



# Fungal Infections in the ICU

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## LEARNING OBJECTIVES

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

## ABBREVIATIONS IN THIS CHAPTER

|         |   |
|---------|---|
| Anti-Mn | Anti-mannan antibody  |
| AST     | Antifungal susceptibility testing                                 |
| ECIL    | European Conference on Infections in Leukemia                     |
| ESCMID  | European Society of Clinical Microbiology and Infectious Diseases |
| IA      | Invasive aspergillosis  |
| IC      | Invasive candidiasis  |
| IDSA    | Infectious Disease Society of America                             |
| IFI     | Invasive fungal infection   |
| Mn      | Mannan antigen  |
| TDM     | Therapeutic drug monitoring                                       |

## INTRODUCTION

Invasive fungal infections (IFIs) are becoming more prevalent as the use of immunosuppressing therapies in the management of malignancy, transplantation, and rheumatology expands. As the population ages and the survival of patients with multiple comorbidities and advanced disease increases, the rates of fungal infection are expected to continue to rise. The presence of multiple risk factors and severe illness makes patients admitted to the ICU particularly vulnerable to these infections.

Over the past 20 years, advances in the management of IFI include new antifungal agents, improved diagnostic testing, and the availability of susceptibility testing. Despite these improvements, outcomes remain poor and resistance to the currently available antifungals is increasing. Mortality rates associated with invasive candidiasis (IC) have been reported to be about 40% to 60% in ICU patients and 80% to 90% in patients with septic shock. These infections also place a significant financial burden on the health care system because of longer hospital stays, use of expensive therapies, and increased consumption of health care resources. The estimated cost of a single episode of candidemia is \$25,000–\$55,000 and a single hospitalization for aspergillosis is \$60,000 (Kett 2011). Clinical pharmacists can play an important role in helping to recognize patients at risk of fungal infection, in providing safe and effective use of antifungal agents, and in reducing costs associated with this disease.

## EPIDEMIOLOGY

### *Candida* Species

*Candida* spp. are common normal flora found on mucosal surfaces. In the presence of mucosal barrier breakdown or immunosuppression, these organisms become significant pathogens that can lead to increased morbidity and mortality. Candidiasis encompasses a host of infections involving mucosal surfaces and the urinary tract, as well as more disseminated disease (e.g., sepsis, meningitis, endocarditis, intra-abdominal infections). Candidiasis is the leading cause of IFI, with 50% of cases occurring in ICU patients. The exact prevalence of these infections is elusive because of variations in surveys used, the number of centers involved, and the type of patients; however, many studies cite a prevalence of about 7 cases per 1000 ICU patients.

#### BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge on the pathophysiology of critically ill patients
- Pharmacology and recommended doses of commonly used antifungal agents
- Basic pharmacokinetic/pharmacodynamic principles of antimicrobials
- Drug-drug interactions common through the CYP enzyme system
- Common procedures used to diagnose infection in the ICU

#### ADDITIONAL READINGS

The following free resources are available for readers wishing additional background information on this topic.

- IDSA. [Treatment of Aspergillosis](#) [homepage on the Internet].
- IDSA. [Management of Candidiasis](#) [homepage on the Internet].
- ESCMID. [Guideline for the Diagnosis and Management of Candida Diseases 2012](#) [homepage on the Internet].
- Maertens J, Marchetti O, Herbrecht R, et al. [European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients](#). Bone Marrow Transplant 2011;46:709-18.
- Lewis RE. [Current concepts in antifungal pharmacology](#). Mayo Clinic Proceed 2011;86:805-17.
- Kullberg BJ, Arendrup MC. [Invasive candidiasis](#). N Engl J Med 2015;373:1445-56.

*Candida* spp. are reported to be the fourth leading cause of blood stream infections overall and the third leading cause of these infections in ICU patients. A recent survey of national acute care hospitals found *Candida* spp. to be the leading cause of hospital-associated bloodstream infections (Magill 2014). This fits with the 5-fold increase in *Candida* bloodstream infections over the past 10 years and the tripling of fungal sepsis cases in the past few decades. In addition, an epidemiologic shift is occurring in the species causing disease. Although *Candida albicans* remains the most common species isolated, it now accounts for only about 50% of the pathogens seen in both hospital wards and ICUs. Rates of non-*albicans* species are increasing in North America; *C. glabrata* is the second most common pathogen isolated, followed by *C. parapsilosis*, which is commonly seen in patients with chronic catheter placement (e.g., total parenteral nutrition). The rates of *C. tropicalis*, *C. krusei*, and *C. lusitaniae* remain stable, and these are still considered important pathogens. This shift in epidemiology has significant implications because non-*albicans* species often have either reduced susceptibility or resistance to fluconazole, a fungistatic drug commonly used preemptively to treat these infections.

### Mold Pathogens

Invasive mold infections, particularly caused by *Aspergillus* spp., are also common among critically ill patients. Traditionally, invasive aspergillosis (IA) was thought to be a disease found mainly in neutropenic and hematopoietic stem cell transplant patients. However, the current understanding is that IA is also an important pathogen in non-neutropenic critically ill patients, such as those receiving corticosteroids and those with chronic lung diseases or liver failure.

*Aspergillus* spp. usually cause pulmonary or sinus disease, although infections of the skin and CNS may occur. Because infection usually starts from inhalation of the conidia, outbreaks of *Aspergillus* have been linked to poor air filtration, construction, and even contaminated medical equipment and hand lotion. The prevalence of IA in ICU patients has been reported to be 0.335% to 6.9%. This wide range is a result of the difficulties in diagnosing infection, as well as a lack of post-mortem reports confirming disease presence. Diagnosing IA in critically ill patients is particularly challenging because classic radiographic signs (e.g., halo sign or air crescent) are not always present in non-neutropenic patients, who do not progress as rapidly to angioinvasive disease. This challenge also explains why diagnostic studies tend to be less sensitive in non-neutropenic patients, further limiting methods for early detection of infection.

Similar to IC, IA is also associated with significant mortality and increased health-care costs. The average mortality rates in ICU patients with IA are 60% to 90%. This high mortality is not completely driven by severity of underlying illness, based on the finding that mortality rates appear similar

between those considered immunocompetent and hematopoietic stem cell transplant recipients with IA.

Other fungal pathogens causing disease in patients with immunocompromise include *Cryptococcus* spp., *Fusarium* spp., *Scedosporium* spp., and *Mucormycoses* spp. These infections are rare in ICU patients but occur more often in patients receiving chronic immunologic therapy for rheumatologic and other chronic conditions. Such infections present particular therapeutic challenges because they are associated with very high mortality.

### High-Risk Patient Populations

It is now well recognized that IFIs are not limited to patients with severe immunosuppression. Critically ill patients have dysfunctional monocytes, macrophages, and impaired neutrophils that put them at risk of these opportunistic pathogens. Risk factors for IFI in the ICU are listed in Box 1-1. The prevalence of these risk factors in ICU patients complicates the decision of when to use prophylactic or preemptive antifungal therapy. Risk prediction models and clinical decision tools have been developed, but these have not been adequately evaluated in prospective multi-center trials. These algorithms have limited diagnostic applicability because of

#### Box 1-1. Risk Factors for Invasive Fungal Infections in the ICU

- Broad-spectrum antimicrobials
- Burns
- Candida* colonization
- Central venous or urinary catheter
- Chemotherapy
- Corticosteroids
- Diabetes mellitus
- Graft-versus-host disease
- Hematopoietic stem cell transplant
- Hemodialysis
- High severity of illness (APACHE II >20)
- Immunosuppressing therapies
- Liver failure
- Major surgery
- Malignancy
- Mucosal damage
- Necrotizing pancreatitis
- Neonates
- Neutropenia
- Prolonged duration of ICU stay
- Prolonged ventilation
- Renal failure
- Solid organ transplant
- Structural lung disease
- Total parenteral nutrition

their low positive predictive values, impracticality, and tendency to promote overuse of antifungal agents.

There is a strong correlation between *Candida* colonization and infection. Rates of colonization increase with longer ICU stays and exposure to risk factors. Most patients who develop IC are colonized to some degree, but only about 5% to 30% of colonized patients develop systemic infection. The *Candida* Colonization Index was developed in surgical ICU patients to evaluate the risk of developing IC in colonized patients. A ratio of the number of colonized sites to the number of cultured sites (e.g., urine, sputum, stool) greater than 0.5 is associated with an increased risk of IC. Using this threshold to start empiric antifungal therapy significantly reduced the incidence of infection compared with historical controls; however, most patients (87%) received preemptive treatment with fluconazole (Piarroux 2004). The concerns with using this index are its low positive predictive value (9%) and the increased use of antifungals, as well as the increased costs and workload associated with obtaining multiple cultures. It is also unknown how this model would apply to other ICU populations.

Other clinical prediction tools that incorporate several risk factors into a scoring system have been evaluated for their ability to predict IC (Table 1-1). These tools have good negative predictive values, making them useful in deterring antifungal therapy if risk factors are not present. The low positive predictive values of these scores may increase the risk of unnecessary antifungal use and lead to increased costs and potential resistance. Therefore, it is important to use these tools in the patient populations for which they were intended and also to take into consideration the specific patient population in the clinician's own institution. A well-designed risk score that identifies subgroups of patients (similar to those being treated at the clinician's ICU) with increased risk over the general population can help in the decision to use preemptive therapy.

## ADVANCES IN DIAGNOSIS OF FUNGAL INFECTIONS

### Limitations of Traditional Culture and Radiologic Methods

Traditional methods for diagnosing fungal infections include clinical signs and symptoms, radiography, cultures, and histopathology. These methods have many limitations and may lead to significant delays in initiating appropriate treatment. Fungal infections often have a delayed clinical course with very nonspecific signs and symptoms. Classic radiographic signs (halo sign or macronodules) are not always present, particularly among patients with immunosuppression, and may not aid in detecting changes early in the course of disease. These radiographic features are also not specific for a particular pathogen, resulting in broad treatment.

Blood cultures remain the gold standard for diagnosing candidemia but are only about 50% sensitive for detecting *Candida* spp. and rarely grow *Aspergillus* spp. or other mold

**Table 1-1.** Clinical Prediction Scores for Invasive Candidiasis

| Score (year)                        | Patient Population  | Model Risk Factors  | Cutoff Value                                    | Sensitivity/<br>Specificity (%) | PPV (%) | NPV (%) |
|-------------------------------------|---|---|---|---------------------------------|---------|---------|
| Dupont Score (1994)                 | Surgical ICU peritonitis  | Female, upper GI tract origin of peritonitis, perioperative cardiovascular failure, antimicrobial therapy at least 48 hours before peritonitis onset  | Grade C= at least three risk factors            | 84/50                           | 67      | 72      |
| <i>Candida</i> Score (2006)         | Medical/ surgical ICUs for $\geq 7$ days                                      | Severe sepsis (2 points), major surgery (1 point), total parenteral nutrition (1 point), multi-focal <i>Candida</i> colonization (1 point)  | Score $\geq 3$                                  | 81/74                           | 16      | 98      |
| Ostrosky Rule (2007, 2011)          | Medical/ Surgical ICUs for $\geq 4$ days                                      | Major criteria: systemic antibiotic use days 1–3, central venous catheter   | Two major factors                               | 89/38                           | 4       | 99      |
|                                     |   | Minor criteria: surgery, immunosuppressants, corticosteroids, pancreatitis, dialysis, total parenteral nutrition  | Two major + at least one minor factor           | 66/69                           | 6       | 98      |
|                                     |   | Modified to add mechanical ventilation for at least 48 hours as an additional major criteria  | One major + at least two minor factors          | 34/90                           | 10      | 97      |
|                                     |   |   | Three major factors + at least one minor factor | 50/83                           | 10      | 97      |
| Nebraska Medical Center Rule (2011) | Medical/ Surgical ICUs for $\geq 4$ days                                      | Broad spectrum antibiotics (1.5 points), central venous catheter (0.9 points), and total parenteral nutrition days 1–3 (0.9 points), steroid use in the 7 days before ICU admission up to day 3 (0.4 points), abdominal surgery (0.9 points), and pre-ICU length of stay $\times 0.039$ | Score $\geq 2.45$                               | 84.1/60.2                       | 4.7     | 99.4    |
| Candidemia Rule (2015)              | All hospitalized patients with culture positive severe sepsis or septic shock | Antibiotics within 30 days, central venous catheter, admitted from nursing home, or total parenteral nutrition (2 points each), transferred from outside hospital or receiving mechanical ventilation (1 point each), lung as presumed source of sepsis (subtract 6 points)             | Score $\geq 3$                                  | 87.6/55.9                       | 18.5    | 97.5    |

NPV = negative predictive value; PPV = positive predictive value.

