole has been assessed as treatment of candidemia. In this study, voriconazole was compared with conventional amphotericin B followed by fluconazole in patients with candidemia who were not neutropenic. Voriconazole was as effective as amphotericin B, with response rates of 41% for both treatment groups. Because voriconazole is not endorsed in the IDSA guidelines as first-line therapy for candidemia, particularly in ICU patients, these data are not as applicable to practice. However, of importance is the low reported success rate in this study. This low efficacy rate is largely explainable by the selection of study end points. Instead of assessing outcome at the end of treatment, the primary efficacy end point was set at 12 weeks after treatment. The low response rate cited in this study highlights another aspect of managing invasive candidiasis: the high rate of disease recurrence. This article features a comparison in tabular format of previous candidemia trials at comparable end points to better evaluate all available treatments. This table is an important resource for any program creating a treatment algorithm for invasive candidiasis.