ISSUE 1 CME/CE Newsletter

Progress in Prevention of IFIs & Promise of New Diagnostic Techniques

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IN THIS ISSUE . . .

During the past two decades, the field of clinical mycology has experienced dramatic advancements with respect to the prevention, diagnosis, and treatment of invasive fungal infections (IFIs). This progress has resulted in reductions of both morbidity and mortality in patients at high risk of infection, including (but not limited to) ICU patients, transplant recipients, and neutropenic patients. Radiographic and serologic diagnostic techniques now facilitate earlier and more accurate detection of these infections. Moreover, recent clinical studies provide insight into antifungal prophylaxis and the identification of those patients who would benefit most from this strategy.

Despite these major advancements, treatment failure remains all too common and mortality rates unacceptably high. Therefore, it is imperative that healthcare professionals involved in the care of patients at risk of IFIs keep abreast with the latest information that may impact prevention, diagnosis, and therapeutic strategies. In this newsletter, two critical areas, diagnostics and prophylaxis, are discussed. Summary of how advances in these areas may favorably impact patient outcomes is also presented.

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ACTIVITY TYPE
Knowledge-based and competence-based

TARGET AUDIENCE
This activity has been developed for clinical pharmacists, infectious diseases physicians, hematologists/oncologists, and transplant physicians responsible for the management of IFIs.

PURPOSE STATEMENT
The purpose of this activity is to educate physicians and pharmacists involved in the management of patients at risk of invasive fungal infections (IFIs) on prevention through the appropriate use of antifungal prophylaxis and early detection using new diagnostic techniques. With this knowledge, healthcare professionals will be able to minimize the incidence of IFIs and diagnose infection during the early stages.

LEARNING OBJECTIVES
At the conclusion of this activity, learners should be able to

- Assess the appropriate use of antifungal prophylaxis in immunocompromised patients
- Evaluate the utility of the latest diagnostic techniques for early detection of IFIs

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ACCREDITATION
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Off-label Disclosure Statement
During this activity, the following off-label uses of antifungal agents are discussed: itraconazole (for antifungal prophylaxis), voriconazole (for antifungal prophylaxis), liposomal amphotericin B (for antifungal prophylaxis), and inhalational formulations of amphotericin B (for antifungal prophylaxis).

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RECENT DIAGNOSTIC APPROACHES TO DETECT IFIs

The incidence of invasive fungal infections (IFIs), associated with high mortality rates in immunocompromised patients, has increased in recent years, most notably for hematologic stem cell and solid organ transplant recipients.[1-3] While *Candida* and *Aspergillus* remain the most common causative pathogens, infections due to other pathogens such as zygomycetes, *Fusarium*, and *Scedosporium* have also increased.[2, 4]

Challenges to timely diagnosis of IFIs

- Non-specific clinical features
- Lack of sensitive, minimally invasive assays
- Limitations associated with traditional diagnostic methods (culture)
  - Slow growth
  - Histological similarities among fungal pathogens
  - Frequent false-negative culture results

Risk factors contributing to ↑ IFIs[3]

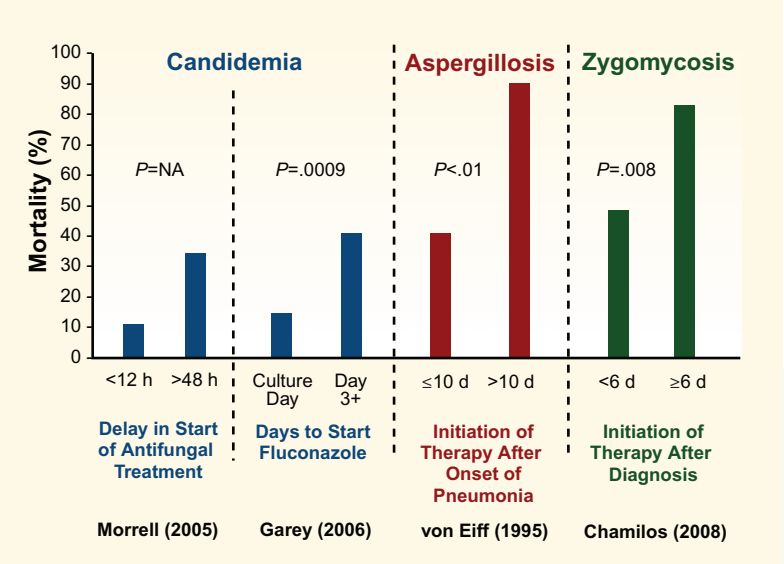
- ↑ IV catheters
- ↑ ICU admissions
- Development of novel immunosuppressive agents
- ↑ Solid organ transplants
- New modalities in stem cell transplantation

Studies have consistently demonstrated a significant increase in mortality if anitfungal therapy is delayed (**Figure 1**).[5-8] Therefore, the challenge is to identify the infection and initiate therapy at an early stage. The development of rapid serological assays and improved radiography has revolutionized the diagnosis of IFIs.

(1→3)-β-D-glucan Assay

The clinical use of the serum (1→3)-β-D-glucan assay is increasing. β-D-glucan is a cell wall constituent of many fungi, including *Candida* and *Aspergillus*, but excluding *Cryptococcus* and zygomycetes.[9] While helpful in making a presumptive diagnosis of IFIs, further follow-up is needed to confirm and identify the specific type of infection.[10] False-positives can occur from sources that can be contaminated with glucan during preparation, such as dialysis filters, gauze, sponges, intravenous immunoglobulin, or albumin.[10-12]

Figure 1. Delayed antifungal therapy = higher mortality in patients with IFIs[5-8]



The utility of this assay was evaluated in a multicenter study involving 333 subjects (163 with proven or probable infection by a variety of pathogens and 170 healthy volunteer control subjects).[10] The subjects with IFIs had a wide range of underlying diseases, including hematologic malignancy (20.2%), organ transplant (12.3%), gastrointestinal surgery (8.6%), solid tumor (8.6%), cardiovascular disease (8.0%), and HIV/AIDS (6.1%). The overall specificity was 87% and the sensitivity was 70%. The negative predictive value and positive predictive value were reasonably good—75% and 84%, respectively.