Information from: Dupont H. Can yeast isolation in peritoneal fluid be predicted in intensive care unit patients with peritonitis? *Crit Care Med* 2003;31:752-57; León C. A bedside scoring system (“*Candida* score”) for early antifungal treatment in non-neutropenic critically ill patients with *Candida* colonization. *Crit Care Med* 2006;34:730-7; Ostrosky-Zeichner L. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. *Eur J Clin Microbiol Infect Dis* 2007;26:271-6; Ostrosky-Zeichner L. Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in the intensive care unit. *Mycoses* 2011;54:46-51; Hermesen ED, Zapapas MK, Maiefski M, et al. Validation and comparison of clinical prediction rules for invasive candidiasis in intensive care unit patients: a matched case-control study. *Crit Care* 2011;15:R198; and Vasquez Guillamet C, Vazquez R, Micek ST, et al. Development and validation of a clinical prediction rule for candidemia in hospitalized patients with severe sepsis and septic shock. *J Crit Care* 2015;30:715–20.

pathogens. Blood cultures also fail to detect deep-tissue infections and can take several days to yield a positive result. Deep tissues and fluid collections are invasive and challenging to obtain, making a histopathologic diagnosis difficult, especially in patients who are unstable or thrombocytopenic. Unless cultures are taken from sterile sites, it also is difficult to differentiate true infection from colonization.

### Rapid Diagnostics

Several advances in rapid diagnostic tests for IFI have been made in the past several years (Table 1-2). These tests may diagnose fungal infections early before signs of infections develop. They also have improved sensitivity and specificity over traditional methods and could potentially be used in conjunction with risk prediction models to help guide preemptive

**Table 1-2.** Rapid Diagnostic Tests for Invasive Fungal Infections

| Test                                       | Application   | Sensitivity %                                    | Specificity %                                    | Limitations   |
|--|---|--|--|---|
| $\beta$ -D-glucan                          | <i>Candida</i> spp. and <i>Aspergillus</i>                        | 57–97  | 56–93  | False-positive: glucan -contaminated tubes/gauze, cellulose-containing dialysis membranes/filters, contaminated albumin/IVIG with fungal elements, gram-positive infections, gut inflammation, some antibiotics (amoxicillin-clavulanic acid)<br>Controversy surrounding optimal cutoff value |
| Mannan antigen/<br>Anti-mannan<br>antibody | <i>Candida</i> spp. only  | Mannan: 58<br>Anti-mannan: 59<br>Combination: 83 | Mannan: 93<br>Anti-mannan: 83<br>Combination: 86 | Positive results occur later in disease course<br>Sensitivity varies depending on species<br>Best results when used together<br>Cutoff value unclear  |
| Nucleic-acid PCR                           | All species, but only available currently for <i>Candida</i> spp. | 96   | 97   | Using test too early may decrease sensitivity<br>Unavailable for many organisms   |
| Galactomannan                              | <i>Aspergillus</i> and some other molds                           | Serum: 71<br>BAL: 76–88                          | Serum: 89<br>BAL: 87–100                         | False-positive: $\beta$ -lactams, Plasma-Lyte<br>Not as sensitive in non-neutropenic patients   |

IVIG = intravenous immunoglobulin; PCR = polymerase chain reaction.

Information from: León C. What's new in the clinical and diagnostic management of invasive candidiasis in critically ill patients. *Int Care Med* 2014;40:808-19; and Perfect JR. Fungal diagnosis: how do we do it and can we do better? *Curr Med Res Opin* 2013;29:3-11.

therapy to target a specific organism, helping limit unnecessary antifungal use.

There are now several rapid diagnostic tests for the detection and identification of *Candida* spp.  $\beta$ -D-glucan is a cell wall constituent of *Candida* spp., as well as other fungi (but not *Cryptococcus* and *Zygomycetes*). The  $\beta$ -D-glucan diagnostic test is an assay that detects activation of the coagulation cascade by  $\beta$ -D-glucan. A meta-analysis reported a sensitivity and specificity of 57%–97% and 56%–93%, respectively, for the diagnosis of IC (Karageorgopoulos 2011). This assay has been shown to detect intra-abdominal candidiasis 5 days earlier than traditional methods. Also, it has a good negative predictive value (80% or greater), making it a potentially useful tool to prevent unnecessary use of antifungals.

False-positive results may occur because of glucan-contaminated collection tubes or gauze dressings, cellulose-containing dialysis membranes or products with cellulose filters, contaminated albumin or intravenous immunoglobulin with fungal elements, gram-positive infections (e.g., *Streptococcus pneumoniae*), gut inflammation, and antibiotics such as amoxicillin/clavulanic acid. Therefore, the positive predictive value of the test is often a limitation, reported in one study at 30% when a cutoff of two consecutive tests > 80 pg/mL was used (Hanson 2012). The recommended cutoff

value is a single test result greater than 80 pg/mL or two consecutive tests > 60 pg/mL if serial monitoring is being used. Higher values (greater than 150 pg/mL for a single test or > 80 pg/mL for consecutive testing) have been suggested for critically ill patients. Two consecutive results (twice within a week) above this threshold are recommended to improve the diagnostic accuracy of this test.

Both the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Conference on Infection in Leukaemia (ECIL) recommend the  $\beta$ -D-glucan diagnostic test as an adjunct to culture; however, it is important to keep in mind that most of the literature evaluating this test is in the setting of hematologic malignancy or surgical ICU patients. The ICU population has also been cited as a group more prone to false-positive results, further complicating interpretation. The accuracy of this assay in other ICU populations has yet to be determined, and the usefulness of serial monitoring of concentrations in guiding treatment response remains unclear, although some initial reports with echinocandin treatment appear promising.

Mannan is a polysaccharide component of the fungal cell wall that is specific to *Candida* spp. A commercially available latex agglutination and enzyme immunoassay exists for both mannan antigen (Mn) and anti-mannan antibodies (Anti-Mn)

that develop in response to mannan. Both tests are more specific than the  $\beta$ -D-glucan diagnostic test, but they are not as sensitive and do not become positive until later in the course of disease. A recent meta-analysis that included several studies in critically ill patients who were non-neutropenic found improved sensitivity and specificity of both tests when used in combination. It also demonstrated the sensitivity of the test varied based on *Candida* spp., with the highest sensitivity reported for *C. albicans* and the lowest for *C. parapsilosis* and *C. krusei* (Mikulska 2010). The reason for this finding is likely because of the different amounts of mannan produced and released by these organisms. It is also important to note that the studies included are limited by their retrospective design in a heterogeneous patient population, as well as by differences in definitions, diagnostic criteria, and cutoff values. The combined Mn and anti-Mn test is recommended by both the ESCMID and ECIL to detect candidemia and hepatosplenic candidiasis.

Galactomannan is an assay similar to Mn but is specific for *Aspergillus* spp. and a few other molds. Serial measurements are recommended in high-risk patients to guide preemptive therapy and potentially diagnose infection long before clinical symptoms develop. Serum samples have a reported sensitivity and specificity of 71% and 89%, respectively, in hematologic malignancy patients. The positive predictive value of this assay is less robust in solid organ transplant and non-neutropenic ICU patients, likely because of a lower prevalence of disease. The risk of obtaining a false-negative result depends on the optical density cutoff value used (optimal value is 0.5), as well as the presence or recent use of antifungal therapy, the degree of fungal burden, the presence of a walled-off infection, and the immunologic status of the patient. Non-neutropenic patients may be more likely to have a negative test result because of the slow progression to angioinvasive forms of the disease compared with the neutropenic population. False-positive results may occur while receiving  $\beta$ -lactams (piperacillin/tazobactam) or Plasma-Lyte. This test can now be performed directly from bronchoalveolar lavage samples, which tends to increase the sensitivity and specificity over serum values in non-neutropenic patients.

Another important tool for diagnosing IFI is the detection of fungal nucleic acids by polymerase chain reaction. Currently an FDA-approved assay is available for detecting *Candida* spp. only. This test allows for the early detection of candidemia and may be better than culture in detecting non-viable organisms and deep-seated infections. This assay has been reported to have a very high sensitivity (96.3%) and specificity (97.3%) in ICU patients, as well as good positive and negative predictive value (greater than 90%). Limited data are available regarding how colonization affects this test, but trends towards lower specificity have been seen. Also, using this test too early in the course of disease may lower its sensitivity. Despite these limitations, nucleic acid

tests have the potential to be a very effective tool in the diagnosis of IFI.

A limitation of traditional blood cultures is the delay in time to positivity. After yeast grows, it takes several more days to identify the species and perform susceptibility testing. Use of molecular-based identification methods such as peptic nucleic acid fluorescence in situ hybridization (PNA FISH) can differentiate several of the most common *Candida* species with a turnaround time of only a few hours. Another technology, matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) is capable of detecting some species of *Candida* directly from whole blood specimens, allowing even earlier initiation of treatment.

Although several advances have been made in rapid diagnostics for IFI, many unknowns remain, as do limitations in incorporating these tests for routine use, especially in ICU patients. These assays tend to be labor intensive, are not routinely available at many institutions, and have not been evaluated for cost-effectiveness. Other factors that must be considered include the degree of immunocompetence, type and site of fungal infection, timing of sample in relation to the clinical picture, and the presence of antifungal therapy or other factors that may interfere with the results. More data are needed regarding the optimal cutoff values for critically ill patients and whether one test or a combination of tests is best for guiding antifungal therapy.

### Antifungal Susceptibility Testing

Antifungal susceptibility testing (AST) plays a vital role in determining resistance patterns and in guiding drug selection and de-escalation of antifungal therapy; however, knowledge about application of these testing results lags significantly behind those for bacteria. Standards for AST were recently updated to include the most commonly used drugs to treat IFIs.

Clinical breakpoints for *Candida* spp. and selected azoles are described as *susceptible*, *susceptible-dose dependent*, and *resistant* (Table 1-3). These breakpoints are based on pharmacokinetic-pharmacodynamic relationships and imply some correlation to clinical outcome. It is important to note that most of the clinical trial data supporting these breakpoints for fluconazole are flawed because of differences in the definition of treatment failure, the low number of non-*albicans* spp. and isolates with elevated MICs, and failure to account for differences in renal function for dose determination. Clinical data supporting breakpoints for voriconazole are from non-neutropenic patients.

A clear dose:MIC relationship that correlates with clinical outcome for azole therapy has not been established from the available literature. This lack of correlation makes it difficult to determine an appropriate treatment regimen for drugs with susceptible-dose dependent activity, which require higher-than-standard doses. Clinical breakpoints do not exist for *C. krusei* to fluconazole because of intrinsic resistance.

