Management of Invasive Mycoses in Hematology Patients: Current Approaches

By John R. Perfect, MD

Candidiasis and aspergillosis are the most common fungal infections in hematopoietic stem cell transplant recipients and other hematology/oncology patients. Strategies for reducing the morbidity and mortality associated with these infections include antifungal prophylaxis, empiric therapy in patients with persistent fever and neutropenia, and preemptive therapy. Antifungal therapies include amphotericin B deoxycholate, lipid formulations of amphotericin B, the triazoles (fluconazole, itraconazole, and voriconazole), and the echinocandins (caspofungin and the investigational agents micafungin and anidulafungin). Fluconazole is a reasonable choice for the treatment of invasive candidiasis if the patient has not previously received a triazole and the institution has a low incidence of triazole resistance. If resistance is a concern, an echinocandin, such as caspofungin, is an appropriate option. Voriconazole may be the initial choice in most patients with invasive aspergillosis. If patients are intolerant of or refractory to conventional therapy, effective alternatives include a lipid formulation of amphotericin B or an echinocandin.

Invasive fungal infections continue to be an important cause of morbidity and mortality in hematopoietic/oncology patients, particularly bone marrow or stem cell transplant recipients. Amphotericin B deoxycholate was once the standard of care; however, this agent is associated with significant adverse reactions, particularly nephrotoxicity. The lipid formulations of amphotericin B are less toxic than amphotericin B deoxycholate, but nephrotoxicity and infusion-related reactions continue to be concerns. These limitations have led to the development of alternative antifungal agents, such as the triazoles and, more recently, the echinocandins. These newer antifungals represent important advances in the prevention and management of invasive fungal infections. This article will review the risk factors for invasive fungal infections, the common organisms, and the concepts of prevention and treatment, focusing on two major infectious diseases—invvasive candidiasis and invasive aspergillosis. This review is based on material presented by Dr. Thomas Walsh. Risk Factors and Organisms Hematology patients at high risk for invasive fungal infections include those with the following:

- Acute leukemia, particularly acute myelogenous leukemia, or those undergoing intensive consolidation and intensification and patients with high-risk acute lymphoblastic leukemia
- Chronic leukemia—specifically subgroups with chronic myelogenous leukemia (CML) in blast crisis, multiply relapsed CML, and advanced chronic lymphocytic leukemia
- Lymphoma (multiply relapsed)
- Ongoing refractory myelodysplasia
- Severe aplastic anemia
- Transplantation (myeloablative or nonmyeloablative)

Risk factors for aspergillosis in hematology patients include prolonged or repeated episodes of profound neutropenia, corticosteroid therapy, and infliximab therapy. Because tumor necrosis factor-alpha is a critical cytokine in host defense against *Aspergillus*, abrogating that cytokine can lead to increased risk for invasive aspergillosis. In addition to pharmacologic immunosuppression, intrinsic immune defects increase the risk of aspergillosis. They include aplastic anemia, advanced HIV infection, chronic granulomatous disease, and Job syndrome.
The most common fungal pathogens to cause significant infections in immunosuppressed patients with malignancy and its treatment are Candida and Aspergillus. Less common species, but ones that are being seen with increasing frequency, include yeast-like pathogens such as Trichosporon species and Cryptococcus neoformans. Other fungal pathogens include the filamentous fungi (particularly the Fusarium species), the Zygomycetes, Scedosporium species, and a variety of dematiaceous molds.

Concepts of Prevention and Treatment

Over the past 25 years, different strategies have emerged for the prevention and treatment of invasive fungal infections; where appropriate, the early initiation of antifungal therapy has been one of the hallmarks of the attempt to reduce complications from these infections. Three different-but overlapping-strategies have been described:

- **Prophylaxis**: The initiation of antifungal therapy at or near the beginning of antineoplastic chemotherapy or hematopoietic stem cell transplant (HSCT) preparative regimen, before any symptoms or signs of infection.
- **Empiric therapy**: A risk-based intervention for patients with persistent fever and neutropenia despite broad-spectrum antibacterials and who are at risk for invasive fungal infections.
- **Preemptive therapy**: A risk-based intervention for high-risk patients who have persistent fever and neutropenia despite broad-spectrum antibiotics plus other evidence of invasive fungal infection, such as positive surveillance cultures, sinus opacification, pulmonary infiltrates, or positive galactomannan antigen.