Most studies involving this assay have been done in stem cell transplant recipients and in patients with hematologic malignancies. Clinicians should be cautious when interpreting these for ICU patients or solid organ transplant recipients, as comprehensive data are lacking for these populations. Recently, β-D-glucan levels were analyzed in 17 patients at one institution who were diagnosed with *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia. Patients predominantly had hematologic malignancies, lymphomas, and solid tumors.[13] Very high levels of β-D-glucan were detected in these patients, suggesting that this assay may also be effective in detecting such infections.

PNA FISH™ Assay

The Peptide Nucleic Acid Fluorescent In Situ Hybridization (PNA FISH™) assay uses fluorescent markers to allow differentiation among *albicans* and non-*albicans Candida* species within 2–3 hours of a positive blood culture[14] reducing the time required for species differentiation from 1–2 days with traditional microbiological methods. This is particularly relevant to selecting an antifungal, since fluconazole remains highly active against *C. albicans* and is often preferred to the echinocandins in such infections given its lower cost and oral formulation.[15] In contrast, echinocandins are preferred in serious infections due to fluconazole-resistant pathogens, more frequent in non-*albicans Candida* species (notably *C. krusei* and *C. glabrata*).[16]

Early *Candida* species identification is associated with clinical advantages and cost savings. This was proven at the University of Maryland Medical Center where patients with candidiasis were treated empirically with an echinocandin until the species was identified, at which point fluconazole could be used if appropriate.[17] Incorporation of the PNA FISH™ assay in diagnosis resulted in decreased use of echinocandins and increased use of fluconazole, resulting in a saving of $1729 per patient.

Newer PNA FISH™ assays utilizing multiple fluorescent probes can differentiate several *Candida* species, including *C. krusei*, *C. glabrata*, and *C. parapsilosis*, and identify mixed *Candida* infections.[18]

Galactomannan Assay

The serum galactomannan assay uses an ELISA assay to measure the presence of galactomannan—a cell wall component generally specific to *Aspergillus* species.[9] False-positives have been reported in the presence of other fungi, with the use of piperacillin/tazobactam or ampicillin/sulbactam, in solid organ transplantation, or with gastrointestinal flora.[19, 20] False-negatives may occur in patients receiving prophylactic or empiric antifungal therapy.[19, 20]

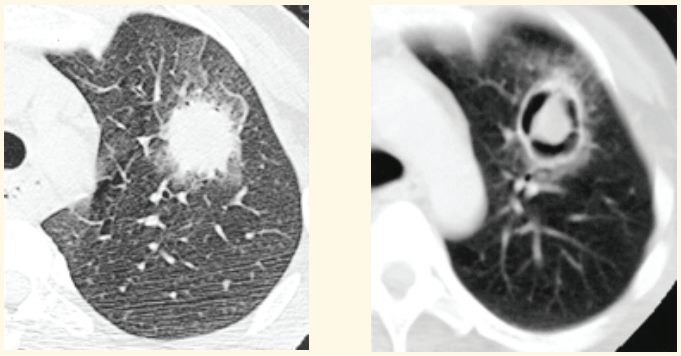
The utility of this assay was evaluated in a meta-analysis that included 27 studies.[21] While the overall sensitivity was 71% and specificity 89%, the sensitivity varied greatly depending on the patient population—70% in patients with hematologic malignancies, 82% in bone marrow transplant recipients, and 22% in solid organ transplant recipients. The specificity and sensitivity were also affected by the type of reference standard used for diagnosis in each study. Given the host-dependent sensitivity of the galactomannan assay, results should be interpreted with caution. A study at MD Anderson Cancer Center showed that the sensitivity of the galactomannan assay can also vary depending on the causative *Aspergillus* species—40% with non-*fumigatus Aspergillus* versus 13% with *A. fumigatus*.[22]

Recent evidence indicates increased sensitivity of the galactomannan assay with bronchoalveolar lavage (BAL) samples compared with serum samples. One study involving 110 patients at high risk of invasive aspergillosis (including 26 with proven infection) showed 88% and 42% sensitivity when using BAL and serum samples, respectively.[23]

High-resolution CT Scan

High-resolution computed tomography (CT) scans are important in early detection of IFIs. An early indicator of pulmonary aspergillosis is a halo sign, which consists of a dense area representing infarcted lung with a "halo" of ground glass density that represents hemorrhage (**Figure 2A**).[24] As time progresses, the dense area cavitates and the dead lung tissue begins to withdraw from the viable lung and produces an air-crescent sign **(Figure 2B)**.