**Table 1-3.** Antifungal Susceptibility Breakpoints for *Candida* spp.

| Antifungal Agent | Species                  | Susceptible (mcg/mL) | Susceptible-Dose Dependent (mcg/mL) | Resistant (mcg/mL) |
|------------------|--------------------------|----------------------|-------------------------------------|--------------------|
| Fluconazole      | <i>C. albicans</i>       | ≤ 2                  | 4                                   | ≥ 8                |
|                  | <i>C. parapsilosis</i>   |                      |                                     |                    |
|                  | <i>C. tropicalis</i>     |                      |                                     |                    |
|                  | <i>C. glabrata</i>       | n/a                  | ≤ 32                                | ≥ 64               |
|                  | <i>C. krusei</i>         | n/a                  | n/a                                 | n/a                |
| Posaconazole     | All <i>Candida</i> spp.  | n/a                  | n/a                                 | n/a                |
| Voriconazole     | <i>C. albicans</i>       | ≤ 0.12               | 0.25–0.5                            | ≥ 1                |
|                  | <i>C. parapsilosis</i>   |                      |                                     |                    |
|                  | <i>C. tropicalis</i>     |                      |                                     |                    |
|                  | <i>C. glabrata</i>       | n/a                  | n/a                                 | n/a                |
|                  | <i>C. krusei</i>         | ≤ 0.5                | 1                                   | ≥ 2                |
| Antifungal Agent | Species                  | Susceptible (mcg/mL) | Intermediate (mcg/mL)               | Resistant (mcg/mL) |
| Anidulafungin    | <i>C. albicans</i>       | ≤ 0.25               | 0.5                                 | ≥ 1                |
|                  | <i>C. tropicalis</i>     |                      |                                     |                    |
|                  | <i>C. krusei</i>         |                      |                                     |                    |
|                  | <i>C. parapsilosis</i>   | ≤ 2                  | 4                                   | ≥ 8                |
|                  | <i>C. guilliermondii</i> |                      |                                     |                    |
|                  | <i>C. glabrata</i>       | ≤ 0.12               | 0.25                                | ≥ 0.5              |
| Caspofungin      | <i>C. albicans</i>       | ≤ 0.25               | 0.5                                 | ≥ 1                |
|                  | <i>C. tropicalis</i>     |                      |                                     |                    |
|                  | <i>C. krusei</i>         |                      |                                     |                    |
|                  | <i>C. parapsilosis</i>   | ≤ 2                  | 4                                   | ≥ 8                |
|                  | <i>C. guilliermondii</i> |                      |                                     |                    |
|                  | <i>C. glabrata</i>       | ≤ 0.12               | 0.25                                | ≥ 0.5              |
| Micafungin       | <i>C. albicans</i>       | ≤ 0.25               | 0.5                                 | ≥ 1                |
|                  | <i>C. tropicalis</i>     |                      |                                     |                    |
|                  | <i>C. krusei</i>         |                      |                                     |                    |
|                  | <i>C. parapsilosis</i>   | ≤ 2                  | 4                                   | ≥ 8                |
|                  | <i>C. guilliermondii</i> |                      |                                     |                    |
|                  | <i>C. glabrata</i>       | ≤ 0.06               | 0.12                                | ≥ 0.25             |

n/a = not applicable.

Information from: Clinical and Laboratory Standards Institute M27–S4.

Susceptibility testing and clinical outcome have not been established for voriconazole to *C. glabrata* and posaconazole to any *Candida* spp.

Clinical breakpoints for *Candida* spp. and the echinocandins used to be reported as susceptible if 2 mcg/mL or lower and non-susceptible if above this threshold. The new breakpoints are now described as *susceptible*, *intermediate*, and *resistant* (see Table 1-3). These breakpoints were derived primarily from clinical trials in non-neutropenic patients. Overall, the echinocandin breakpoints are identical across the class.

The exception is micafungin and *C. glabrata*, for which lower breakpoints are used based on methodologic differences, and not differences in clinical efficacy between agents.

Much controversy surrounds the revision of these breakpoints and a lack of data correlating MIC with clinical outcome. The reason for this change in breakpoints is based on evidence suggesting that the presence of resistance mutations may better correlate with response to therapy than the actual MIC. Many reports identify hotspot genetic mutations leading to echinocandin resistance in some *Candida* spp. that have

lower MICs than the previously reported susceptibility cutoff of 2 mcg/mL. Therefore, the previous cutoff value failed to identify which isolates carry these resistant mutations, and the new clinical breakpoints have been lowered to help segregate wild-type isolates from ones with mutations. Several institutions have also reported increased caspofungin MICs (specifically in *C. glabrata*) above the new cutoffs that would be considered resistant, but these cases responded to echinocandin therapy. This finding demonstrates that elevated MICs do not necessarily imply poor outcome and further reduces the reliability of the breakpoints to help guide therapy. Recent literature suggests micafungin or anidulafungin may be more reliable than caspofungin to detect resistant mutations and predict treatment failure even in those treated with caspofungin (Shields 2013).

## Resistance

Resistance to the commonly used antifungal agents among both yeast and mold species is an area of ongoing investigation. With the introduction and increased use of AST, the detection of resistance amongst identifiable species is now possible. Overall, resistance rates for most species are low but are trending upwards. Even more concerning are the increasing rates of drug resistance in treatment-naïve patients. This shift is in part a result of selective pressure from increased use of antifungals in the prophylaxis of patients with immunocompromise; increased preemptive and empiric use, particularly in ICU patients because of poor diagnostics; overuse of antifungals in the community for treating minor fungal infections; and widespread use of agricultural fungicides.

Fluconazole resistance in *C. albicans* is very rare (less than 5% of isolates). Resistance to other species of *Candida* is increasing, with rates approaching 10% for several common species. Intrinsic resistance of some *Candida* spp. (e.g., *C. krusei*) to fluconazole is well known. For other species/medication pairs, it is less clear. For example, *C. parapsilosis* has been reported to have higher MICs to the echinocandins than other *Candida* spp., but this finding has not resulted in treatment failure in clinical trials. About 20% to 30% of candidemia cases involve intrinsically resistant species, and prior use of antifungals is the most common risk factor for selecting these pathogens.

Acquired resistance, or resistance that develops during therapy, is more difficult to predict, and much remains to be elucidated. Acquired resistance has been reported during treatment of *Candida* infections, particularly *C. glabrata*, with fluconazole. These species are often cross-resistant to other azoles and may even display multi-drug resistant phenotypes. Acquired resistance to echinocandins has also been noted in patients receiving long-term therapy for *Candida* infections. *Candida* resistance to amphotericin B is rare (1%–3% of isolates) but difficult to determine because of inadequate susceptibility testing methods. In Europe, *C. glabrata* and

*C. krusei* typically have higher MICs to amphotericin B, and increasing rates of resistance to polyenes are being reported.

Less is known about resistance patterns in *Aspergillus* spp., likely because of a lack of national surveillance programs, routine susceptibility testing, and species identification. The reported prevalence of resistance to the mold-active azoles varies geographically but has been reported on average to be about 4% for *A. fumigatus*. Higher rates of resistance are found in some European and Asian countries, likely a result of increased agricultural use of azole fungicides in these areas. Some of the more rare species of *Aspergillus* (e.g., *A. terreus*, *A. flavus*) are intrinsically resistant to amphotericin B. Variable resistance to the echinocandins has been reported with these species. Resistance may develop to azoles during long-term therapy for the treatment of chronic or allergic forms of aspergillosis. Acquired resistance to amphotericin B and the echinocandins is rare, but this may be underreported because of a lack of susceptibility testing.

Resistance mechanisms found in fungal pathogens include the induction of efflux pumps and genetic mutations or increased expression of genes encoding these mechanisms. Biofilms are also an important cause of resistance in *Candida* spp. because of poor penetration of azoles into these complex cellular matrixes. *Aspergillus* spp. also form biofilms in the lung that contribute to the difficulty in treating these infections. The common mechanisms for each class of antifungal drug are listed in Table 1-4.

Much more evidence is required for a full understanding of antifungal resistance. The rates of infection from resistant species are increasing, and there are limited options available to treat these pathogens. To combat this growing problem will require improvements in AST that better correlate MIC values with clinical efficacy, as well as the discovery of molecular methods for detecting resistant mutations.

## EVIDENCE-BASED APPROACH TO INVASIVE CANDIDIASIS TREATMENT

Delays in initiating appropriate antifungal therapy negatively affect survival in critically ill patients with IFI. Several challenges exist in confirming a definitive diagnosis of these infections and in identifying high-risk patients. Therefore, a strategy to prevent these infections or preemptively treat them is warranted.

### Prophylactic Therapy

The 2009 Infectious Disease Society of America (IDSA) guidelines for the management of IC support a prophylactic approach to prevent disease in high-risk patients. In several single center studies and meta-analyses, the use of prophylactic fluconazole therapy in ICU patients reduced the incidence of *Candida* infections by about 50%; however, this strategy had questionable mortality benefit because of conflicting results and the heterogeneity of the populations studied.

**Table 1-4.** Common Antifungal Resistance Mechanisms

| Drug Class    | Site of Action  | Resistance Mechanism                      | Implications  |
|---------------|---|---|---|
| Azoles        | Inhibit lanosterol-14 $\alpha$ -demethylase<br>ERG11 <i>Candida</i><br>CYP51 <i>Aspergillus</i> | Up-regulation of efflux pumps             | Decrease drug entry into cell (all azoles)                                |
|               |   | ABC transporters/CDR1,CDR2 genes          | Decrease drug entry into cell (fluconazole)                               |
|               |   | TAC1 transcription factors                | Decrease binding affinity, increase MIC                                   |
|               |   | Up-regulation of efflux pumps             | Counteract drug effects   |
|               |   | MFS transporters/MDR1 gene                | Ergosterol replaced by another sterol (cross-resistance all azoles)       |
|               |   | MRR1 transcription factors                | Inhibit drug penetration  |
|               |   | ERG11 and CYP51 mutations                 | Increase tolerance to drug  |
|               |   | ERG11 and CYP51 overexpression            |   |
|               |   | ERG3 inactivation                         |   |
| Echinocandins | Inhibit Fksp catalytic subunit of (1,3)- $\beta$ -D-glucan synthase                             | FKS1 and FKS2 mutations                   | Alter catalytic capacity, increase MIC (cross-resistance to entire class) |
|               |   | Increase in cell wall chitin content      | Increase tolerance to drug, paradoxical growth                            |
|               |   |   | May correlate better with response to therapy than actual MIC             |
| Polyenes      | Bind ergosterol<br>Induce oxidative stress  | ERG2, ERG3, ERG5, ERG6, ERG11 mutations   | Decrease ergosterol biosynthesis  |
|               |   | Increase in anti-oxidative enzymes        | Decrease oxidative stress   |
|               |   | Alteration in production of free radicals |   |
|               |   |   |   |

ABC = ATP-binding cassette; MFS = major facilitator superfamily.

Information from Spampinato C. *Candida* infections, causes, targets, and resistance mechanisms: Traditional and alternative antifungal agents. *Biomed Res Int* 2013;204237; Cuenca-Estrella, M. Antifungal drug resistance mechanisms in pathogenic fungi: from bench to bedside. *Clin Microbiol Infect* 2014;20(suppl 6):54-9; and Maubon D. Resistance of *Candida* spp. to antifungal drugs in the ICU: where are we now? *Int Care Med* 2014;40:1241-55.

This approach would require administering antifungal therapy to hundreds of patients to prevent one infection. Administering prophylactic fluconazole therapy to a broad population of ICU patients has the potential to increase resistance and select fluconazole-resistant species, which may result in breakthrough infections. Prophylactic therapy might also mask poor infection control procedures, especially with central venous catheters and prolonged use of Foley catheters. This risk outside of the ICU has been clearly documented in patients with HIV (for esophageal candidiasis) and cancer, as well as in transplant recipients. Data supporting this concern in ICU patients have been inconclusive.

