



Update on the Management of Invasive Fungal Infections

The management of invasive fungal infections was the subject of one of three CE in the Mornings topics at the 45th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in December 2010 (which are available at www.ashpadvantage.com/cemornings). The program was presented by Peggy L. Carver, Pharm.D., FCCP. Attendees submitted questions about unresolved issues and controversies that were later addressed by Dr. Carver in a live webinar conducted on February 8, 2011. Some of the highlights of the webinar pertaining to the management of invasive fungal infections in non-neutropenic patients were described in an e-Newsletter released in April. Highlights of the webinar pertaining to the management of invasive fungal infections in neutropenic and transplant patients are described in this e-Newsletter.

Patients undergoing hematopoietic stem cell transplantation (HSCT) or with neutropenia from cancer chemotherapy or hematologic malignancies are at high risk for invasive fungal infection because of a compromised immune system. Opportunistic infections involving yeasts (especially *Candida* species) and moulds (especially *Aspergillus* species) are major causes of morbidity and mortality in these patient populations.¹

In the past, *Candida albicans* (*C. albicans*) was the most common pathogen and the azole antifungal agent fluconazole was the drug of choice for prophylaxis in neutropenic and transplant patients.¹ The epidemiology of opportunistic infections in this patient population has changed over the past several decades to involve non-*C. albicans* yeasts and moulds, and breakthrough infections involving moulds and resistant *Candida* species have become increasingly common despite antifungal prophylaxis. Fluconazole provides coverage against most *Candida* species (except *Candida krusei*), although its activity against *Candida glabrata* is dose dependent, but it lacks coverage against *Aspergillus* species and other moulds.²

The risk for opportunistic infection in allogeneic HSCT recipients varies with the host immune system defect and recovery during the preengraftment phase (neutropenia, mucositis, and acute graft-versus-host disease in the first 30 days after HSCT), postengraftment phase (impaired cellular immunity and acute and chronic graft-versus-host disease 30-100 days after HSCT), and late phase (impaired cellular and humoral immunity and chronic graft-versus-host disease >100 days after HSCT).³ The risk for *Candida* infection is particularly high during the preengraftment and postengraftment phases. The risk for *Aspergillus* infection is bimodal, with a peak during the preengraftment phase and another peak during the late postengraftment and early late phases (Figure on next page).

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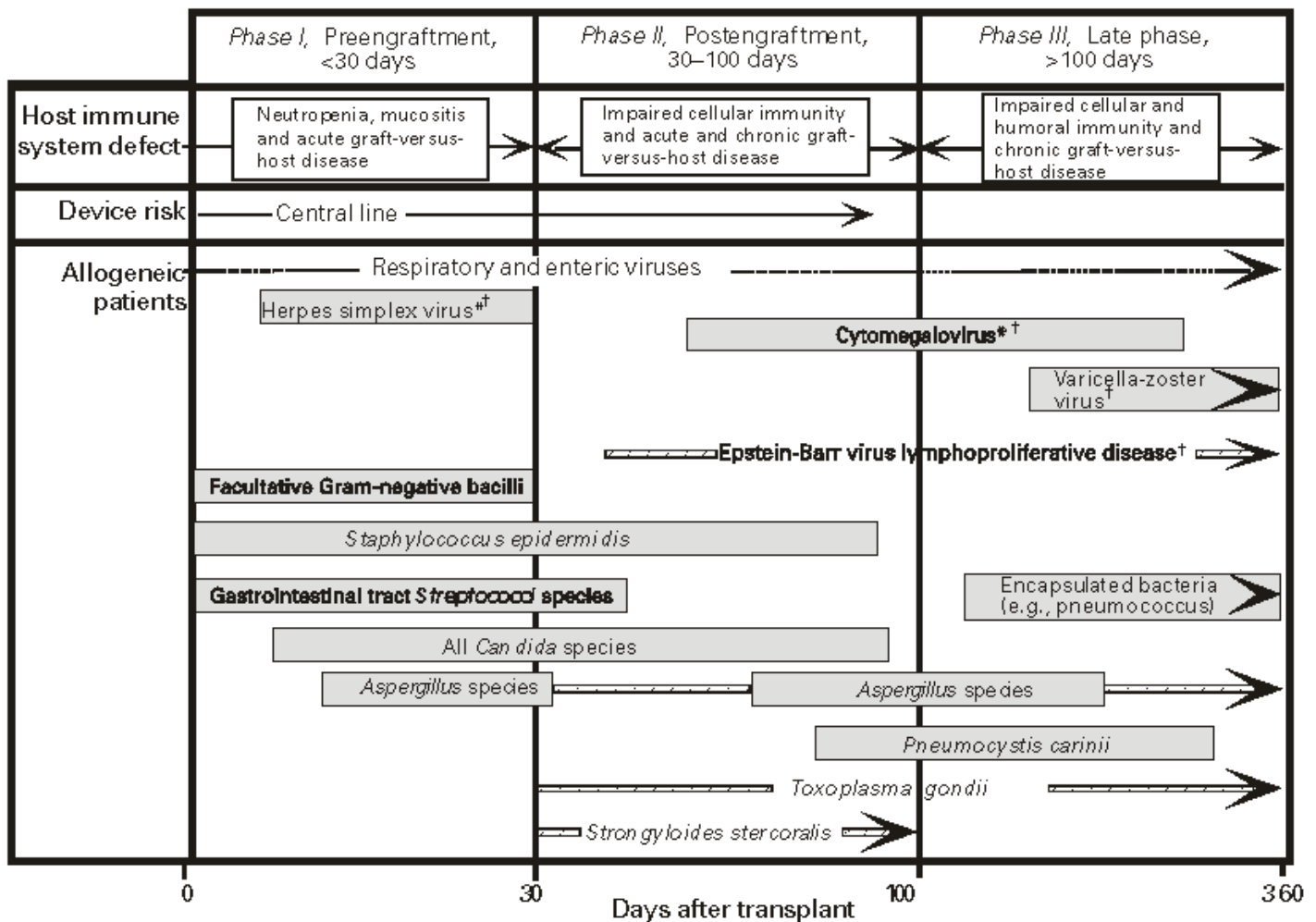
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FIGURE. Phases of opportunistic infections among allogeneic HSCT recipients