Figure 2. Radiologic diagnosis of invasive pulmonary aspergillosis using high-resolution CT scans[24]



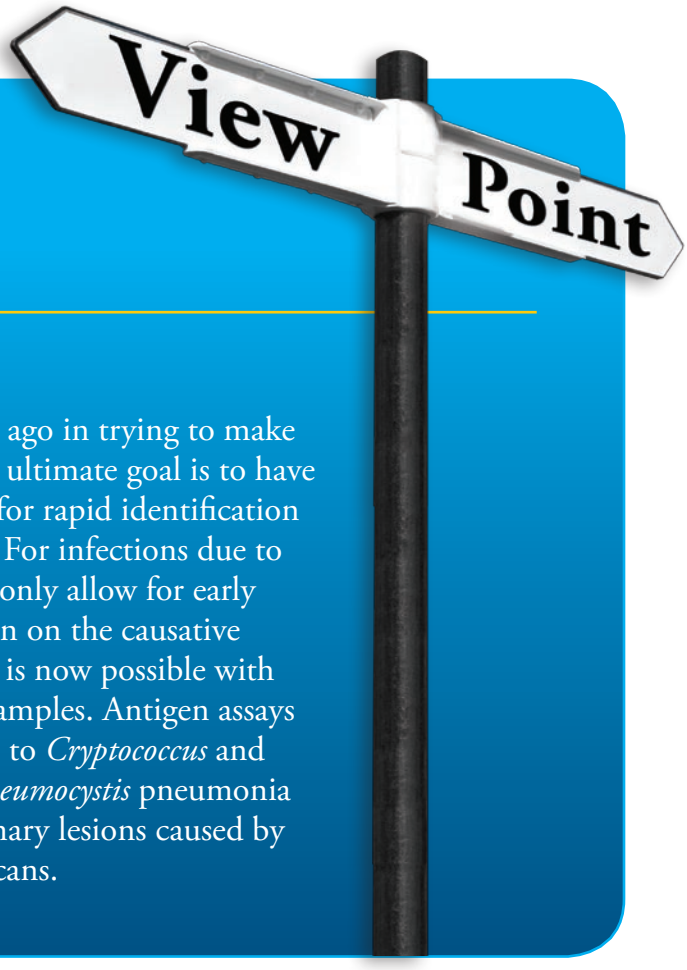
A. Halo Sign **B. Air-crescent Sign**

However, a halo sign is only suggestive of pulmonary aspergillosis. Conditions such as nocardiosis and tuberculosis can mimic this sign. The size of the nodule can be an important indicator of an IFI. Nodules greater than 1 cm have a higher likelihood to be due to an IFI, while smaller nodules and ground glass opacities are non-specific.[25]

More recently, zygomycetes infections have been associated with a reversed halo sign, characterized by focal ground glass opacity in the middle surrounded by a solid ring where hemorrhaging has occurred.[26] Though more research is needed, this early indicator may be useful to differentiate zygomycosis from aspergillosis.

PCR Techniques

Polymerase chain reaction (PCR) assays for IFI diagnosis are largely in the experimental stages. Anecdotal data suggest that these techniques may be valuable in detecting IFIs, particularly in combination with other diagnostic tools.[27] These techniques are not yet standardized and more data are needed before they can be utilized in the clinical setting.



Where do we stand today in IFI diagnosis?

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We have come a long way as compared to even 5 years ago in trying to make an early diagnosis of IFIs using non-invasive tests. The ultimate goal is to have non-invasive tests with high sensitivity and specificity for rapid identification of IFIs which in turn allows for early targeted therapy. For infections due to *Candida*, the β-D-glucan assay and PNA FISH™ not only allow for early detection of infection, but can also provide information on the causative species. Early detection of infections due to *Aspergillus* is now possible with the galactomannan assay using both serum and BAL samples. Antigen assays are effective in identifying patients with infections due to *Cryptococcus* and *Histoplasma*, while the β-D-glucan assay can detect *Pneumocystis* pneumonia and may eliminate the need for bronchoscopy. Pulmonary lesions caused by filamentous fungi can be detected early by using CT scans.

APPROPRIATE USE

Early placebo-controlled clinical trials have demonstrated that antifungal prophylaxis protects select populations of high-risk patients against IFIs.[28, 29]

Characteristics of an ideal antifungal agent for prophylaxis

- Efficacy proven by adequately controlled trials
- Active against "target" pathogens
- Stability against resistance
- Well-tolerated
- Predictable dose requirements
- Both IV and oral formulations
- Limited drug–drug interactions
- Low cost

Polyenes

Amphotericin B (AmB) deoxycholate and its lipid-based formulations exhibit broad-spectrum activity against yeasts and molds. Exceptions include pathogens less commonly encountered in the clinical setting, such as *Aspergillus terreus* and *Candida lusitaniae*. AmB, a fungicidal agent exhibiting concentration-dependent activity, has a high stability against resistance. It has been well studied in the clinical setting for both prevention and treatment of various IFIs, though fewer studies have been done with the lipid-based formulations as primary therapy.[30-32]

Significant limitations associated with AmB include nephrotoxicity, infusion-related reactions, and electrolyte depletion (such as hypokalemia). Significant reductions in nephrotoxicity have been noted with the lipid-based formulations (relative to AmB deoxycholate).[33]

AmB has limited drug–drug interactions, though caution should be exercised when using it concomitantly with other nephrotoxic agents. Availability only in IV formulations makes it impractical for long-term use. Lipid formulations are more costly compared to AmB deoxycholate.

Azoles

The azoles include fluconazole, itraconazole, voriconazole, and posaconazole. Differences in their spectrum of activity relative to pathogens targeted for prophylaxis are summarized in **Table 1**.[34, 35]

The azoles have been widely studied in a variety of clinical settings, including for prophylaxis and treatment of candidiasis and aspergillosis.[28, 36-38] Though generally well-tolerated, select azoles have been associated with gastrointestinal intolerance (itraconazole solution) and increased incidence of hepatotoxicity and visual disturbances (voriconazole).[37] Since all azoles inhibit cytochrome P-450 (CYP450) 3A4, drug interactions should be monitored.[34] Relative to other azoles, the potential for drug interactions increases with voriconazole due to inhibition of other CYP450 enzymes. All azoles are available in oral formulations, while fluconazole and voriconazole are also available for IV administration.

Itraconazole, voriconazole, and posaconazole serum concentrations may not be accurately predicted by dose.[34] Therefore, drug concentration monitoring may be necessary in select clinical settings (such as treatment of invasive disease or in settings where oral absorption may be compromised) to ensure that safe and effective serum drug concentrations are maintained.[34] Voriconazole and posaconazole are more expensive than fluconazole. Currently, IV voriconazole is contraindicated in patients with severe renal insufficiency.