A recent retrospective study was performed in a surgical ICU in France, where 13% of the population received preemptive fluconazole therapy for high-grade *Candida* colonization. An evaluation of colonization trends over an 8-year period found a significant increase in acquired *C. glabrata* colonization and a decrease in *C. parapsilosis* colonization clearing; however, changes in susceptibility were not evaluated (Ferreira 2015). Current recommendations in the IDSA guidelines are to administer prophylactic fluconazole therapy

only to those patients with a 10% or higher risk of infection as determined by a risk prediction score.

Identifying high-risk patients who may benefit from prophylactic therapy remains a challenge. As previously mentioned, risk prediction scores tend to overestimate the number of patients who would benefit from this strategy. One particular at-risk group includes those recently undergoing intra-abdominal surgery with recurrent anastomotic leakages. Prophylactic antifungal therapy has been shown to reduce the incidence of intra-abdominal candidiasis in these patients.

A multi-center, randomized, double-blind, placebo-controlled study evaluated the use of caspofungin to prevent IC; a previously validated risk prediction tool (Ostrosky Rule Modified 2011) was used to identify patients at high risk of infection. There was a reduction in the rate of proven or probable infection with prophylactic caspofungin (n=102) versus placebo (n=84), (9.8% and 16.7% respectively, p=0.14), but this did not reach statistical significance (Ostrosky-Zeichner 2014). However, the study was likely underpowered based on the lower-than-expected rate of invasive disease found in the placebo arm.

Finally, only a few studies have evaluated the use of an echinocandin for prophylaxis; most of the data are with fluconazole. Until more data are available, the choice of drug for prophylactic therapy should depend on the epidemiology of *Candida* spp. at the institutional level.

### Empiric Therapy

An empiric therapy approach involves waiting until a patient displays signs and symptoms of infection before starting antimicrobials. This strategy avoids the widespread use of prophylactic therapy but may provide therapy too late in the course of disease. Furthermore, once empiric therapy is started it is difficult to determine when to stop therapy if a definitive diagnosis is not made on the basis of culture results. Delaying appropriate antifungal therapy has been associated with worse outcomes, but data indicating improved survival with early empiric therapy are lacking. Guidelines for empiric therapy for IC are available from the IDSA and are similar to the treatment recommendations discussed in the following section.

### Preemptive Therapy

Preemptive therapy may be a more promising approach to managing IFI, especially in ICU patients. This strategy involves using diagnostic markers to screen high-risk patients before or just as symptoms begin to develop. This screening limits the number of patients exposed to drug therapy but also catches patients earlier in the course of disease. As with prophylactic therapy, the problem lies in which patients to target. An unpublished study (INTENSE NCT01122368) comparing micafungin versus placebo for preemptive treatment in high-risk surgical patients with intra-abdominal infections failed to show a difference in the incidence of IFI, mortality, or any improvement of organ function. This study was likely underpowered because of a low incidence of infection in the placebo arm during the treatment period. Also, the abdominal penetration of echinocandins has recently been called into question.

A team looking at the rate of resistant *Candida* spp. in patients with abdominal candidiasis with recent echinocandin exposure found the abdomen to be a reservoir for the growth of resistant *Candida* spp. (Shields 2014). This study found FKS mutant *Candida* spp. in 24% of patients with an overall echinocandin failure rate of 52%, which may explain the lack of benefit with micafungin in the INTENSE study.

Given that new rapid diagnostic tests are more readily available, a preemptive approach to managing IC using fungal specific antigens and nucleic acids may be more effective. One study demonstrated the feasibility of using (1,3)- $\beta$ -D-glucan concentrations to guide preemptive therapy with anidulafungin (Hanson 2012). The prophylactic study mentioned earlier also evaluated the role of caspofungin in preventing IC using a preemptive approach (Ostrosky-Zeichner 2014). Subjects were screened twice weekly with

(1,3)- $\beta$ -D-glucan concentrations. Two consecutive concentrations of 80 pg/mL or greater were considered diagnostic for IC. Using this approach, the rate of proven or probable IC was significantly reduced in subjects receiving caspofungin versus placebo (18.8% vs. 30.4% respectively,  $p=0.04$ ). However, no significant differences in mortality or length of stay were observed. This calls into question the utility of using this biomarker, at a cutoff of 80 pg/mL, as a diagnostic tool; it also leads to consideration of whether a higher cutoff should be used for ICU patients.

The FUNGINOS study prospectively assessed the utility of the  $\beta$ -D-glucan diagnostic test versus other diagnostic tests in diagnosing intra-abdominal candidiasis in high-risk surgical patients. In patients with GI perforation, two consecutive  $\beta$ -D-glucan diagnostic tests greater than 80 pg/mL were superior to the *Candida* Score and Colonization Indexes in discriminating candidiasis from colonization with a 72% positive predictive value and 80% negative predictive value. Elevated  $\beta$ -D-glucan levels preceded positive cultures and antibiotic therapy by a median of 5 and 6 days, respectively. Levels above 400 pg/mL predicted both severity of infection and worse outcome, and decreasing levels were seen in those responding to therapy (Tissot 2013). This study demonstrates the usefulness of the  $\beta$ -D-glucan diagnostic test in guiding preemptive therapy in a disease that is commonly culture negative.

Many challenges exist in identifying appropriate patients who would benefit from antifungal therapy in the absence of definitive cultures. One approach to preemptive and empiric therapy using non-culture based diagnostic tests can be found in Figure 1-1. Further information is needed on the role of using (1,3)- $\beta$ -D-glucan or other rapid diagnostics in initiating preemptive antifungal therapy in ICU patients, particularly to determine which patients to target and what cutoff values should be used in ICU patients to confirm diagnosis.

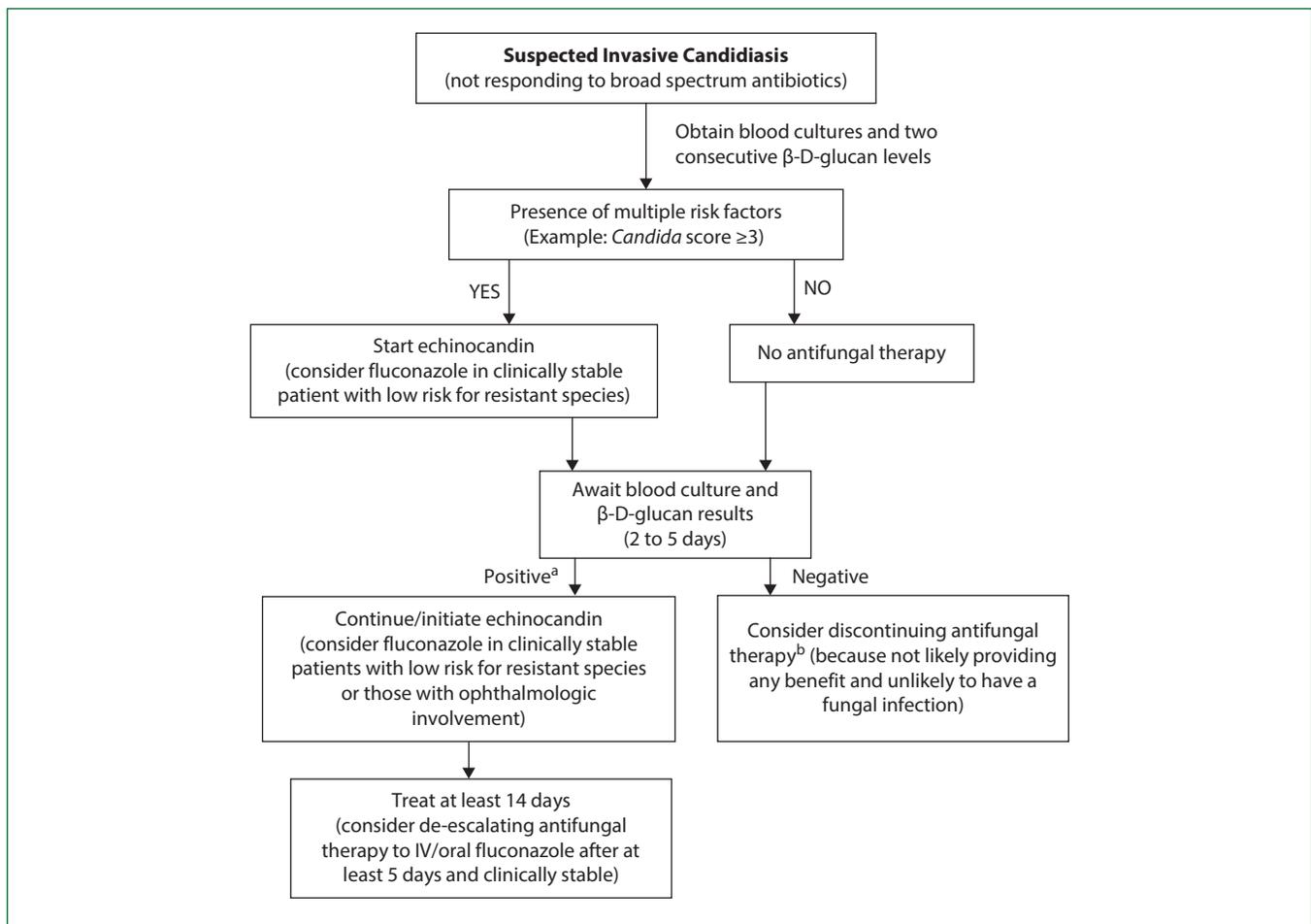
The EMPIRICUS trial (NCT01773876) aims to evaluate the efficacy of micafungin in improving IC-free survival in high-risk ICU patients with septic shock, multi-organ failure, and *Candida* colonization. This trial will also be looking at trends in serum biomarkers. The study is completed and once published, results and post hoc analysis of this study should help further delineate the role of both empiric and preemptive therapy.

## TREATMENT STRATEGIES FOR PATIENTS WITH INVASIVE FUNGAL DISEASE

### *Candida* Infections

#### *Candidemia*

The 2009 IDSA treatment guidelines for the management of IC (to be revised in the near future) recommend initial treatment with an echinocandin for moderately to severely



**Figure 1-1.** General approach to preemptive/empiric antifungal therapy.

<sup>a</sup>Positive β-D-glucan diagnostic test result is two consecutive tests > 80 pg/mL.

<sup>b</sup>If clinically improving on antifungal therapy, then consider a short course of therapy for no more than 7 days.

Information from: Blot S, Charles PE. Fungal sepsis in the ICU: are we doing better? Trends in incidence, diagnosis, and outcome. *Minerva Anestesiologica* 2013;79:1396-405.

ill patients with candidemia and patients already receiving azole prophylaxis. The 2012 European guidelines strongly recommend an echinocandin as first-line treatment for all patients.

All the echinocandins have proven efficacy for the treatment of candidemia and are considered interchangeable for the management of this disease. One exception is in neutropenic patients, for whom caspofungin may be preferred for empiric therapy because of a lack of data with the other agents. Support for this class as first-line agents comes from the shift in epidemiology towards non-*albicans* spp. and low levels of resistance seen. Anidulafungin is superior to fluconazole for the treatment of candidemia caused by *C. albicans* and in patients with a high severity of illness. A meta-analysis of randomized trials evaluating antifungal therapy for the management of IC/candidemia indicated a survival benefit

in subjects receiving echinocandin therapy versus those on polyenes or azoles (Andes 2009).