These approaches have been most clearly described in the setting of neutropenia during the period of bone marrow transplantation, as illustrated in Figure 1. There is substantial overlap between these strategies, especially between empiric and preemptive therapy. For example, approximately 45% of patients enrolled in an empiric antifungal trial may have pulmonary infiltrates; if so, the intervention is-by definition-preemptive therapy. Perhaps what matters most is that a risk-based approach is used to prevent invasive fungal infections in high-risk neutropenic patients. **Prophylaxis**

Toxicity is a key factor in determining whether a compound will be used early (prophylactically) or later (empirically) for the prevention of invasive mycosis. For example, if amphotericin B deoxycholate did not have significant dose-limiting nephrotoxicity, it would be given as prophylaxis at a dosage of 1 mg/kg/d. In a 1982 landmark study, Pizzo et al[1] delayed initiation of empiric amphotericin B (0.5 mg/kg/d) until at least day 7 of persistent fever and neutropenia to justify the use of this toxic drug only for higher-risk neutropenic patients. This approach contrasts with the use of fluconazole, where the therapeutic dosage (400 mg/d) is used for prophylaxis before the...
development of neutropenia in HSCT recipients. The seminal studies of Goodman et al[2] and Slavin et al[3] and subsequent trials[4,5] demonstrate that fluconazole has stood the test of time as an effective agent against Candida albicans, particularly for the prevention of invasive candidiasis in HSCT recipients. Fluconazole prevented infection with all strains of Candida except Candida krusei. Breakthrough infections do occur with fluconazole, and concerns about resistance of certain yeast species and molds have led to studies of prophylaxis with newer antifungal drugs. The use of itraconazole to prevent fungal infections in this setting has been studied,[6,7] and although it has been shown to be effective in high-risk patients, there continue to be concerns about safety and potential toxicity with this particular drug. For instance, frequent gastrointestinal side effects, including nausea, vomiting, diarrhea, or abdominal pain, are associated with itraconazole; this drug can be difficult to administer in some patient populations, and inconsistent oral absorption is always an issue.

Van Burik et al,[8] of the Mycosis Study Group, recently studied a strategy of prophylaxis with the investigational echinocandin micafungin. It was compared with fluconazole as prophylaxis in patients during the neutropenic phase of HSCT. The overall success rate was higher with micafungin (80.0%) than with fluconazole (73.5%). The antifungal agents were equally effective in the prevention of invasive candidiasis, but micafungin was more effective than fluconazole in preventing mold infections such as aspergillosis. The two agents had comparable safety profiles. Mattiuzzi et al[9] compared caspofungin (50 mg/d IV) and itraconazole (200 mg/d IV) prophylaxis in 192 patients with hematologic malignancies. The incidence of invasive fungal infections was similar: 5.7% in the caspofungin group (n = 106) and 5.8% in the itraconazole group (n = 86). Fewer Candida infections developed in the caspofungin group. It is clear that in very high-risk patients, a prophylaxis strategy that includes either an extended-spectrum azole or an echinocandin will be necessary to prevent deadly mold infections.

Empiric Therapy

The rationale for empiric antifungal therapy in persistently febrile neutropenic patients is to provide early treatment of occult invasive fungal infection and prevent subsequent breakthrough fungal infection in high-risk patients. It is likely that early treatment of a fungal infection is associated with a better outcome. This approach to therapy should complement antifungal prophylaxis. The timing of empiric therapy is later in the course of neutropenia, so the population receiving treatment is smaller, but the risk of invasive fungal infection is higher. Many of the studies of empiric antifungal therapy have been relatively large. These studies have included more than 3,000 patients and have evaluated many different antifungal agents, including amphotericin B deoxycholate,[1,10] liposomal amphotericin B,[11,12] fluconazole, and itraconazole.[13] Voriconazole has been demonstrated to be effective in preventing breakthrough fungal infections in high-risk patients with fever and neutropenia.[14] This drug was compared with liposomal amphotericin B as empiric therapy in 837 patients with neutropenia and persistent fever. The overall success rates were not significantly different. However, the incidence of breakthrough infections was significantly lower in the voriconazole group compared with the liposomal amphotericin B group (1.4% vs 9.2%).
# Table 1