*Without standard prophylaxis

†Primarily among persons who are seropositive before transplant

High incidence (≥10%)
 Low incidence (<10%)
 Episodic and endemic
 Continuous risk

Source:Centers for Disease Control and Prevention. *MMWR Recomm Rep.* 2000; 49(RR-10):1-125.]



Prophylaxis

Strategies to reduce the morbidity and mortality from invasive fungal infection in neutropenic and transplant patients include prophylactic antifungal therapy in patients with risk factors for invasive fungal infections (e.g., advanced age, prolonged neutropenia, graft-versus-host disease, diabetes, or other comorbid conditions), empiric therapy in patients with fever unresponsive to antibacterial agents for 3-5 days, preemptive therapy for patients with signs of infection (e.g., positive test results from polymerase chain reaction or other assays or scans), and specific treatment when there is proof of infection.^{1,4} Part of the difficulty in determining which strategy to use relates to the fact that serious infections affect only small numbers of patients. Demonstration of a significant therapeutic benefit is possible only in patients at the highest risk for invasive fungal infection. The use of antifungal therapy is associated with toxicity, resistance, drug interactions, and associated costs.¹ Nevertheless, prophylactic antifungal therapy is widely used in neutropenic and transplant patients because of their high risk for and the serious consequences of invasive fungal infection.

Table 1 lists antifungal options for prophylaxis in transplant and oncology patients based on guidelines for the management of candidiasis from the Infectious Diseases Society of America.⁵ The choice of antifungal prophylaxis should take into consideration local epidemiology, activity against non-*Candida* species, route of administration, available dosage forms, potential for drug-drug and drug-food interactions, adverse effect profile, and need for dosage adjustment in patients with renal or hepatic impairment and plasma concentration monitoring in all patients.¹ For example, although fluconazole lacks activity against *Aspergillus*, itraconazole, voriconazole, posaconazole, echinocandins, and amphotericin B are active against the pathogen.² Breakthrough *Aspergillus* infections can occur during itraconazole prophylaxis in HSCT recipients despite *in vitro* activity.¹ Other pathogens commonly associated with breakthrough infections during antifungal prophylaxis in neutropenic and transplant patients are listed in Table 2.

Table 1. **Infectious Diseases Society of America Recommendations for Antifungal Prophylaxis for Patients at Risk for Candidiasis⁵**

Solid organ (liver, pancreas, small bowel) transplant (postoperative)

- Fluconazole 200-400 mg (3-6 mg/kg) daily or
- Liposomal amphotericin B 1-2 mg/kg/day for 7-14 days

Stem cell transplant recipients with neutropenia

- Fluconazole 400 mg (6 mg/kg) daily,
- Posaconazole 200 mg three times daily, or
- Micafungin 50 mg daily

Chemotherapy-induced neutropenia (during induction chemotherapy for the duration of neutropenia)