Fluconazole therapy can be considered for patients with mild disease in institutions with a low incidence of non-*albicans* spp. and fluconazole resistance. Voriconazole is also effective for candidemia, but adverse effects, drug-interactions, cost, and the potential for cross-resistance to fluconazole limit its use. Another role for fluconazole therapy is in the setting of ocular involvement of infection. Echinocandins have poor eye penetration; therefore an azole, if susceptible, would be preferred.

Treatment of candidemia should continue for at least 14 days after the first negative blood culture, but longer courses may be needed in the presence of abscesses or deep-tissue infections. The question of when to de-escalate to oral fluconazole therapy, if susceptible, is much debated.

The IDSA guidelines recommend at least 5 days of echinocandin therapy, but the European guidelines recommend 10 days based on recent data indicating a potential superiority over fluconazole. An open-label, non-comparative trial looked at the efficacy and safety of step-down therapy to an oral azole after 5 days of anidulafungin in patients who were afebrile, were hemodynamically stable, were non-neutropenic, had documented clearance of *Candida* from the bloodstream, and were able to tolerate oral therapy. This strategy resulted in a global response rate of 83.7% and was well tolerated (Vazquez 2014). Therefore, step-down to oral therapy is reasonable, taking into consideration the clinical condition and stability of the patient as well as source control when determining time course for de-escalation.

Determining and addressing the source of candidemia can be challenging in critically ill patients. The IDSA guidelines recommend that all patients with candidemia receive a dilated funduscopic examination within the first week of diagnosis to rule out optic involvement. Intravenous catheters are often the source; therefore, catheter removal should be considered. Symptoms should resolve within 72 hours, so the persistence of symptoms beyond this point should give reason to consider inadequate source control versus suboptimal drug exposure or resistance.

### **Intra-Abdominal Infections**

As previously mentioned, patients undergoing intra-abdominal surgery are at increased risk of IC. About 30%–40% of patients with secondary or tertiary peritonitis will have *Candida* peritonitis or abscesses. There is a paucity of data related to the management of these infections, and standardized definitions and diagnostic criteria do not exist.

A recent multinational expert panel developed practice recommendations for the management of intra-abdominal candidiasis in immunocompetent patients (Bassetti 2013). Patients with suspected infections should have a culture taken during surgery or shortly after (less than 24 hours) a percutaneous drain is placed. Empiric therapy can be considered in patients with intra-abdominal infections and the presence of either risk factors or positive serologic markers for *Candida*. Definitive antifungal therapy is only recommended if *Candida* is recovered from an adequate specimen. Positive *Candida* cultures taken from drains placed more than 24 hours ago should be considered contamination and not be treated. Therapy with an echinocandin or lipid-based amphotericin B is preferred. Azole therapy, similar to treatment of candidemia, can be considered for mild disease or step-down therapy. Treatment should continue for 10–14 days in those with confirmed infection. Empiric therapy should be discontinued if *Candida* is not found after 3–5 days and the patient improves; or immediately if no improvement is seen, because the likelihood of any benefit is minimal. As mentioned previously,  $\beta$ -D-glucan levels may be useful in guiding treatment in this typically culture-negative disease

by both helping to decipher true infection from colonization and assessing response to therapy.

### **Urinary Tract Infections**

Isolation of *Candida* from the urinary tract of critically ill patients is common. The decision to treat is complicated by the inability to determine if classic signs and symptoms of infection are present. Most patients can simply be managed by removing the Foley catheter. Treatment with antifungal therapy should be considered in patients with sepsis of unknown origin; those with neutropenia; or those undergoing urologic procedures, because of the high risk for systemic disease.

Choice of antifungal agent is limited by poor penetration of most antifungals into the urine. Fluconazole remains the drug of choice, and treatment should continue for 14 days. Amphotericin B bladder washes are difficult to administer, and data supporting their efficacy are lacking. In one report, the procedure was associated with only transient clearance and higher overall mortality (Jacobs 1996).

### **Lung Infections**

Although isolation of *Candida* spp. from the respiratory tract of critically ill patients is common, the occurrence of true pneumonia from this organism is rare because of innate mechanisms of defense within the lung. Diagnosis is challenging because of a lack of specific signs, symptoms, and radiographic findings; and because this requires lung biopsy. The decision to treat should be based on evidence of disseminated disease or host factors suggesting a high risk of infection with no other source. Specific host factors include neutropenia, hematopoietic stem cell transplant, immunosuppressing therapies, corticosteroids, and severe immunodeficiency. All of the available antifungal agents penetrate the lung well and are reasonable options. Empiric therapy with voriconazole may be preferred because aspergillosis is also a potential cause of lung infections in these patient populations.

### **Invasive Mold Infections**

#### **Prophylaxis and Empiric Treatment**

Recommendations for the management of invasive mold infections in critically ill patients are largely extrapolated from data evaluating treatment in hematologic malignancies. Amphotericin B and its lipid formulations remain the most broad-spectrum antifungals available and should be strongly considered for empiric therapy in the setting of an unidentified mold infection or in patients on previous azole therapy. Voriconazole is now recommended as first-line therapy for *Aspergillus* infections. This recommendation is based on data indicating more successful outcomes and improved survival compared with amphotericin B, while causing less adverse effects.

The echinocandins have been shown to have activity against *Aspergillus*. Only caspofungin is approved for this indication, but all three agents have been used clinically.

Echinocandins are usually reserved for patients intolerant of other therapies or in refractory disease. However, more recent data regarding the combination of voriconazole and anidulafungin for treatment of IA suggest an earlier role for combination therapy including the echinocandins in patients with presumed IA.

Prophylactic therapy in non-neutropenic, immunocompetent patients cannot be recommended based on insufficient data. Empiric therapy should begin, even in those without traditional risk factors, at the earliest signs or clinical suspicion for IA. This approach is appropriate because delays in appropriate therapy for IA have been shown to increase length of stay, health care costs, and mortality. The use of biomarkers, mentioned earlier, may help identify patients that may benefit from antifungal therapy earlier. The optimal duration of treatment has not been determined. Most patients will require a prolonged course of several weeks based on resolution of clinical symptoms and radiographic findings.

### **Combination Therapy**

Combination antifungal therapy for IA is recommended as an option for salvage therapy in patients not responding or with breakthrough symptoms. Up to 30% of ICU patients have been reported to have refractory disease, and observational studies have indicated up to 50% of patients often receive combination therapy. Typical combination regimens involve using two agents with different mechanisms of action, such as an echinocandin (cell wall target) with either an azole or amphotericin (cell membrane target). Because of the potential for antagonism, combination therapy with an azole and amphotericin is not recommended.

Despite the frequent use of combination therapy in the ICU for refractory IA, very few data exist supporting its benefit. Most data are derived from retrospective cohorts with very small sample sizes that reported conflicting outcomes. A prospective, randomized trial comparing the combination of voriconazole and anidulafungin with voriconazole alone demonstrated a trend towards reduced mortality in hematologic malignancy/hematopoietic stem cell transplant patients with combination therapy (Marr 2015). A post hoc subgroup analysis from this study indicated the greatest difference in mortality seen with combination therapy was in patients with baseline galactomannan optical density values of 0.5 to 1.5 and those treated with combination early in the course of disease.

## **ANTIFUNGAL PHARMACOTHERAPY**

### **Amphotericin B**

Amphotericin B, despite its toxicities, still remains an important treatment option for fungal infections in the critically ill. This agent has broad fungicidal activity against most fungal pathogens infecting patients in the ICU and is particularly useful for severe infections in patients with immunocompromise,

with CNS infections, or when alternative options are limited by resistance, toxicities, or drug interactions.

Amphotericin B deoxycholate was the gold standard formulation until the 1990s, when three liposomal-based products (i.e., amphotericin B lipid complex, liposomal amphotericin B, and amphotericin B colloidal dispersion) were marketed. These newer formulations have similar efficacy but significantly less nephrotoxicity than the parent compound. The liposomal product is reported to have less nephrotoxicity than the other two lipid formulations; however, this finding does not appear to be clinically significant. Nephrotoxicity can be reduced with all amphotericin B products by adequately hydrating and sodium loading with a normal saline bolus (250–500 mL) before each dose and by avoiding concomitant nephrotoxic drugs, particularly diuretics. Continuous infusions of amphotericin B may prevent nephrotoxicity but should be avoided because the concentration-dependent pharmacodynamics of amphotericin B would not be optimized.

Lipid amphotericin products, with the exception of amphotericin B colloidal dispersion, have an approximate 50% lower rate of infusion-related reactions than the deoxycholate product. Because of the high rate of infusion reactions, the use of the colloidal dispersion product has fallen out of favor. Infusion-related reactions can be minimized with the use of acetaminophen and diphenhydramine 30 minutes before the infusion and should be considered standard of care. Another rare reaction reported with the liposomal product manifests with hypoxia, chest pain, flushing, and possibly flank pain and urticaria. These symptoms often mimic respiratory failure or an acute myocardial infarction. Clinicians should be aware of this reaction to minimize unnecessary escalation of care.

Electrolyte disorders commonly occur in critically ill patients. Amphotericin B therapy is nearly always associated with hypokalemia and hypomagnesemia. Just as amphotericin B binds to the fungal cell wall of ergosterol, thereby altering permeability, drug-tissue binding also can occur in mammalian renal cells and cause loss of potassium. Furthermore, hypomagnesemia can worsen potassium homeostasis. Close monitoring and repletion as necessary are recommended.

### **Echinocandins**

In 2001, the first of the three available echinocandins was approved by the FDA and changed the way disseminated fungal infections are managed. These agents have a unique mechanism of action specific to the fungal cell wall. They provide fungicidal activity against *Candida* species and fungistatic activity against mold, as well as activity against biofilms. They are all equally efficacious and have minimal toxicity and drug interactions; therefore, choice of agent depends on institutional preference, cost, and the approved indications.

Adverse effects associated with the echinocandins are relatively benign, with rare reports of liver toxicity and infusion

reactions being of most concern. The infusion reaction reported with this class of antifungals is histamine-mediated and can be compared with the red man syndrome seen with vancomycin. Slowing down the infusion rate will prevent the reaction from recurring, and it typically subsides once the infusion is completed.

The echinocandins do not have any significant activity on CYP hepatic enzymes; therefore, drug interactions are minimal. Caspofungin and micafungin are reported to increase cyclosporine and tacrolimus serum concentrations. Because this drug interaction is minor, empiric dose reductions are not necessary; monitoring of serum concentrations is recommended.

### Extended-Spectrum Triazoles

Voriconazole and posaconazole offer enhanced activity against *Candida* and other yeast, as well as a variety of mold pathogens. The addition of these agents expanded the treatment options for management of invasive fungal disease, including providing an oral treatment option. Despite their proven efficacy, several factors make the use of these drugs in the ICU a challenge.

Oral absorption of these agents can be significantly reduced depending on how they are administered. Voriconazole requires administration on an empty stomach because food can decrease absorption by 20%. It is recommended to hold tube feedings 1 hour before and 1 hour after administration. Posaconazole suspension, in contrast, should be given with a high-fat meal. In situations in which this approach is not possible, administering a high-fat nutritional supplement or administering posaconazole as 200 mg every 6 hours can provide similar plasma concentrations as giving 400 mg every 12 hours with a high-fat meal.

Gastric acid improves absorption of posaconazole; this can be optimized by administering it with ginger ale. Gastric acid suppression therapy is a concern in patients also receiving posaconazole suspension. Proton pump inhibitors should be avoided. H<sub>2</sub>-antagonists may also reduce exposure but likely to a lesser degree. Most bioavailability data with H<sub>2</sub>-antagonists indicating reduced absorption are with cimetidine; therefore, cimetidine should not be used concomitantly with posaconazole. Alternative agents such as famotidine and ranitidine have conflicting data, but these agents are preferred over a proton pump inhibitor. Posaconazole delayed-release tablets improve absorption, but this approach is not an option for most ICU patients because the tablets cannot be given in a nasogastric tube. Patients already taking these tablets must be switched to the suspension; however, plasma concentrations of the suspension will be reduced when given through a nasogastric tube. Recommendations for dose adjustments do not exist; therefore, close monitoring of clinical effect or therapeutic drug monitoring (TDM) may be necessary. An intravenous formulation of posaconazole was recently approved that

will likely be a better option for ICU patients requiring this antifungal. It requires only a once-daily dose after the initial loading dose, but it will require a central line and has a short stability.