Table 1. Comparison of relative in vitro activity of azole antifungal agents[34]

Azole	*C. albicans*	non-*albicans Candida*	*Aspergillus*	Zygomycetes
Fluconazole[16]	+	+/-	-	-
Itraconazole	+	+/-	+	-
Posaconazole	+	+	+	+
Voriconazole	+	+	+ Treatment of choice for aspergillosis (IDSA management guidelines)[35]	-

IDSA, Infectious Diseases Society of America.

Echinocandins

Echinocandins (caspofungin, micafungin, and anidulafungin) are the newest class of antifungal agents with in vitro fungicidal activity against *Candida* species and fungistatic activity against *Aspergillus*.[39] They lack activity in vitro against a number of potential fungal pathogens, such as *Cryptococcus*, zygomycetes, or *Trichosporon*, and show slightly reduced in vitro activity against *Candida parapsilosis* (relative to other *Candida* species).[16] Since they lack cross-resistance to the azoles, they have been proven effective against fluconazole-resistant *Candida* strains. The latest IDSA guidelines recommend echinocandins as the first-line therapy for invasive candidiasis in certain patient populations, such as neutropenic patients or in patients likely or proven to be infected with azole-resistant strains.[15]

Generally well-tolerated, echinocandins have limited drug–drug interactions.[33] They are only available in IV formulation and are more expensive than fluconazole. Published clinical experience with echinocandins as a prophylactic strategy is limited in certain high-risk patient populations, such as solid organ transplant recipients.

TARGET POPULATIONS

ICU Patients

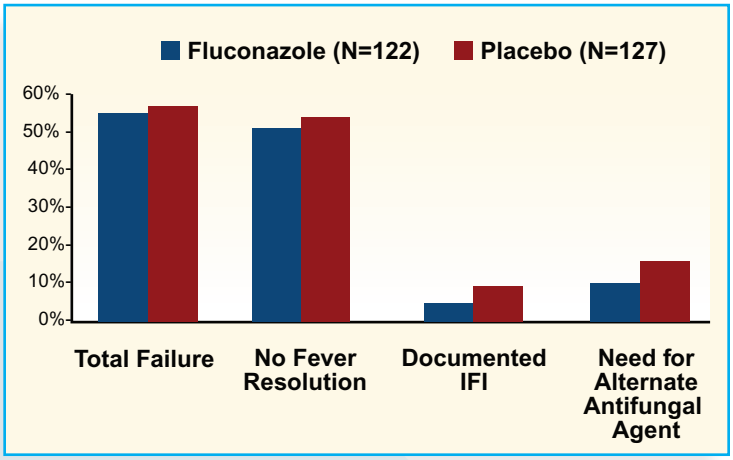
It may be worthwhile to consider antifungal prophylaxis in select ICU patients at high risk of an IFI, particularly invasive candidiasis in the surgical patient population.

Risk factors for candidiasis in ICU patients[15]

- Neutropenia
- Renal failure
- Total parenteral nutrition
- Broad-spectrum antibacterials
- Central venous catheter
- Implantable prosthetic devices
- Immunosuppressive therapy

Identifying ICU patients who should receive antifungal prophylaxis can be difficult as clinical trials do not demonstrate consistent benefits of prophylaxis in this patient population. One recent study compared outcomes of ICU patients who received fluconazole versus placebo.[40] All patients in the study were in the ICU for at least 96 hours, had high APACHE II scores (≥16), had fever for 4 days, were receiving broad-spectrum antibacterials, and had a CVC for over 24 hours. While fluconazole use was associated with a lower incidence of documented IFI and a decreased need for alternate antifungal agents than placebo use, the difference was not statistically significant (**Figure 3**). It is important to note that many of the patients in this study potentially had an active infection at the start of fluconazole treatment, and therefore this may not be considered prophylaxis.

Figure 3. Fluconazole (800 mg/day) versus placebo for IFIs in ICU patients[40]



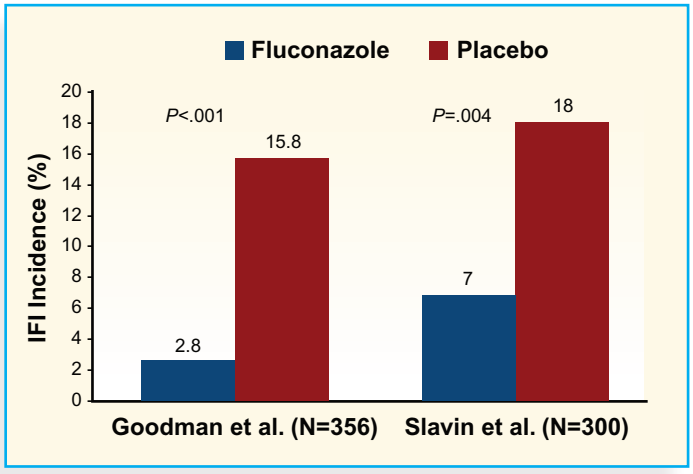
In another example that evaluated the benefits of antifungal prophylaxis in severely ill patients, a meta-analysis was conducted that included four randomized, placebo-controlled trials of fluconazole prophylaxis in surgical ICU patients.[41] This study demonstrated that prophylaxis significantly decreased the incidence of fungal infections (pooled OR: 0.44; 95% CI: 0.27–0.72; *P*<.001). However, the analysis did not show any significant improvement in survival (pooled OR for mortality: 0.87; 95% CI: 0.59–1.28; *P*: NS). The rates of candidemia were similar and low for those given fluconazole and those receiving placebo (2.2%). The authors concluded that further studies are needed to more precisely identify patients at high risk of infection.