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th>Caspofungin (n = 556)</th>
<th>Liposomal Amphotericin B (n = 539)</th>
</tr>
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<tbody>
<tr>
<td>Males</td>
<td>57.2%</td>
<td>54.2%</td>
</tr>
<tr>
<td>Median age</td>
<td>51 yr (range: 17–83 yr)</td>
<td>49 yr (range: 16–83 yr)</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>65.5%</td>
<td>62.9%</td>
</tr>
<tr>
<td>ALL</td>
<td>10.3%</td>
<td>9.3%</td>
</tr>
<tr>
<td>NHL</td>
<td>10.4%</td>
<td>11.5%</td>
</tr>
<tr>
<td>High risk</td>
<td>26.3%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Allograft HSCT</td>
<td>6.5%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Relapsed leukemia</td>
<td>19.8%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Antifungal prophylaxis</td>
<td>56.3%</td>
<td>56.4%</td>
</tr>
<tr>
<td>ANC &lt; 100 μL</td>
<td>71.9%</td>
<td>75.3%</td>
</tr>
<tr>
<td>Mean/median duration of treatment</td>
<td>13/11 d (range: 1–90 d)</td>
<td>12.5/10 d (range: 1–90 d)</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; ANC = absolute neutrophil count; HSCT = hematopoietic stem cell transplantation; NHL = non-Hodgkin's lymphoma.

Adapted from Walsh et al. [21]
The number of patients discontinuing the study drug because of toxic effects was similar in the two groups. However, there were more discontinuations because of lack of efficacy in patients who received voriconazole (22 vs 5; \(P = .001\)), with persistent fever being the most common reason for withdrawal. Patients receiving voriconazole also experienced more episodes of infusion-related visual toxicity (21% vs 1%; \(P < .001\)). This agent is not currently FDA-approved for this indication. The recent data on the efficacy of the echinocandins for empiric antifungal therapy are very encouraging. The echinocandins are a new class of antifungal agent that inhibit the synthesis of cell wall glucans critical to the integrity of many yeasts and molds. As such, they have a unique mechanism of action; cross-resistance with conventional antifungal agents is unlikely. The antifungal spectrum of the echinocandins includes \textit{Candida} species, \textit{Aspergillus} species, and \textit{Pneumocystis carinii}. Although no clinical data for pneumocystosis are available, the in vivo data are noteworthy. However, the echinocandins have no significant activity against \textit{C neoformans}. The major antifungal activity of echinocandins against \textit{Candida} and \textit{Aspergillus} species can be explained by their chemical structure (Figure 2). The rationale for the early use of echinocandins in the treatment and prevention of invasive mycoses in patients with hematologic malignancies is based on the strong data on the impact of these agents on invasive candidiasis and refractory invasive aspergillosis.[15,16] The echinocandins have demonstrated encouraging activity against invasive candidiasis and invasive aspergillosis, both in the laboratory and in clinical trials.[17-20] Laboratory investigations have demonstrated that echinocandins are particularly active in the early treatment and prevention of invasive aspergillosis. The impact on early disease is striking. However, little clinical evidence had been available concerning the role of echinocandins in empiric antifungal therapy in persistently febrile neutropenic subjects. Therefore, to address this lack of knowledge, the largest empiric antifungal therapy trial was conducted, involving more than 1,000 patients.[21] The patients had persistent febrile neutropenia with hematologic malignancies (Table 1). Approximately three-quarters of the patients had acute leukemia, and the treatment groups were balanced with respect to patient age, gender, and underlying disease. The trial compared caspofungin (70 mg on day 1, then 50 mg/d) with liposomal amphotericin B (3 mg/kg/d) as empiric antifungal therapy. The primary end point was defined as survival to 7 days post treatment, successful outcome of baseline
invasive fungal infection, the absence of breakthrough fungal infections to 7 days post treatment, no premature discontinuation because of lack of efficacy or drug toxicity, and resolution of fever during neutropenia. The results are shown in Figure 3. Overall success rates were equivalent in the two treatments, but caspofungin was much more effective against baseline fungal infection. The groups did not differ with respect to breakthrough infections or resolution of fever, but there was a significant survival advantage in patients receiving caspofungin. Also, in the caspofungin group, there were fewer cases of discontinuation of treatment. In evaluating the efficacy against baseline fungal infections, the results were consistent with the activity observed in the laboratory, with caspofungin demonstrating virtually a twofold higher rate of successful outcome (Table 2). With respect to the impact on survival at 7 days, caspofungin was superior to liposomal amphotericin B (92.6% vs 89.2%, \( P = .044 \); Figure 4).