Voriconazole and posaconazole, like all azoles, can cause hepatotoxicity, adrenal suppression, and QT prolongation. In addition, voriconazole has been known to cause significant visual disturbances as well as a theoretical risk of renal toxicity with the intravenous formulation. Visual disturbances occur with oral and intravenous therapy and are usually transient, with patients adjusting to them after 1–2 weeks of therapy. These vision issues are typically related to the initiation and temporal administration of the drug and have been described as bright flashing lights or hallucinations.

The intravenous formulation of voriconazole contains a second-generation cyclodextrin-solubilizing agent. First-generation cyclodextrins have been shown to cause renal toxicity and can accumulate in renal failure. It is therefore recommended to use oral voriconazole when possible in patients with CrCl less than 50 mL/min. Multiple studies addressing the risk of nephrotoxicity with intravenous voriconazole have failed to show a correlation, and recent safety data with second-generation cyclodextrins show poor penetration into renal tubular cells and no risk of toxicity. In addition, hemodialysis appears to remove cyclodextrin to a considerable extent. Based on this information and experience from pre-marketing trials, it is reasonable to use intravenous voriconazole in patients with reduced renal function when the benefit exceeds this theoretical risk.

All azole antifungals inhibit CYP hepatic enzymes, with voriconazole and posaconazole being strong inhibitors of CYP3A4. This inhibition may lead to significant increases in cyclosporine, tacrolimus, and sirolimus serum concentrations. The interaction with sirolimus is of particular concern because the increases in drug exposure are completely unpredictable. Concurrent administration of sirolimus with these newer azoles requires frequent concentration monitoring if the combination cannot be avoided. Additional clinically relevant drug interactions that may occur in critically ill patients receiving voriconazole or posaconazole include increased exposure to fentanyl, midazolam, phenytoin, corticosteroids, quetiapine, and warfarin.

Voriconazole is a substrate and moderate inhibitor of CYP2C19. Voriconazole should be used with caution in combination with strong inhibitors or inducers of CYP2C19, such as rifampin, and with drugs metabolized by CYP2C19, such as clopidogrel. This route of metabolism combined with non-linear pharmacokinetics can make voriconazole dose adjustments challenging in the setting of a complicated critical care regimen.

Lastly, because of the risks of QT prolongation, administration of azoles with other moderate to strong QT-prolonging drugs should be monitored closely or avoided.

## Dose Considerations

Inadequate doses of antimicrobials are common in the ICU because of the pharmacokinetic-pharmacodynamic changes that occur in critically ill patients (e.g., increased volume of distribution, enhanced elimination). This inadequacy may lead to treatment failure, increased resistance, and worsened outcomes. Fluconazole is often under-dosed when loading doses are not given and when fixed (400-mg) versus weight-based (6-mg/kg) doses are used to treat IFI.

A single-center retrospective cohort study found inadequate doses of fluconazole were used in 16% of patients (n=356) and was an independent determinant of mortality (Labelle 2008). The DALI study, a multi-center point-prevalence study looking at pharmacokinetic-pharmacodynamic target attainment of fluconazole in critically patients, found that 33% of fluconazole patients (n=15) did not achieve the desired AUC/MIC ratio of 100 or greater. This study also found the median dose needed to achieve this goal was 5 mg/kg (Sinnollareddy 2015).

Obesity is another factor altering the pharmacokinetics of antifungal agents. Obese patients tend to have alterations in volume of distribution. Fat mass, as well as lean body mass are increased in obese patients, whereas blood flow to adipose tissue is reduced. These patients also can have reduced hepatic blood flow and metabolism caused by fatty liver infiltration. Specifically, CYP3A4 metabolism has been shown to be reduced in obese patients. Renal clearance tends to increase as lean body mass increases; therefore, obese patients tend to have enhanced renal clearance of drugs. Only a few studies have specifically investigated antifungal agent pharmacokinetics in obese patients. The general consensus is that amphotericin products do not distribute into adipose tissue and should be dosed based on lean body weight; fluconazole should be dosed on total body weight at the higher end of the dose range; voriconazole and posaconazole should be dosed on lean body weight; and dose increases of 20%–50% should be considered for the echinocandins.

## Therapies on the Horizon

The introduction of extended-spectrum azoles and the echinocandins have significantly improved the treatment options for IFIs. Despite these advances, only three unique classes of antifungal agents are currently available. All have considerable limitations, toxicities, and drug interactions. Furthermore, clinical outcomes in patients with fungal infections remain poor, and resistance to current therapies is increasing. As rates of fungal infections are mounting with the increased use of immunosuppressing therapies, new agents with unique or synergistic mechanisms of action are needed. Unfortunately, several challenges exist in finding new drug targets specific to fungal pathogens, as well as discovering new assays that are better at detecting growth inhibition and activity against fungal biofilms. With only a few new drugs close to being marketed, antifungal drug

development may not keep up with clinical demands for these agents.

In March 2015, the FDA approved isavuconazonium sulfate, an azole antifungal, for the treatment of adult patients with IA and mucormycosis. Isavuconazonium is a prodrug that is rapidly hydrolyzed to isavuconazole, the active drug that offers the advantage of once-daily dosing. The efficacy of isavuconazonium has been shown in clinical trials to be noninferior to voriconazole in the treatment of IA. It was also shown to be effective in noncomparative trials for the treatment of primary mucormycosis or mucor infections refractory or intolerant to other agents. Limitations to the mucor data include a small number of patients analyzed with no comparison group, as well as finding the MICs for some common Mucorales may surpass plasma levels achieved with currently recommended dosing.

It is unknown how isavuconazole compares with either amphotericin B or posaconazole for the treatment of mucormycosis, but mortality rates appeared to be similar based on retrospective comparisons to posaconazole salvage studies and case-control studies with amphotericin B. The spectrum of activity also includes *Candida* spp. such as *C. glabrata* (including fluconazole-resistant strains) and *C. krusei*, as well as *Cryptococcus*, *Histoplasmosis*, *Blastomycoses*, and *Coccidioides*. Isavuconazole is available in an intravenous formulation that does not contain the cyclodextrin excipient, although it does require an in-line filter. An oral formulation is also available, but these capsules cannot be opened and administered via a nasogastric tube.

Like other azoles, isavuconazole is a substrate of CYP3A and a moderate inhibitor of CYP3A4. Reported drug-drug interactions appear less significant with isavuconazole than with other azoles, although the data were obtained using doses lower than currently recommended. Further investigations as well as clinical experience are awaited and caution should be used when co-administering with drugs known to interact via CYP3A. Therefore, close TDM of concomitant cyclosporine, tacrolimus, and sirolimus is warranted, but empiric dose adjustments are not currently recommended. Administration of isavuconazonium with strong CYP3A inhibitors and inducers is contraindicated.

Compared with voriconazole, isavuconazole appears to be better tolerated with a lower incidence of visual disturbances and hepatotoxicity. Adverse effects are mostly GI (nausea, vomiting, diarrhea, constipation), but hypokalemia, liver toxicity, shortened QT interval, and infusion reactions have been seen in clinical trials. The long half-life of this drug may make managing drug interactions and adverse effects challenging because of the prolonged toxicities and delays in starting therapy until the drug has been fully eliminated.

An additional drug that inhibits  $\beta$ -(1,3)-glucan synthase under development is bialfungin (CD101), a novel long-acting echinocandin. This agent is being developed for the prevention and treatment of candidiasis including infections caused

by resistant species. Its long half-life may allow for a once-weekly dose that could prevent the need to switch agents and also allow for earlier discharge.

Several antifungal agents are currently in development that target specific components of the fungal cell wall such as  $\beta$ -(1,6)-glucan synthase and glycosylphosphatidylinositol-linked protein acyltransferase, as well as leucyl tRNA synthetase and poly(A) polymerase. However, because of the slow pace of drug development, these agents are not likely to be soon available.

## CONCENTRATION MONITORING

The use of TDM to guide antifungal therapy is becoming increasingly common. Although routine monitoring is not recommended for all patients, there are several circumstances in which TDM may be useful in the critically ill (Box 1-2). The challenges with concentration monitoring include differences in available assays in terms of sensitivity and specificity, increased expenses, long turnaround times, and the difficulty in determining the effect on clinical outcomes. It is important to remember the recommended therapeutic ranges are based on small numbers of patients often stemming from populations that may not be similar to the individual patient in the ICU. Therefore, knowing the MIC of the organism, using clinical judgment, and adequately monitoring clinical response to therapy must be used in conjunction with serum drug concentration data. Concentration monitoring should not take precedence over changing antifungal agents in someone who is clearly being failed by therapy.

Antifungal concentration monitoring is mainly limited to the triazoles that cover mold pathogens (i.e., itraconazole, voriconazole, and posaconazole) and flucytosine. The goal trough concentrations, timing of serum sampling, and recommendations for dose adjustments for these agents are listed

### Box 1-2. When to Consider Concentration Monitoring

- Age extremes
- Compliance questionable
- Concomitant use with acid suppressing therapy
- Drug interactions, significant
- Extensive, bulky, or disseminated infection (e.g., CNS, mediastinal)
- Malabsorption
- Obesity
- Organ dysfunction
- Prophylaxis in high-risk patients
- Renal replacement therapy
- Use of extracorporeal membrane oxygenation or cardiopulmonary bypass

Information from Ashbee HR. Therapeutic drug monitoring of antifungal agents: guidelines from the British Society of Medical Mycology. *J Antimicrob Chemother* 2014;69:1162-76.

in Table 1-5. There is no role in monitoring concentrations of amphotericin B (despite its toxicities) or the echinocandins. Fluconazole concentration monitoring is also not typically recommended; however, it may be considered when the MIC of the pathogen is increased, when treating CNS disease, or in patients requiring renal replacement therapy. Recommendations for isavuconazole TDM have not been clearly defined. It has excellent oral bioavailability, linear kinetics, and very little intersubject variability in concentrations; therefore, TDM is not likely to be necessary.

Itraconazole displays non-linear pharmacokinetics with significant variability in oral absorption because of formulation differences (30% higher AUC with the oral solution vs. capsules), food, and gastric pH. Therefore, TDM can be recommended for most patients receiving this antifungal to ensure adequate absorption is achieved. The strongest evidence to support TDM of itraconazole comes from studies looking at exposure-response relationships in the prevention of fungal disease in patients with immunocompromise. The recommendations for therapeutic treatment concentrations are mostly extrapolated from these data, making it difficult to interpret. The guidelines from the British Society of Medical Mycology (BSMM) recommend a concentration greater than 0.5 mg/L for both prophylaxis and treatment; however, the limited evidence available indicates a target trough concentration of at least 1 mg/L for treatment regimens may be preferred.

Voriconazole also exhibits non-linear pharmacokinetic variability in adult patients, mainly because of saturable hepatic metabolism and genetic polymorphisms of the CYP2C19 hepatic enzyme. Evidence also suggests that the FDA-approved fixed non-weight-based oral doses of voriconazole may be inadequate to achieve effective serum concentrations. This issue is of particular concern in obese patients and those with active disease, for whom the maximal recommended dose may need to be exceeded. Children have linear nonsaturable pharmacokinetics with voriconazole (requiring much higher weight-based doses) as well as lower oral bioavailability.