Clinical trials generally fail to show a benefit of antifungal prophylaxis in non-neutropenic ICU patients. However, it is important to maintain continued vigilance in high-risk patients, either through the use of serological markers or one of the risk assessment scoring systems, such as the *Candida* Score or the BASMG predictive rule.[41, 42] It is also important to consider discontinuation of treatment in patients who receive early empiric therapy and who are stable and lack any supportive diagnostic evidence for an infection.

Patients with Hematologic Malignancies

Early studies showed that antifungal prophylaxis with fluconazole provided a significant benefit in preventing IFIs in patients with hematologic malignancies (**Figure 4**).[28, 29] A placebo-controlled study by Winston and colleagues demonstrated that fluconazole prophylaxis in patients with acute leukemia decreased proven overall (systemic plus superficial) infections (9% versus 21%; *P*=.02) and IFIs (4% versus 8%; *P*=.3), though the latter was not statistically significant.[43] Other studies comparing fluconazole with itraconazole tend to show that both are equally effective in preventing overall IFIs though itraconazole may offer added protection against invasive aspergillosis.[44, 45]

Figure 4. Early placebo-controlled trials demonstrating the benefit of fluconazole prophylaxis in bone marrow transplant recipients[28, 29]



A study comparing caspofungin with itraconazole in AML/MDS patients showed no significant difference in preventing IFIs (51% infection-free with itraconazole versus 52% with caspofungin).[46] An evaluator-blinded study in AML/MDS patients receiving chemotherapy compared posaconazole with fluconazole or itraconazole for IFI prevention.[36] Posaconazole was associated with a significantly lower percentage of proven or probable IFIs (2% versus 8%; *P*<.001). Both treatment groups had similar rates of candidiasis. Posaconazole was more effective in preventing aspergillosis (1% versus 7%; *P*=.001).

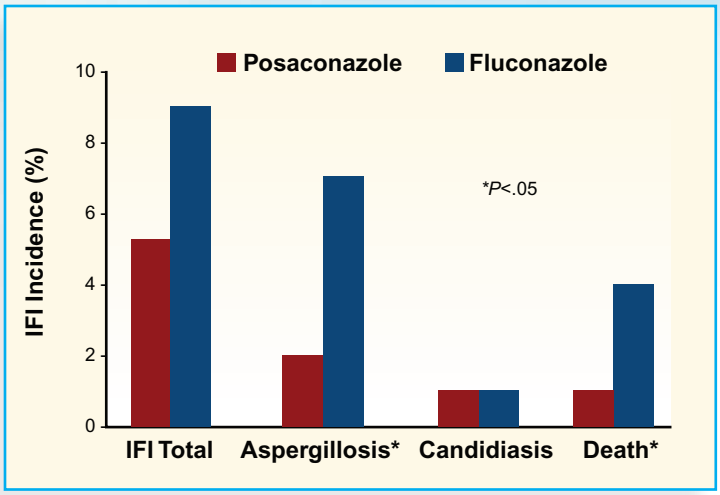
Guidelines from the National Comprehensive Cancer Network (NCCN) provide recommendations for antifungal prophylaxis in various subsets of neutropenic patients with hematologic malignancies.[47] For patients at lesser risk of mold infections (acute lymphocytic leukemia patients), either fluconazole or a lipid-based formulation of AmB is recommended for prophylaxis. For patients at greater risk of mold infections (MDS and AML patients), agents with anti-mold activity are recommended, including posaconazole, voriconazole, and lipid-based formulation of AmB.

HSCT Recipients

In hematopoietic stem cell transplant (HSCT) recipients, *Candida* species remain the main cause of IFIs immediately following the procedure[48] and *Aspergillus* becomes a major concern for longer periods after transplantation, particularly in patients who experience graft-versus-host disease (GvHD).[2, 48] Antifungal prophylaxis can be beneficial in these patients.

A study by Marr and colleagues showed a survival benefit in HSCT recipients who received fluconazole versus placebo (*P*=.0018).[49]A study by van Burik and colleagues comparing micafungin with fluconazole showed a significantly higher overall success rate with micafungin (80% versus 73.5%; *P*=.03).[50] Breakthrough infections, including aspergillosis, were not significantly different, though the use of empiric antifungal therapy was lower in the micafungin group (15.1% versus 21.4%; *P*=.024). Posaconazole, when compared with fluconazole in HSCT recipients with GvHD, was associated with a lower percentage of patients with IFIs (5.3% versus 9.0%; *P*=.07), and a significantly lower incidence of aspergillosis (*P*=.006) and death (*P*=.01) (**Figure 5**).[51]

Figure 5. Posaconazole versus fluconazole for prophylaxis in HSCT recipients with GvHD[51]