**Table 2**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Caspofungin (51.9%)</th>
<th>Liposomal Amphotericin B (25.9%)</th>
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<tr>
<td>Overall(^a)</td>
<td>14/27 (51.9%)</td>
<td>7/27 (25.9%)</td>
</tr>
<tr>
<td>Aspergillus species</td>
<td>5/12 (41.7%)</td>
<td>1/12 (8.3%)</td>
</tr>
<tr>
<td>Candida species</td>
<td>8/12 (66.7%)</td>
<td>5/12 (41.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>1/3 (33.3%)</td>
<td>1/3 (33.3%)</td>
</tr>
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</table>

**Figure 4: Survival Rates**—Empiric therapy with caspofungin was associated with a better survival rate compared with liposomal amphotericin B (92.6% vs 89.2%, \( P = .044 \)) in persistently febrile neutropenic patients.\[21\]

Findings from the safety analysis showed that statistically fewer patients treated with caspofungin suffered
drug-related adverse events, nephrotoxicity, or infusion-related events (Figure 5). Caspofungin was significantly better tolerated throughout the study. The results of this very large, rigorously controlled clinical trial represent an important advance in our understanding of the impact of the echinocandins on early intervention in patients with hematologic malignancies. The results could potentially change the face of empiric antifungal therapy. Since the final outcome of most of these studies showed no difference in final outcome with azoles, polyenes, or echinocandins, there are some choices for clinicians to make in their strategies. However, it is clear that caspofungin, with its safety, lack of drug interactions, and efficacy, will become an attractive choice to use as empiric therapy in high-risk febrile neutropenic patients.

Invasive Candidiasis Types of Candidiasis
Infections with *Candida* species are common at all levels of clinical practice, evoking a broad range of diseases, from mucocutaneous infections, such as oral thrush, to life-threatening invasive candidiasis within the hospital setting. In considering how to definitively treat invasive candidiasis, it is important to note that there are different forms of infection. Candidemia is characterized by a positive blood culture and usually signifies deep tissue infection. The mortality and morbidity associated with candidemia are similar to those of bacteremia caused by *Staphylococcus aureus*.[22] Thus, all cases of candidemia require treatment. Acute disseminated candidiasis, which represents an even greater burden of tissue infection, is candidemia complicated by clinically overt deep tissue infection. It is characterized by cutaneous lesions, myalgias, hypotension, multiorgan dysfunction, and septic shock. Chronic disseminated candidiasis occurs in stable ambulatory patients who typically have fever, abdominal pain, and elevated alkaline phosphatase levels. There is usually a history of neutropenia with or without candidemia. In patients with chronic disseminated candidiasis, the findings are striking. For example, CT may show radiolucent lesions riddling the liver and spleen. Laparoscopy or open biopsy usually shows multiple lesions. *Candida* Species
The most common cause of candidemia is *C albicans*, which is responsible for approximately 50% of cases.[23] *Candida glabrata* is the second most common cause of candidemia, responsible for as many as 25% of cases.[24] *Candida tropicalis* causes about 10% to 15% of cases, but it is highly virulent in neutropenic patients, causing severe fulminant acute disseminated candidiasis. *Candida parapsilosis* is notorious for adhering to catheters and prosthetic devices and for contaminating total parenteral nutrition solutions. It often causes a persistent fungemia. *C krusei* accounts for fewer than 5% of bloodstream isolates, but it is resistant to fluconazole.[25,26] Although *C glabrata* is less virulent than some of the other *Candida* species, it often breaks through fluconazole and voriconazole prophylaxis. Most blood isolates of *C albicans* are susceptible in vitro to fluconazole but
occasionally a resistant strain will appear. Approximately 10% of *C. glabrata* isolates are fully resistant to azoles, and about 10% are now resistant to amphotericin B. *Candida lusitaniae*, *Candida guilliermondii*, and *Candida lipolytica* also are resistant to amphotericin B, and there are increasing reports of amphotericin B-resistant isolates of *C. glabrata*, *C. krusei*, and *C. tropicalis*. The National Committee for Clinical Laboratory Standards has established interpretive break points for the minimum inhibitory concentrations (MICs), which are used to determine whether an isolate is susceptible or resistant. For fluconazole, "susceptible" is defined as a MIC of 8 g/mL or less, "susceptible dose-dependent" is 16 to 32 g/mL, and "resistant" is 64 g/mL or higher. **Antifungal Therapy**