There is a clear exposure-response relationship demonstrated with voriconazole in both pre-clinical and clinical trials. Therefore, TDM can be considered in patients at high risk for genetic polymorphism (i.e., those of Asian descent), those receiving drugs known to alter voriconazole metabolism, those transitioning to oral therapy, and in pediatric patients. Again, the BSMM recommends similar target trough concentrations for both treatment and prophylaxis because most of the literature exploring exposure-response relationships comes from treatment doses. However, there is limited evidence to suggest a target trough of 0.5 mg/L in the prophylaxis of fungal infections is adequate.

Because of the transient nature of the visual disturbances associated with voriconazole and the rare reports of neurologic and liver toxicity seen with typical doses, TDM for the

**Table 1-5.** Recommendations for Therapeutic Drug Monitoring

| Drug                      | Minimum Target Concentrations <sup>a</sup>       | Timing of Concentration <sup>b</sup> | Concentrations Associated with Toxicity | Strategies to Increase Low Concentrations  |
|---------------------------|--|--------------------------------------|---|--|
| Itraconazole              | P: 0.5 mg/L<br>T: 0.6–1 mg/L                     | 7–14 days                            | > 17 mg/L <sup>c</sup>                  | Change to solution<br>Avoid acid suppressants with capsules<br>Take solution in fasting state<br>Increase dose from 200 mg twice daily to 300 mg twice daily   |
| Voriconazole              | P: > 1 mg/L<br>T: > 1 mg/L<br>Trough: MIC of 2–5 | Within 7 days <sup>d</sup>           | > 5.5 mg/L                              | Increase dose:<br>IV: up to 6 mg/kg twice daily<br>PO: up to 300 mg twice daily  |
| Posaconazole <sup>e</sup> | P: 0.35 mg/L<br>P: > 0.7 mg/L<br>T: > 1 mg/L     | At 48 hours<br>Within 7 days         | Unknown                                 | Increase total daily dose to 800 mg<br>Administer total daily dose divided four times daily<br>Switch to the delayed-release tablets<br>Avoid acid suppressants<br>Take with food or high-fat supplement |
| Flucytosine               | T: Peak 20–40 mg/L                               | Within 72 hours                      | Peak >100 mg/L                          | Increase dose by 50%, use caution due to toxicity  |

<sup>a</sup>Trough concentrations measured using high performance liquid chromatography (HPLC)/mass spectrometry unless otherwise specified.

<sup>b</sup>Time listed is the number of days after the initiation of therapy.

<sup>c</sup>Concentration measured with bioassay, would expect 5-fold lower concentration with HPLC/mass spectrometry.

<sup>d</sup>Repeat level may be necessary because of fluctuations in concentrations due to Michaelis-Menten kinetics.

<sup>e</sup>Recommendations are for oral solution only.

IV = intravenous; P = prophylaxis; PO = oral; T = treatment.

Information from Ashbee HR. Therapeutic drug monitoring of antifungal agents: guidelines from the British Society of Medical Mycology. *J Antimicrob Chemother* 2014;69:1162-76.

sole reason of minimizing toxicity cannot be recommended. It can be considered in patients demonstrating signs of toxicity, especially if multiple reasons for this toxicity exist (to rule out a drug effect) or in patients receiving doses higher than recommended by the manufacturer. In patients not displaying signs of toxicity with trough concentrations greater than 5 mg/L, dose reductions may not be necessary but should be assessed case-by-case considering the status of the underlying infection.

Posaconazole TDM is recommended in most patients receiving the suspension because of poor bioavailability from saturable absorption and reduced absorption in the setting of mucositis, graft-versus-host disease, the concomitant administration with acid-suppressing therapies, or administration without a high-fat meal. Concentrations have been found to be suboptimal in 50% of patients receiving posaconazole suspension for fungal prophylaxis. Target trough concentrations in prophylactic studies have varied from 0.5 to 0.7 mg/L, but have all consistently shown a trend towards a better likelihood of response with increased drug exposure. Similar trends for

a better response with increased drug exposure have been seen in studies for the treatment of aspergillosis. The MIC breakpoints recently set for posaconazole susceptibility to *Aspergillus* spp. are only considered valid if target serum concentrations have been achieved. Most studies indicate adequate exposure of posaconazole from the delayed-release tablets and the intravenous formulation; therefore, routine TDM with these preparations is not recommended at this time unless toxicity, treatment failure, or breakthrough infection is suspected.

Flucytosine is a pyrimidine analog commonly used with amphotericin B to treat cryptococcal meningitis. Implications for TDM include its toxicity profile, significant intra- and inter-patient pharmacokinetic variability, dependence on renal elimination where nephrotoxicity is common, and its risk of developing resistance. Evidence from pharmacodynamics studies indicates a strong exposure-toxicity relationship with a higher incidence of bone marrow suppression and hepatotoxicity seen at peak concentrations exceeding 100 mg/L. Although historically flucytosine

dosing has targeted a peak concentration to limit toxicity, the correlation between flucytosine serum concentration and efficacy is less clear, and even lower targets may be adequate. Maintaining concentrations above the MIC for at least 50% of the interval has been associated with improved clinical outcomes in the treatment of *Candida* infections and may prevent the emergence of resistance. Unfortunately, even less is known about target concentrations for cryptococcal disease or in combination with amphotericin B, where flucytosine is more commonly used. It is recommended that peak concentrations be performed to prevent toxicity and minimize the risk of resistance.

For all antifungal agents, it is important to know what assay was used to determine drug concentrations. Bioassay is still commonly employed in some commercial laboratories and can overestimate drug exposure, particularly when combination antifungal therapy is used. Interpretation should also take into consideration past use of agents with long terminal half-lives. For example, if bioassay is being used to ensure adequate concentrations of an oral agent, activity from a previously discontinued amphotericin B product may

be contributing to antifungal activity, resulting in false security in the azole concentration.

Adjusting doses for sub- or supra-therapeutic concentrations should be done with caution. For recommendations on increasing doses for sub-therapeutic concentrations after assessing for compliance and drug interactions, see Table 1-5. Guidance on how to adjust for supra-therapeutic concentrations is less clear and cannot always be recommended unless signs of toxicity are present. One exception to this approach is with flucytosine, because toxicity is more common and the exposure-toxicity relationship is clear. Another case may be with voriconazole, for which it is recommended to decrease the dose by 50%, but, because of Michaelis-Menten kinetics, smaller adjustments may be necessary.

## ANTIFUNGAL STEWARDSHIP

Pharmacists are recognized as key members of antimicrobial stewardship teams and have an important role in optimizing antifungal use in the ICU. Recent advances in diagnostic tools, susceptibility testing, and newly approved

### Patient Care Scenario

A 67-year-old white man with acute myeloid leukemia after bone marrow transplant is on high-flow oxygen in the medical ICU and receiving voriconazole 4 mg/kg intravenous twice daily for pulmonary *Aspergillus*. His oxygenation has not been improving, so the ICU team ordered a voriconazole concentration.

|                                   |          |
|-----------------------------------|----------|
| Day of therapy                    | 5        |
| Voriconazole trough concentration | 1.2 mg/L |

### ANSWER

According to the guidelines from the British Society of Medical Mycology, a voriconazole trough concentration more than 1 mg/L taken within 7 days of treatment is considered an adequate serum concentration for treatment of invasive fungal infections. Therefore, this level taken on day 5 of therapy should be representative of a therapeutic steady state concentration. However, because of the non-linear pharmacokinetics and lack of data strongly correlating drug concentration and clinical outcome, it is important to interpret this level also based on the clinical picture of the patient. The reasons for this patient to have concentrations on the lower side of therapeutic include

The ICU team asks for recommendations on how to interpret this concentration and adjust his voriconazole dose. At this time the patient's clinical condition has not improved and he is close to needing intubation. He is not displaying any signs of voriconazole toxicity.

a genetic polymorphism of CYP-2C19 and his history of bone marrow transplant (this population tends to have lower concentrations than healthy volunteers). There is evidence to suggest that trough concentrations less than 2 mg/L may be associated with clinical failure in patients with invasive aspergillosis. Therefore it would be reasonable to increase the dosage to 6 mg/kg intravenous twice daily and monitor for signs of toxicity. It would also be reasonable to repeat another trough concentration in 5 to 7 days because of the non-linear kinetics. If the clinical picture worsens significantly, it may be time to consider alternate or combination therapy for this patient.

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agents highlight the complexity in managing IFIs and the need for a medical team member with expertise in antifungal agents be involved. The ICU pharmacist is the most qualified member of the health care team to optimize antifungal therapy by identifying appropriate patients in need of antifungals, by ensuring appropriate choice and dose of drug based on susceptibilities and TDM, by identifying drug interactions and adverse effects, and by helping to develop guidelines focused on minimizing overuse to prevent resistance and reduce health care costs.

## CONCLUSION

Fungal infections are associated with considerable morbidity and mortality in ICU patients even when appropriately treated. Delays in therapy can negatively impact outcomes and increase health-care costs. Several challenges exist in identifying patients at risk of these infections and in achieving an accurate diagnosis. Furthermore, antifungal pharmacotherapy has become very complex with the introduction of new

### Practice Points

When considering empiric and definitive antifungal therapy in the critically ill, several factors should be taken into consideration:

- What is the overall risk of invasive fungal disease?
  - Clinical prediction scores can be used to help rule out infection.
  - Clinical prediction scores can be used in addition to the clinical status of the patient, cultures, and other diagnostic tests to help rule in the likelihood of infection.
- Should a rapid diagnostic test be sent?
  - This approach is based on the availability and turnaround time of the test as well as the presence of any factors that may lead to a false-positive or –negative result.
  - If the test result is negative, then it could be useful to help discontinue unnecessary antifungals.
- Are positive cultures true infection versus colonization?
  - *Candida* in the blood is usually reflective of true infection, whereas *Candida* in the sputum or urine is most likely contamination.
- What are the common pathogens and susceptibilities seen at your institution?
  - Choice of drug will depend on the prevalence of non-*albicans* or fluconazole resistant species.
- What patient specific factors exist that may influence choice of drug?
  - Consideration of these factors is needed: drug interactions, organ dysfunction, severity of illness, source/eye involvement, oral route/diet, obesity, and potential for polymorphisms.

agents, susceptibility testing, and TDM. Clinical pharmacists can play a huge role in optimizing therapy and help develop institutional protocols and algorithms to better manage these patients.

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# Self-Assessment Questions

## Questions 1–4 pertain to the following case.

P.T. is a 56-year-old man who is transferred to the ICU and intubated for hypoxic respiratory failure 21 days after a bone marrow transplant for acute myeloid leukemia. He was found to have pulmonary aspergillosis and is being treated with voriconazole 300 mg intravenous twice daily and caspofungin 50 mg intravenous daily. P.T. has a history of hypertension and gastroesophageal reflux disease, and he has developed acute kidney injury with an estimated CrCl of 40 mL/minute as well as graft versus host disease of the skin and gut. During the infusion of caspofungin the nurse notes that P.T. has become febrile, flushed, and has some facial swelling.