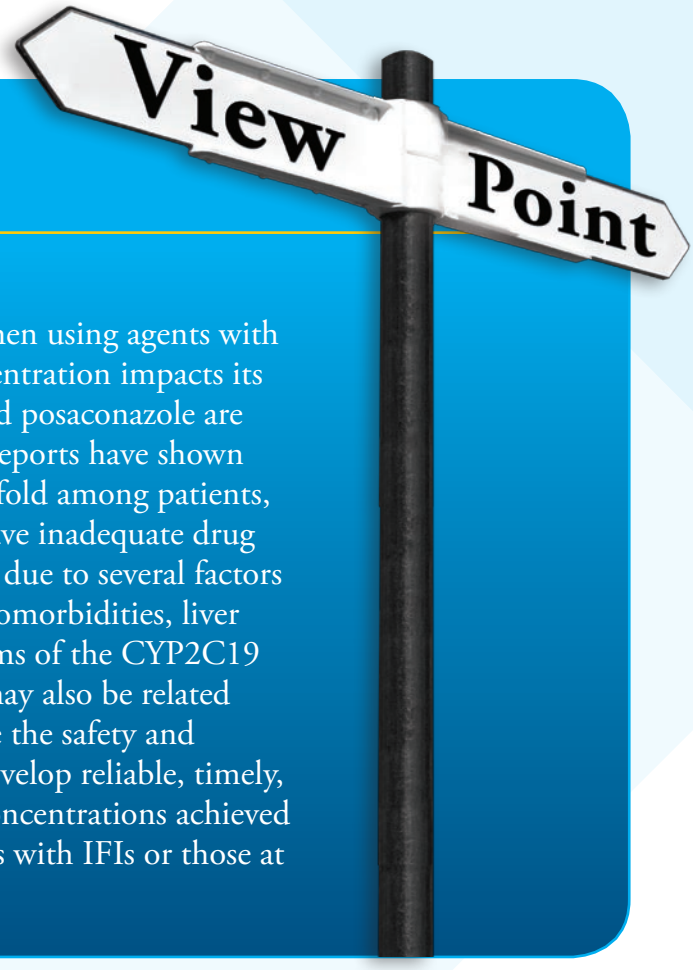


Solid Organ Transplant Recipients

When considering antifungal prophylaxis for solid organ transplant recipients, it is important to take into account the type of transplant. Aspergillosis is more common in heart and lung transplant recipients while candidiasis is common in kidney, liver, small bowel, or pancreas transplant recipients.[52] This is important when considering the prophylactic agent—fluconazole or an anti-mold agent.

The benefit of antifungal prophylaxis in liver transplant recipients has been demonstrated in a meta-analysis that included 6 studies using fluconazole, itraconazole, or liposomal AmB as prophylactic agents.[53] Antifungal prophylaxis was associated with a decreased risk of total fungal infections and IFIs. Moreover, a relatively low number of patients were needed to be treated to prevent one infection.

Published experience with inhalational formulations of AmB indicate that this may be a potential prophylactic strategy. The goal is to achieve high concentrations at the site of invasion with minimal adverse events. Clinical trials in lung transplant and HSCT recipients have demonstrated some success with this approach, though more research is needed to fully assess its utility in the clinical setting.[54-56]



Role of TDM

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Therapeutic drug monitoring (TDM) is important when using agents with unpredictable pharmacokinetics and when drug concentration impacts its effectiveness and safety. Itraconazole, voriconazole, and posaconazole are good candidates for TDM in select clinical settings. Reports have shown that voriconazole serum concentrations can vary 100-fold among patients, and up to 25% of allogeneic HSCT recipients may have inadequate drug exposure when using standard dosing.[57] This could be due to several factors including voriconazole pharmacokinetics, age, dose, comorbidities, liver function, drug interactions, and genetic polymorphisms of the CYP2C19 pathway.[58] Posaconazole effectiveness as prophylaxis may also be related to serum drug concentrations.[59] Therefore, to improve the safety and effectiveness of these agents, it will be important to develop reliable, timely, and cost-effective assays to measure the serum drug concentrations achieved when administering these agents, especially in patients with IFIs or those at increased risk of impaired oral absorption.