The antifungal compounds available for primary treatment of candidemia include the polyenes (amphotericin B formulations), the triazoles, and the echinocandins. The triazoles include fluconazole and, recently, voriconazole. Voriconazole does not have FDA approval for the treatment of candidiasis, but data on salvage therapy for refractory candidiasis are interesting.[27] Furthermore, data from a randomized clinical trial of voriconazole for candidemia have been presented in abstract form. Amphotericin B or fluconazole has been recommended for the primary treatment of candidemia.[28] However, as previously noted, dose-limiting nephrotoxicity may complicate the use of amphotericin B. Although fluconazole has a good safety profile, it has limited activity against *C. krusei*, some strains of *C. glabrata*, and molds,[25,26,29,30] and the development of resistance is a concern among non-albicans *Candida* species. The echinocandins represent a novel alternative to amphotericin B and fluconazole for the primary treatment of invasive candidiasis.[31] Micafungin and anidulafungin are investigational agents, with similar mechanisms of action, but comparative data are available only for caspofungin—showing that the drug is comparable to amphotericin B in the treatment of candidemia.[15] With respect to the selection of primary antifungal therapy for candidemia, there is no single correct choice, but possible approaches include the following:

- For institutions that have a low frequency of triazole resistance or for patients who have not previously received antifungal triazoles, fluconazole is a reasonably safe and cost-effective option.
- For institutions with a high frequency of triazole resistance or for patients receiving triazoles (including fluconazole prophylaxis), it is appropriate to consider caspofungin. Furthermore, caspofungin is a good choice if there is a concern regarding drug-drug interactions with the polyenes or azoles.
- For a patient who is hemodynamically unstable, consider using an agent with greater fungicidal activity, such as caspofungin, should be considered.
- For patients with hepatotoxicity, therapy with a triazole should be avoided; therefore, it is appropriate to use liposomal amphotericin B or caspofungin.
- For patients with nephrotoxicity, avoid amphotericin B because of the risks of further adverse effects on the renal system and amphotericin B toxicity.

If a patient has a positive blood culture, there are additional considerations. Removal of vascular catheters is recommended, but the caveat "where feasible" should be added. In many patients, the central venous catheters are not readily removable; moreover, the catheter may not be incriminated in the infection. Ophthalmoscopy and abdominal CT scanning are recommended to rule out endophthalmitis and hepatosplenic candidiasis and to stage the patient's disease. However, if the patient is neutropenic, this assessment should be done upon recovery from neutropenia, because the inflammatory response can mute the CT findings and prevent the detection of positive vitreolar opacities. Thus, it is necessary to ascertain infection at these sites after recovery from neutropenia. **Invasive Aspergillosis**