- Fluconazole 400 mg (6 mg/kg) daily,
- Posaconazole 200 mg three times daily, or
- Caspofungin 50 mg daily



Table 2.
Common Causes of Breakthrough Infection During Antifungal Prophylaxis in Neutropenic and Transplant Patients⁶⁻¹⁸

Fluconazole and itraconazole

- *Aspergillus* species
- Azole-resistant *Candida* species

Voriconazole

- *Zygomycetes*
- *Candida glabrata*
- Others (e.g., *Acremonium*, *Scedosporium*)

Micafungin and caspofungin

- *Trichosporon*

Posaconazole

- *Rhizopus microsporus*

Posaconazole has expanded activity against *Candida*, *Aspergillus*, and *Zygomycetes*, another increasingly common mould that is not susceptible to fluconazole, itraconazole, or voriconazole.¹ Posaconazole is available only for oral administration and should be taken with a full meal to ensure adequate plasma concentrations. Itraconazole is available for oral and intravenous (i.v.) administration, but the oral dosage form should be taken without food because of its low oral bioavailability, although taking the drug on an empty stomach increases the risk of gastrointestinal (GI) adverse effects. Azole antifungal agents interact with many other drugs and tend to be poorly tolerated because of GI adverse effects, rash, and liver enzyme elevations.¹ Nephrotoxicity limits the use of amphotericin B for prophylaxis.

The echinocandins caspofungin and micafungin are active against *Candida* and *Aspergillus* (but not *Zygomycetes*) and available only for i.v. administration, but they are better tolerated and less likely to interact with other drugs than are azole antifungal agents.¹ Plasma concentration monitoring is not needed for echinocandins, although it is needed for itraconazole, voriconazole, and possibly posaconazole (but not fluconazole). Echinocandins and posaconazole do not require dosage adjustment in patients with renal impairment, although adjustment or avoidance of fluconazole, itraconazole, and voriconazole is warranted in such patients. Caspofungin and voriconazole dosage adjustment are needed for patients with hepatic impairment.

HSCT Recipients

Whether antifungal prophylaxis decreases all-cause mortality or mortality due to invasive fungal infection in HSCT recipients has yet to be definitively demonstrated. Antifungal prophylaxis should be targeted to the type of HSCT (i.e., autologous, allogeneic), local epidemiology, and risk factors for invasive fungal infection.^{1,19} The risk of invasive fungal infection is lower in autologous transplant recipients than allogeneic transplant recipients.¹ The optimal duration of antifungal prophylaxis in HSCT recipients remains to be determined.



The optimal time to initiate antifungal prophylaxis with mould coverage in HSCT recipients at high risk for invasive fungal infection is unclear. One possible approach is to administer fluconazole during the preengraftment and postengraftment phases, with mould coverage provided only during the late postengraftment phase.¹ Another possible approach is to begin mould-active prophylaxis in the preengraftment period and continue it through the late postengraftment period. The potential benefits of antifungal prophylaxis depend on the basal rate of fungal infections; if there is a low rate of *Aspergillus* infections in an institution, mould prophylaxis probably is not warranted.¹

In a randomized, double-blind study of 600 patients with severe graft-versus-host disease (grade II-IV or chronic) or who were receiving intensive immunosuppressive therapy after allogeneic HSCT, oral posaconazole was significantly more effective than oral fluconazole in preventing invasive *Aspergillus* infections, breakthrough invasive fungal infections, and breakthrough invasive fungal infections due to *Aspergillus*.²⁰ There were fewer deaths due to proven or probable invasive fungal infections in the posaconazole group than in the fluconazole group, although the difference in mortality was not significant. These findings suggest that this patient population stands to benefit from the expanded mould coverage provided by posaconazole, although fluconazole remains the gold standard for autologous and most allogeneic transplant recipients. Itraconazole and micafungin are alternative mould-active agents that may be used in this population. The optimal times to initiate and discontinue mould prophylaxis remain unknown.

“Fluconazole is the gold standard for antifungal prophylaxis in autologous and most allogeneic transplant recipients, but patients with severe graft-versus-host disease or receiving intensive immunosuppressive therapy after allogeneic transplants may benefit from the use of posaconazole instead because of its expanded mould coverage.”