REFERENCES

1. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. *Clin Infect Dis.* 2008;47(8):1041-1050.
2. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mold infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2002;34(7):909-917.
3. Singh N. Trends in the epidemiology of opportunistic fungal infections: predisposing factors and the impact of antimicrobial use practices. *Clin Infect Dis.* 2001;33(10):1692-1696.
4. McNeil MM, Nash SL, Hajjeh RA, et al. Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997. *Clin Infect Dis.* 2001;33(5):641-647.
5. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother.* 2005;49(9):3640-3645.
6. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis.* 2006;43(1):25-31.
7. von Eiff M, Roos N, Schulten R, Hesse M, Zuhlsdorf M, van de Loo J. Pulmonary aspergillosis: early diagnosis improves survival. *Respiration.* 1995;62(6):341-347.
8. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. *Clin Infect Dis.* 2008;47(4):503-509.
9. Jones BL, McLintock LA. Impact of diagnostic markers on early antifungal therapy. *Curr Opin Infect Dis.* 2003;16(6):521-526.
10. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1→3)β-D-glucan assay as an aid to diagnosis of fungal infections in humans. *Clin Infect Dis.* 2005;41(5):654-659.
11. Kanda H, Kubo K, Hamasaki K, et al. Influence of various hemodialysis membranes on the plasma (1→3)β-D-glucan level. *Kidney Int.* 2001;60(1):319-323.
12. Usami M, Ohata A, Horiuchi T, Nagasawa K, Wakabayashi T, Tanaka S. Positive (1→3)β-D-glucan in blood components and release of (1→3)β-D-glucan from depth-type membrane filters for blood processing. *Transfusion.* 2002;42(9):1189-1195.
13. Marty FM, Koo S, Bryar J, Baden LR. (1→3)β-D-glucan assay positivity in patients with *Pneumocystis (carinii) jiroveci* pneumonia. *Ann Intern Med.* 2007;147(1):70-72.
14. PNA FISH™. Available at *www.advandx.com.* Accessed May 1, 2009.
15. 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(5):503-535.
16. Ostrosky-Zeichner L, Rex JH, Pappas PG, et al. Antifungal susceptibility survey of 2,000 bloodstream *Candida* isolates in the United States. *Antimicrob Agents Chemother.* 2003;47(10):3149-3154.
17. Forrest GN, Mankes K, Jabra-Rizk MA, et al. Peptide nucleic acid fluorescence in situ hybridization-based identification of *Candida albicans* and its impact on mortality and antifungal therapy costs. *J Clin Microbiol.* 2006;44(9):3381-3383.
18. Reller ME, Mallonee AB, Kwiatkowski NP, Merz WG. Use of peptide nucleic acid-fluorescence in situ hybridization for definitive, rapid identification of five common *Candida* species. *J Clin Microbiol.* 2007;45(11):3802-3803.
19. Aquino VR, Goldani LZ, Pasqualotto AC. Update on the contribution of galactomannan for the diagnosis of invasive aspergillosis. *Mycopathologia.* 2007;163(4):191-202.
20. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. *Lancet Infect Dis.* 2005;5(10):609-622.
21. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. *Clin Infect Dis.* 2006;42(10):1417-1427.
22. Hachem RY, Kontoyiannis DP, Chemaly RF, Jiang Y, Reitzel R, Raad I. Utility of galactomannan enzyme immunoassay and (1→3)β-D-glucan in diagnosis of invasive fungal infections: low sensitivity for *Aspergillus fumigatus* infection in hematologic malignancy patients. *J Clin Microbiol.* 2009;47(1):129-133.
23. Meersseman W, Lagrou K, Maertens J, et al. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. *Am J Respir Crit Care Med.* 2008;177(1):27-34.
24. Caillot D, Couaillier JF, Bernard A, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol.* 2001;19(1):253-259.
25. Escuissato DL, Gasparetto EL, Marchiori E, et al. Pulmonary infections after bone marrow transplantation: high-resolution CT findings in 111 patients. *Am J Roentgenol.* 2005;185(3):608-615.
26. Wahba H, Truong MT, Lei X, Kontoyiannis DP, Marom EM. Reversed halo sign in invasive pulmonary fungal infections. *Clin Infect Dis.* 2008;46(11):1733-1737.
27. Donnelly JP. Polymerase chain reaction for diagnosing invasive aspergillosis: getting closer but still a ways to go. *Clin Infect Dis.* 2006;42(4):487-489.
28. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med.* 1992;326(13):845-851.
29. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. *J Infect Dis.* 1995;171(6):1545-1552.
30. Patterson TF, Miniter P, Dijkstra J, Szoka FC, Jr., Ryan JL, Andriole VT. Treatment of experimental invasive aspergillosis with novel amphotericin B/cholesterol-sulfate complexes. *J Infect Dis.* 1989;159(4):717-724.
31. Walsh TJ, Finberg RW, Arndt C, et al; National Institute of Allergy and Infectious Diseases Mycoses Study Group. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *N Engl J Med.* 1999;340(10):764-771.
32. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis.* 2007;44(10):1289-1297.
33. Rapp RP. Changing strategies for the management of invasive fungal infections. *Pharmacotherapy.* 2004;24(2 Pt 2):4S-28S.
34. Dodds Ashley ES. Treatment options for invasive fungal infections. *Pharmacotherapy.* 2006;26(6 Pt 2):55S-60S.
35. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;46(3):327-360.
36. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole versus fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med.* 2007;356(4):348-359.
37. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med.* 2002;346(4):225-234.
38. Cha R, Sobel JD. Fluconazole for the treatment of candidiasis: 15 years experience. *Expert Rev Anti Infect Ther.* 2004;2(3):357-366.
39. Bowman JC, Hicks PS, Kurtz MB, et al. The antifungal echinocandin caspofungin acetate kills growing cells of *Aspergillus fumigatus* in vitro. *Antimicrob Agents Chemother.* 2002;46(9):3001-3012.
40. Schuster MG, Edwards JE, Jr., Sobel JD, et al. Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial. *Ann Intern Med.* 2008;149(2):83-90.
41. Leon C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system ("Candida score") for early antifungal treatment in non-neutropenic critically ill patients with *Candida* colonization. *Crit Care Med.* 2006;34(3):730-737.
42. Paphitou NI, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. *Med Mycol.* 2005;43(3):235-243.
43. Winston DJ, Chandrasekar PH, Lazarus HM, et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia: results of a randomized placebo-controlled, double-blind, multicenter trial. *Ann Intern Med.* 1993;118(7):495-503.
44. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood.* 2004;103(4):1527-1533.
45. Morgenstern GR, Prentice AG, Prentice HG, Ropner JE, Schey SA, Warnock DW; UK Multicentre Antifungal Prophylaxis Study Group. A randomized controlled trial of itraconazole versus fluconazole for the prevention of fungal infections in patients with haematological malignancies. *Br J Haematol.* 1999;105(4):901-911.
46. Mattiuzzi GN, Alvarado G, Giles FJ, et al. Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies. *Antimicrob Agents Chemother.* 2006;50(1):143-147.
47. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™. Available at *http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.* Accessed May 1, 2009.
48. Marty FM, Rubin RH. The prevention of infection post-transplant: the role of prophylaxis, pre-emptive, and empiric therapy. *Transpl Int.* 2006;19(1):2-11.
49. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. *Blood.* 2000;96(6):2055-2061.
50. 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(10):1407-1416.
51. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med.* 2007;356(4):335-347.
52. Singh N. Antifungal prophylaxis for solid organ transplant recipients: seeking clarity amidst controversy. *Clin Infect Dis.* 2000;31(2):545-553.
53. Cruciani M, Mengoli C, Malena M, Bosco O, Serpelloni G, Grossi P. Antifungal prophylaxis in liver transplant patients: a systematic review and meta-analysis. *Liver Transpl.* 2006;12(5):850-858.
54. Drew RH, Dodds Ashley E, Benjamin DK, Jr., Duane Davis R, Palmer SM, Perfect JR. Comparative safety of amphotericin B lipid complex and amphotericin B deoxycholate as aerosolized antifungal prophylaxis in lung transplant recipients. *Transplantation.* 2004;77(2):232-237.
55. Alexander BD, Dodds Ashley ES, Addison RM, Alspaugh JA, Chao NJ, Perfect JR. Non-comparative evaluation of the safety of aerosolized amphotericin B lipid complex in patients undergoing allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis.* 2006;8(1):13-20.
56. Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. *Clin Infect Dis.* 2008;46(9):1401-1408.
57. Trifilio S, Pennick G, Pi J, et al. Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. *Cancer.* 2007;109(8):1532-1535.
58. Lewis RE. What is the "therapeutic range" for voriconazole? *Clin Infect Dis.* 2008;46(2):212-214.
59. Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. *Pharmacotherapy.* 2007;27(12):1627-1636.