*Aspergillus* infection is now the most common cause of infectious pneumonic mortality in HSCT recipients and patients with leukemia. It is also a major cause of pneumonia in solid-organ transplant recipients. It is important to understand that there is a bimodal distribution of aspergillosis in HSCT recipients. There is an early neutropenic phase of infection that is related to both the depth and the duration, and there is also a later postengraftment phase. Epidemiologic studies have described the bimodal distribution in frequency of aspergillosis in bone marrow transplant recipients. The peaks of infection occur at a median of 16 and 96 days after bone marrow transplant. The risk factors for invasive aspergillosis during the first peak include the following: donor type, underlying disease, season (summer), and transplantation outside an LAF environment. Risk factors for invasive aspergillosis during the second peak include donor type, underlying disease, age, graft-vs-host disease, corticosteroid therapy, and neutropenia.[32] **Clinical Presentation and Diagnosis**
Aspergillosis can cause sinusitis, of which nasal congestion may be the only symptom, although physical examination may reveal eschars on the nasal turbinates. Early epistaxis may occur. A more ominous development is palatal hemierythema as the palatine veins are invaded, and there can be dissemination to the CNS. Among the early manifestations of aspergillosis, the emergence of pneumonia is a major concern. The presentation can be very subtle, with pleuritic pain, cough, and hemoptysis. Any one of these symptoms in a neutropenic patient or otherwise immunocompromised patient clearly signifies the possibility of invasive aspergillosis. In the radiologic assessment of pneumonia in this setting, the chest radiograph lacks sensitivity, but the CT scan may show bronchopneumonia, nodules, wedge-shaped infiltrates, halo signs, and cavities far more distinctively. The definitive diagnosis of invasive pulmonary aspergillosis may involve procedures such as bronchoalveolar lavage, percutaneous needle aspiration, thoracoscopy, and, rarely, open lung biopsy. Microbiologic detection involves direct examination of specimens, histology, and culture. However, culture of respiratory secretions are positive in only about 50% of patients in whom polymerase chain reaction (PCR) results are positive. PCR remains investigational in this setting, and there are technical challenges for its effective use. Blood cultures are usually negative. Diagnostic tests for aspergillosis include serologic methods to detect circulating antigens, such as cell wall galactomannan and the 1,3-beta-Dgalactomannan test recently approved by the FDA. The galactomannan detection system is an enzyme immunoassay format, which will enhance and complement our diagnostic armamentaria. Galactomannan is a major heteropolysaccharide present in the cell wall, and it is a large molecular weight molecule (between 25,000 and 75,000). It was originally described by Reiss and Lehman,[33] who first recognized its diagnostic utility. A number of studies have evaluated the use of galactomannan detection in the diagnosis of invasive aspergillosis.[34,35] Maertens et al[34] found that galactomannan detection had a sensitivity of 94.5% and a specificity of 98.8% in allogeneic stem cell transplant recipients who had invasive aspergillosis. This statistical profile was better than that of other variables, such as unexplained fever, new pulmonary infiltrates, isolation of *Aspergillus* species, and CT abnormalities. Antigenemia preceded the diagnosis on the basis of radiologic examination by 8 days in 80% of patients; antigenemia preceded the diagnosis based on *Aspergillus* isolation by 9 days in 89% of patients.[34] In contrast, Herbrecht et al[35] found that the sensitivity of this test may not be as high as anticipated. Their study had four patient groups: patients with fever of unknown origin during neutropenia, patients with suspected pulmonary infection, those with nonpulmonary aspergillosis, and those undergoing surveillance after HSCT. A total of 3,294 serum samples were collected during 797 febrile episodes. There were 153 episodes of invasive aspergillosis: 31 definite, 67 probable, and 55 possible, and the sensitivity was 64.5%, 16.4%, and 25.5% respectively. The sensitivity was lower in patients who were positive for anti-*Aspergillus* antibodies than in antibody-negative patients. Two recent publications have illustrated the possible false-positive results that can occur with the galactomannan test in patients receiving piperacillin-tazobactam.[36,37] In both series, significant false-positive results were reported, and batches of piperacillin-tazobactam tested positive by this assay.[36,37] It should be emphasized to the reader that this test was primarily assessed in patients with bone marrow transplant and hematologic malignancies, and it may not perform as well in other high-risk populations.
Treatment