—Peggy L. Carver, Pharm.D., FCCP

Practice Changes

Attendees at the CE in the Mornings program on the management of invasive fungal infections at the ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, in December 2010 were asked what changes to current practice or new services they planned to implement based on the knowledge acquired by participating in the program and what barriers might interfere with these plans. Roughly half (51%) of the 534 respondents plan to use evidence-based recommendations (including guidelines of the Infectious Diseases Society of America for 39% of respondents) when selecting antifungal therapy. Forty-two percent of respondents plan to consider initiating empiric antifungal therapy within 12 hours after drawing a positive blood culture in high-risk critically-ill and neutropenic patients to minimize hospital mortality. Approximately one in three (36%) respondents plan to develop a strategy for monitoring antifungal therapy (e.g., evaluating local epidemiology data, adverse events, drug interactions, and cost). Various barriers to implementing the plans were identified:

- Lack of availability of recommended antifungal agents in the institution
- Lack of time and personnel and financial constraints
- Low frequency of invasive fungal infection in local patient population
- Lack of cooperation from infectious diseases and other physicians
- Lack of clinical laboratory capabilities and resources

Information provided in the CE in the Mornings program on the management of invasive fungal infections should help overcome these barriers and improve patient care and outcomes.



Cost-Effectiveness

The cost-effectiveness of posaconazole, fluconazole, or itraconazole for preventing invasive fungal infection in neutropenic patients was compared using a model based on clinical trial data from patients with acute myelogenous leukemia or myelodysplastic syndromes and chemotherapy-induced neutropenia.¹⁹ Posaconazole was found cost-effective for preventing invasive fungal infection in neutropenic patients, with a 73% probability that posaconazole is cost saving compared with fluconazole and itraconazole and a 96% probability that the incremental cost-effectiveness ratio for posaconazole compared with the other two drugs is \$50,000 or less per life-year saved, a threshold commonly used to determine whether an expenditure is worthwhile for society.



References

1. McCoy D, Depestel DD, Carver PL. Primary antifungal prophylaxis in adult hematopoietic stem cell transplant recipients: current therapeutic concepts. *Pharmacotherapy*. 2009; 29:1306-25.
2. Arian & Rex. Manual of clinical microbiology. 8th ed. Washington, DC: American Society for Microbiology; 2003:1859.
3. Centers for Disease Control and Prevention, Infectious Disease Society of America, American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep*. 2000; 49(RR-10):1-125. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm>. [CDC/HSCT]
4. Grenouillet F, Millon L, Blasco G et al. Preemptive antifungal therapy in critically ill surgical patients. *J Invasive Fungal Infect*. 2007; 1(2):42-9.
5. Pappas PG, Kauffman CA, Andes D et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009; 48:503-35.
6. Chamilos G, Marom EM, Lewis RE et al. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. *Clin Infect Dis*. 2005; 41:60-6.
7. Imhof A, Balajee SA, Fredricks DN et al. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clin Infect Dis*. 2004; 39:743-6.
8. Alexander BD, Schell WA, Miller JL et al. *Candida glabrata* fungemia in transplant patients receiving voriconazole after fluconazole. *Transplantation*. 2005; 80:868-71.
9. Myoken Y, Kyo T, Kohara T et al. Breakthrough fungemia caused by azole-resistant *Candida albicans* in neutropenic patients with acute leukemia. *Clin Infect Dis*. 2003; 36:1496-7.
10. Matsue K, Uryu H, Koseki M et al. Breakthrough trichosporonosis in patients with hematologic malignancies receiving micafungin. *Clin Infect Dis*. 2006; 42:753-7.
11. Goodman D, Pamer E, Jakubowski A et al. Breakthrough trichosporonosis in a bone marrow transplant recipient receiving caspofungin acetate. *Clin Infect Dis*. 2002; 35:E35-6.



12. van Burik JA, Ratanatharathorn V, Stepan DE et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis*. 2004; 39:1407-16.
13. Walsh TJ, Tepler H, Donowitz GR et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med*. 2004; 351:1391-402.
14. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. *N Engl J Med*. 2004; 350:950-2.
15. Siwek GT, Dodgson KJ, de Magalhaes-Silverman M et al. Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. *Clin Infect Dis*. 2004; 39:584-7.
16. Kontoyiannis DP, Lionakis MS, Lewis RE et al. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. *J Infect Dis*. 2005; 191:1350-60.
17. Mousset S, Bug G, Heinz WJ et al. Breakthrough zygomycosis on posaconazole prophylaxis after allogeneic stem cell transplantation. *Transpl Infect Dis*. 2010; 12:261-4.
18. Schlemmer F, Lagrange-Xélot M, Lacroix C et al. Breakthrough Rhizopus infection on posaconazole prophylaxis following allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2008; 42:551-2.
19. O'Sullivan AK, Pandya A, Papadopoulos G et al. Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prevention of invasive fungal infections among neutropenic patients in the United States. *Value Health*. 2009; 12:666-73.
20. Ullman AJ, Lipton JH, Vesole DH et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007; 356:335-47.