- Which one of the following toxicities is P.T. most likely experiencing?
  - Anaphylactic reaction to caspofungin; stop the infusion and administer epinephrine.
  - Infusion reaction to caspofungin; discontinue caspofungin.
  - Histamine-mediated reaction to caspofungin; slow the infusion rate.
  - Accumulation of cyclodextrin in the intravenous voriconazole formulation; discontinue voriconazole.
- In the next 72 hours, P.T. does not show much clinical improvement in respiratory function. His kidney function is worsening, and he is having high residuals from his tube feeds. Despite this, the oncology fellow would like to switch the voriconazole from intravenous to oral out of concern for cyclodextrin accumulation. Which one of the following is best to recommend for P.T.?
  - Switch the voriconazole to oral because the risks of cyclodextrin outweigh the benefit of intravenous therapy.
  - Continue with intravenous therapy because the risk of toxicity from cyclodextrin is theoretical and the patient is unlikely to absorb oral therapy.
  - Change to liposomal amphotericin B because of concern for toxicity and lack of oral absorption.
  - Discontinue voriconazole and continue caspofungin monotherapy as the toxicity being seen is from voriconazole itself.
- P.T.'s graft versus host disease (GVHD) is nonresponsive to steroid treatment. The team is contemplating whether an IL-2 receptor antibody (e.g., etanercept), a mammalian target of rapamycin (mTOR) inhibitor (sirolimus), or therapy with daclizumab would be best to treat steroid refractory disease. Which one of the following is best to recommend for P.T.?
  - Avoid sirolimus because of significant drug-drug interaction with voriconazole.
  - Avoid etanercept because of the treatment for active fungal infection.
  - Avoid daclizumab because monoclonal antibodies complicate identification of the cause of the patient's flushing and facial swelling.
  - Avoid all of the above therapies because they will result in accumulation of caspofungin.
- P.T. has now had 7 days of combination antifungal treatment, and the team is debating the need for antifungal therapeutic drug monitoring (TDM). They are considering converting to oral voriconazole in the next several days. Which one of the following is the most compelling reason to avoid TDM in B.L. at this time?
  - It is too early to determine whether or not he is responding to treatment.
  - High performance liquid chromatography (HPLC) will not be able to detect differences between caspofungin and voriconazole concentrations.
  - The patient demonstrates no signs of toxicity and will be converted to oral therapy before test results are available (7–10 days at your institution).
  - There is no need for TDM when using the intravenous formulation of voriconazole.

## Questions 5–9 pertain to the following case.

B.L. is a 37-year-old man admitted to the trauma ICU after a motor vehicle crash. He sustained multiple fractures and a splenic laceration and is currently intubated after repair of a right pelvic fracture. B.L. has a right-sided chest tube in place for pneumothorax, as well as a Foley catheter that was placed at admission. He had no contributory medical history. His current drug regimen includes ampicillin/sulbactam for prophylaxis secondary to facial fractures, hydromorphone PCA, docusate, senna, and enteral feeding supplements.

- Forty-eight hours after B.L. arrived in the ICU, surveillance cultures were obtained. They were notable for yeast in the sputum and urine (taken from Foley collection bag) but not the other two sites that were cultured. Which one of the following is best to recommend for B.L.?
  - Initiate fluconazole 400 mg daily.
  - Initiate nystatin five times a day.
  - Initiate daily  $\beta$ -D-glucan testing.
  - Monitor for signs and symptoms of infection.
- It is now day 10 of B.L.'s hospital admission. Overnight, he has become febrile (39.7°C) and hypotensive. His antibacterial therapy is being broadened to piperacillin/tazobactam and vancomycin. Blood cultures were drawn peripherally and through his central line. Which one

of the following is best to recommend regarding B.L.'s antifungal regimen?

- A. Add a galactomannan test to the above ordered cultures.
  - B. Continue without change until initial culture results.
  - C. Change treatment to lipid amphotericin B product at 5 mg/kg every 24 hours.
  - D. Initiate amphotericin B bladder irrigation daily.
7. Twenty-four hours later, B.L.'s cultures return; both peripheral blood and cultures obtained through the catheter are positive for yeast. The patient remains febrile. Which one of the following is best to recommend as empiric treatment for B.L.'s fungemia?
- A. Fluconazole 800 mg intravenous every 24 hours.
  - B. Amphotericin B 0.5 mg/kg intravenous every 24 hours.
  - C. Micafungin 100 mg intravenous every 24 hours.
  - D. Micafungin 50 mg intravenous every 24 hours.
8. Twenty-four hours later, the microbiology laboratory reports that B.L.'s culture is positive for *Candida albicans*. Antifungal susceptibility testing is not standard at your institution, and a send-out laboratory test has a 5–7 day turnaround time. Which one of the following is best to recommend for B.L.?
- A. Continue/initiate micafungin 100 mg intravenous every 24 hours.
  - B. Convert to oral voriconazole 200 mg every 12 hours.
  - C. Continue/initiate fluconazole 800 mg intravenous every 24 hours.
  - D. Call the laboratory to request susceptibility testing.
9. B.L. is now in day 5 of treatment; he is afebrile, and blood cultures obtained at 48 hours of treatment remain negative. His central line has been replaced over a guide wire. He is otherwise clinically stable and being weaned from the vent. Which one of the following treatment durations is recommended for B.L.'s episode of candidemia?
- A. Additional 14 days of therapy.
  - B. Additional 7 days of therapy.
  - C. Additional 9 days of therapy.
  - D. Additional 11 days of therapy.

**Questions 10 and 11 pertain to the following case.**

The antibiotic stewardship committee at HealthHome Hospital has recently begun to focus on antifungal stewardship. You are invited to a meeting to discuss proposed new diagnostic technologies for HealthHome Hospital.

10. Which one of the following points is the most compelling to present to the HealthHome committee, especially for patients in the ICU?
- A. PNA FISH should be performed to allow earlier initiation of appropriate antifungal therapy; use can be justified based on decreased echinocandin therapy.

- B. Beta-glucan should be added to facilitate shorter courses of antifungal agents; use can be justified based on decreased overall antifungal therapy.
- C. Galactomannan testing should be added to allow more rapid diagnosis of aspergillosis; use can be justified based on decreased need for voriconazole prophylaxis.
- D. Mannan/anti-mannan testing should be added to allow earlier initiation of appropriate antifungal therapy; use can be justified based on decreased echinocandin therapy.

11. In lieu of any of the new diagnostic technologies discussed, the HealthHome committee decided to add susceptibility testing at the local level. You are asked to create a guideline for preemptive therapy for invasive fungal infections in the ICU. The reference laboratory has supplied the following information for the past 100 isolates of *Candida* spp at HealthHome Hospital:

| Organism              | Number of isolates | % susceptible to fluconazole |
|-----------------------|--------------------|------------------------------|
| <i>C albicans</i>     | 51                 | 80                           |
| <i>C parapsilosis</i> | 20                 | 98                           |
| <i>C glabrata</i>     | 13                 | 60                           |
| <i>C krusei</i>       | 6                  | -                            |
| <i>C tropicalis</i>   | 10                 | 74                           |

Which one of the following drugs would be best to use for HealthHome patients who qualify for preemptive antifungal therapy per your guideline?

- A. Lipid amphotericin B
  - B. Caspofungin
  - C. Fluconazole
  - D. Flucytosine
12. A 35-year-old woman is receiving home TPN therapy. She presents to the ED septic and is being admitted to the medical ICU. The team wishes to cover likely fungal pathogens and asks your advice. Which one of the following drugs is best to recommend for this patient's empiric antifungal therapy?
- A. Caspofungin
  - B. Amphotericin B
  - C. Amphotericin B lipid complex
  - D. Fluconazole
13. The pharmacy and therapeutics committee is reviewing drugs newly approved by the FDA. They have interest in reviewing isavuconazonium. Which one of the following is the best guidance to give to the committee regarding isavuconazonium?
- A. It has a similar spectrum to voriconazole with possible enhanced activity against Zygomycetes but fewer adverse events.

- B. It has a spectrum similar to posaconazole but must be administered more frequently.
- C. It has a slightly broader spectrum than fluconazole but more concerns regarding administration with acid suppressive agents.
- D. It is similar in spectrum to itraconazole but lacks an intravenous formulation.

14. A 56-year-old woman is receiving treatment for influenza in the medical ICU. She is intubated and sedated. Her medical history includes Crohn disease, hypertension, and hyperlipidemia. Her current drugs include fentanyl and midazolam continuous infusions, infliximab 5 mg/kg (monthly), atorvastatin 40 mg daily, valsartan 40 mg daily, and pantoprazole 40 mg every 12 hours. On day 2 of her hospital admission, she is noted to have a new patchy infiltrate in the right lower lobe on routine chest radiography. A sputum culture reveals *Candida* spp. but nothing else grows. The patient is running a low-grade fever (38.1°C) and has a slightly elevated WBC ( $6.8 \times 10^3$  cells/mm<sup>3</sup>). Which one of the following is best to recommend regarding antifungal therapy for potential candidiasis for this patient?

- A. Initiate fluconazole 800 mg daily.
- B. Initiate voriconazole 4 mg/kg every 12 hours.
- C. Do not treat, administer nystatin to decontaminate oral cavity.
- D. Do not treat.

**Questions 15 and 16 pertain to the following case.**

Z.K. is a 45-year-old man admitted to the surgical ICU after a gunshot wound to the abdomen. On day 8 post-surgery he remains intubated and is now febrile (40°C). His condition had been improving but he is now septic, requiring pressors. For the past 3 days Z.K. has received anti-bacterial therapy with ciprofloxacin for a positive urine culture with *E. coli*, and he continues to have a urinary catheter in place.

15. According to which clinical prediction score would Z.K. meet criteria for early antifungal therapy based on a > 75% sensitivity?
- A. Dupont score
  - B. *Candida* score
  - C. Ostrosky rule
  - D. Modified Ostrosky rule
16. Cultures are obtained from Z.K. and empiric antifungal therapy is started with fluconazole 400 mg daily because of an ongoing echinocandin shortage at your hospital. Blood cultures are subsequently reported positive for *C. glabrata*. Susceptibility testing is performed and the fluconazole MIC is 16. Which of the following is best to recommend for Z.K.'s antifungal treatment?
- A. Continue fluconazole but increase dose to 800 mg daily.

- B. Continue fluconazole but obtain drug concentrations after 5–7 days of therapy.
- C. Change antifungal therapy to voriconazole.
- D. Change antifungal therapy to a lipid preparation of amphotericin B.

**Questions 17–19 pertain to the following case.**

M.R., a 45-year-old woman with acute myelogenous leukemia (AML), recently visited family members in Arizona. Now she is admitted for her third cycle of induction chemotherapy. Over the past 2 months M.R. has developed significant neuropathic pain; she recently begun carbamazepine but otherwise her medications are unchanged. She receives voriconazole 200 mg every 12 hours as prophylaxis with each cycle. On day 7 of hospital admission, M.R. is transferred to the ICU for mental status changes and acute hypoxia. She is started on empiric therapy for pneumonia (piperacillin/tazobactam and vancomycin), and her antifungal therapy is continued. Chest CT reveals new nodules. The primary team wishes to obtain rapid fungal diagnostic testing.

17. Which one of the following tests would best determine whether M.R. has developed fungal infection?
- A. PCR of a blood sample
  - B. PCR of BAL sample
  - C. Galactomannan of blood sample
  - D. Galactomannan of BAL sample
18. M.R.'s health care team is worried this may be a breakthrough infection on voriconazole. Which of the following puts M.R. at greatest risk of breakthrough fungal disease?
- A. Recent travel to Arizona
  - B. Recent chemotherapy
  - C. Failure of voriconazole prophylaxis due to drug interaction
  - D. Duration of stay in the ICU
19. Which one of the following is the most compelling reason to modify M.R.'s antifungal therapy?
- A. Development of breakthrough fungal infection on treatment
  - B. A voriconazole concentration of 0.5 mg/L
  - C. Concerns for carbamazepine/voriconazole drug-drug interaction
  - D. Need to initiate combination antifungal treatment
20. Which one of the following would best monitor to predict efficacy of voriconazole in a patient being treated for invasive aspergillosis?
- A. Voriconazole peak concentrations
  - B. Voriconazole trough concentrations
  - C. Galactomannan
  - D. Voriconazole MIC