The antifungal compounds for the treatment of invasive aspergillosis include amphotericin B deoxycholate, lipid formulations of amphotericin B, voriconazole, itraconazole, and caspofungin. Amphotericin B was previously considered the gold standard. It has the advantage of being active against most species of *Aspergillus*, although an exception is *Aspergillus terreus*, which is resistant to amphotericin B. Itraconazole is available in both IV and oral forms and is active against most species of *Aspergillus*. Studies have reported good treatment responses in invasive aspergillosis, with 32% of itraconazole-treated patients achieving a complete or partial response. Patients must be able to take oral medications, and drug interactions can be problematic.[38] A study by Herbrecht et al.[35] has established our understanding of the role of voriconazole as primary therapy for aspergillosis. This study was an open, randomized comparison trial of voriconazole and amphotericin B deoxycholate, followed by other licensed antifungal therapy for invasive aspergillosis. The regimen for voriconazole was 6 mg/kg IV for two loading doses on day 1, then 4 mg/kg q12h for at least 7 days, with an option to follow by 200 mg q12h orally. Amphotericin B was given 1 to 1.5 mg/kg/d IV. The study included 392 patients, most of whom were oncology patients and HSCT recipients, and was conducted in Western Europe and North America. The results demonstrated voriconazole's superiority over amphotericin B with respect to both complete and partial responses, survival, overall outcome, and benefits in duration of therapy (Table 3). The echinocandins also are well tolerated and are active against most *Aspergillus* species. However, they have been studied only in the salvage setting for advanced disease. In a study of invasive aspergillosis in high-risk patients who were refractory or intolerant to other antifungal agents, a partial or complete response was seen in 41% of patients receiving caspofungin, compared with 17% of patients who had received more than 1 week of standard therapy.[39] The optimal dose of caspofungin in invasive aspergillosis is still uncertain because of varying results in different animal models. The role of echinocandins may be much more definitive for early empiric intervention in neutropenic patients or in those with *Candida* infection. Guidelines for the treatment of invasive pulmonary aspergillosis begin with assessment of the patient's need for parenteral vs oral therapy. Important considerations are host factors, time factors, and bioavailability. Voriconazole improves survival compared with conventional amphotericin B and is the initial choice for most settings. If patients are intolerant of, or refractory to, conventional therapy, a lipid formulation of amphotericin B or caspofungin is recommended. Use of combination therapy remains imprecise, and such decisions must generally be made at the bedside, with consideration of all clinical factors. Other Management Options

The role of surgery is important in the management of invasive aspergillosis, and the indications for surgery have been defined in a number of reports.[40,41] Indications for surgery include the presence of infected catheters or implants, skin or softtissue infections, invasion of the chest wall or pericardium, hemoptysis from a single cavitary lesion, and endocarditis or osteomyelitis (Table 4). Sinusitis is also an indication for surgery in selected patients; however, this should not be considered during a period of profound neutropenia. In this setting, stabilization of disease can, upon recovery, be followed by more aggressive intervention. In addition, in order to augment the host response against invasive aspergillosis, discontinue or rapidly taper corticosteroids when feasible.
persistent but reversible neutropenia is also recommended. There are individual reports of the role of interferon-gamma for augmenting the host response, as well as supportive laboratory data; however, in the setting of BMT, this approach could accelerate a T_{H1} response that promotes graft vs host disease. Granulocyte transfusions have a role, particularly in patients with refractory infection and persistent but reversible neutropenia. **Emerging Fungal Pathogens** Although this article has focused on *Candida* species and *Aspergillus fumigatus*, there are other *Aspergillus* species that may be more resistant to amphotericin B. *Fusarium* is being recognized more frequently as an invasive pathogen in immunocompromised patients. *Fusarium* species may be very unpredictable, and although voriconazole has a second-line indication for infections caused by these pathogens, many cases of fusariosis do not respond to any of the available classes of agents. *Trichosporon* species are clearly resistant to the fungicidal effects of amphotericin B. They are amenable to triazole therapy but not to the echinocandins. The responses of *Pseudallescheria boydii* or *Scedosporium* species are quite variable; some of them can use amphotericin B as a nutrient carbon source. Amphotericin B remains the definitive treatment of choice for Zygomycetes; there are promising data for the investigational triazole posaconazole, but this agent is not currently available. Infections caused by the dematiaceous molds, such as *Phaeohyphomycetes*, may respond to the extended-spectrum azoles.

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**References:**


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