POST TEST | EVALUATION | AND CREDIT APPLICATION

Release Date: July 9, 2009 Expiration Date: July 9, 2010 Center Serial #: CV3102-1

Select your professional title: ☐ Physician ☐ Pharmacist Other _____

Select your practice setting: ☐ Teaching hospital ☐ Community hospital ☐ LTAC ☐ Other _____

Your evaluation and suggestions will help improve the quality of future continuing education activities. Please answer the following general questions, provide written comments, and evaluate the individual faculty. Additional space for your comments and suggestions is available. Thank you for your cooperation.

POST TEST (Please check the most appropriate answer)

1. β-D-glucan assay does not detect . . .
☐ *Candida albicans* ☐ *Aspergillus flavus* ☐ *Cryptococcus neoformans* ☐ *Pneumocystis jiroveci*

2. PNA FISH™ allows differentiation among species of . . .
☐ *Candida* ☐ *Aspergillus* ☐ Zygomycetes ☐ *Fusarium*

3. At the University of Maryland Medical Center, PNA FISH™ resulted in decreased use of . . .
☐ Fluconazole ☐ Voriconazole ☐ Echinocandins ☐ Polyenes

4. False-negatives with galactomannan assay have been associated with . . .
☐ Piperacillin/tazobactam ☐ Solid organ transplantation ☐ Ampicillin/sulbactam ☐ Antifungal prophylaxis

5. Early sign of pulmonary aspergillosis on a high-resolution CT scan is . . .
☐ Halo ☐ Air-crescent ☐ Reversed halo ☐ Nodules >1 cm

6. The adverse event NOT typically associated with amphotericin B deoxycholate is . . .
☐ Infusion-related reactions ☐ Visual disturbances ☐ Nephrotoxicity ☐ Hypokalemia

7. Which azole lacks activity against *Aspergillus*?
☐ Fluconazole ☐ Itraconazole ☐ Voriconazole ☐ Posaconazole

8. The echinocandins lack activity against . . .
☐ *Candida krusei* ☐ *Candida tropicalis* ☐ *Cryptococcus neoformans* ☐ *Aspergillus fumigatus*

9. Which of the following is NOT a risk factor for candidiasis in ICU patients?
☐ Neutropenia ☐ Antifungal prophylaxis ☐ Central venous catheter ☐ Total parenteral nutrition

10. For the posaconazole vs. fluconazole prophylaxis study in HSCT recipients with GvHD, which statement is FALSE?
☐ No difference in candidiasis between treatment groups ☐ Posaconazole significantly reduced aspergillosis
☐ Posaconazole significantly reduced IFI-related deaths ☐ Posaconazole significantly reduced total IFIs

LEARNING OBJECTIVES: Were the learning objectives met?	Yes	Somewhat	No
1. Assess the appropriate use of antifungal prophylaxis in immunocompromised patients	☐	☐	☐
2. Evaluate the utility of the latest diagnostic techniques for early detection of IFIs	☐	☐	☐

If you answered 'No' to any objective, please explain.

SCIENTIFIC CONTENT: Please rate	Excellent	Good	Fair	Poor
1. The scientific content of this activity was	☐	☐	☐	☐
2. The level of expertise of the authors was	☐	☐	☐	☐

OVERALL EVALUATION	Yes	Somewhat	No
1. This activity met my expectations.	☐	☐	☐
2. The content was relevant to my practice.	☐	☐	☐
3. This activity was fair and balanced.	☐	☐	☐
4. This activity was without commercial bias.	☐	☐	☐

If you answered "No" to 3 or 4, please explain.

LEARNING FORMAT	Yes	Somewhat	No
1. The format enhanced achievement of learning objectives.	☐	☐	☐
2. The format was easy to follow and understand.	☐	☐	☐

PRACTICE APPLICATION

1. What aspects of this activity were most relevant to your practice?

2. Please list one diagnostic tool that can be used for early detection of an IFI that you learned in this activity.

3. Will you make changes to your practice based on participation in this activity? If yes, please specify.

4. What aspects of IFIs do you need to learn more about to improve your practice performance?

DO YOU HAVE (1) ANY SUGGESTIONS FOR IMPROVING THIS ACTIVITY or (2) ANY ADDITIONAL COMMENTS?

CREDIT APPLICATION (Please Print)

Name and Degree _____

Address _____

City _____ State _____ ZIP _____

E-mail _____ May we contact you by e-mail? ☐ Yes ☐ No

Type of credit requested ☐ Pharmacy CPE ☐ MD/DO *AMA PRA Category 1 Credit™*

I certify that I have reviewed *Progress in Prevention of IFIs & Promise of New Diagnostic Techniques.*

Signature _____ Date _____

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This Newsletter is part of the Initiative *Preventing & Managing IFIs: Progress & Promise in the 21st Century*. The first step in this Initiative consisted of 2 Live Webinars, now available as On-demand Webinars in which experts in medical mycology discuss scientific evidence. Podcasts represent the second step in this Initiative. Scientific evidence presented in the Webinars is reinforced and placed in clinical context through case discussions between physician and pharmacist experts. This approach highlights clinical considerations that both specialties should be aware of when formulating and evaluating their management approach.

To access these On-demand Webinars and Podcasts, please visit *www.vemcomeded.com* (go to CME Portal).