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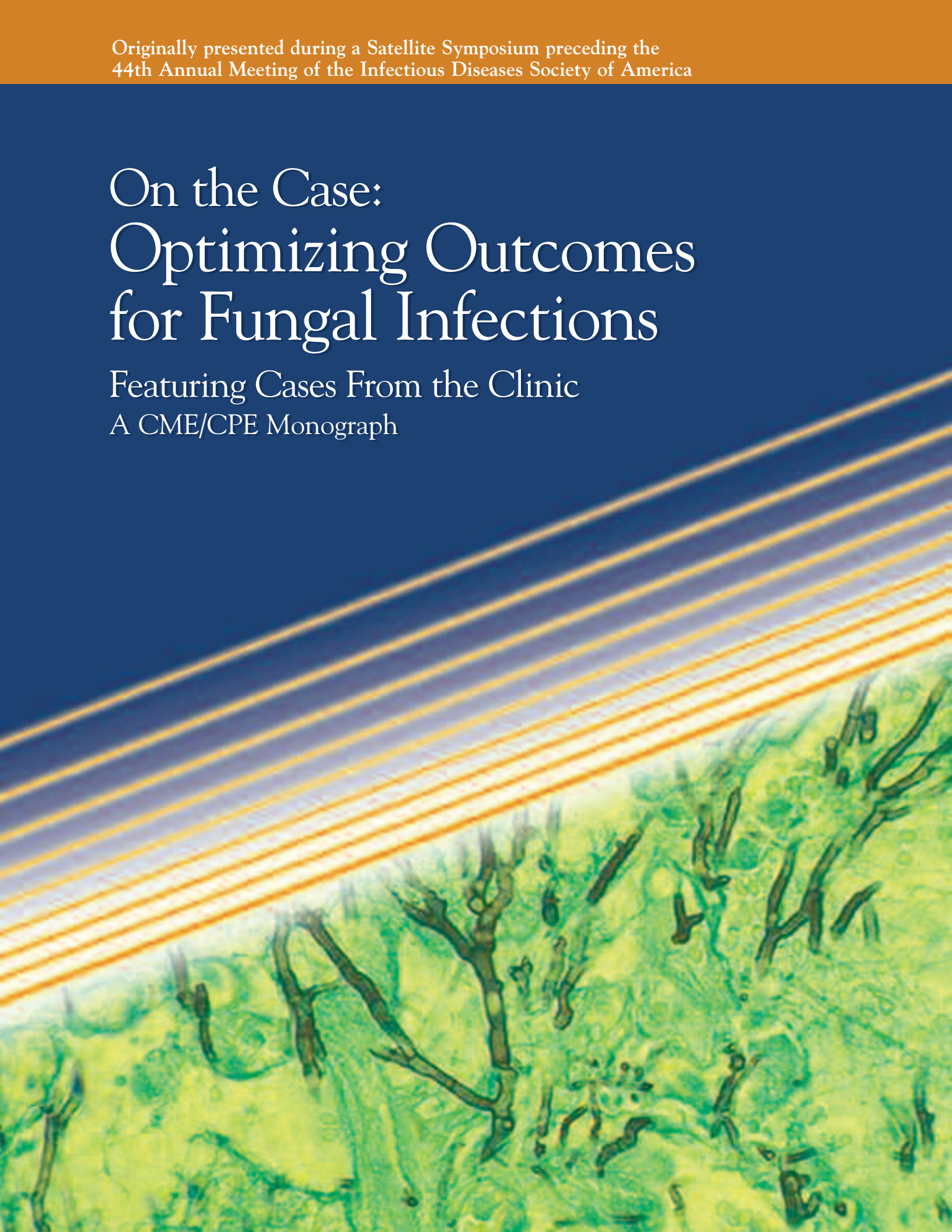
On the Case: Optimizing Outcomes for Fungal Infections

Featuring Cases From the Clinic

A CME/CPE Monograph



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Accreditation

Activity Purpose

This activity is intended to assist physicians and pharmacists in the management of life-threatening invasive fungal infections using real cases from the clinic to address key issues.

Educational Objectives

Upon completion of this activity, clinicians should be able to:

- Identify patient and pathogen risk factors contributing to the development of fungal infections
- List key clinical signs and symptoms as well as appropriate diagnostic tests for the accurate diagnosis of fungal infections
- Select appropriate therapeutic strategies for the treatment of fungal infections as well as understand the potential role of new and emerging treatment options
- Assess the role of prophylactic and empiric therapy for the prevention and treatment of fungal infections

Target Audience

This educational activity is intended for physicians, pharmacists, and other healthcare professionals who treat patients with or who are at risk for serious invasive fungal infections.

Accreditation Statements

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Faculty Disclosures

Jack D. Sobel, MD has received grants from Pfizer Inc., Merck & Co., Inc., and Astellas Pharma. He is a member of the Speakers Bureaus of Merck & Co., Inc. and Pfizer and participates in an advisory board for Merck & Co., Inc.

Carol A. Kauffman, MD has received research grants from Merck & Co., Inc., Astellas Pharma, and Schering-Plough Corporation. She is a member of the Speakers Bureaus of Merck & Co., Inc., Astellas Pharma, Pfizer Inc., and Schering-Plough Corporation.

John E. Bennett, MD does not have any relevant financial relationships to disclose.

Discussion of Off-Label Use

At the time of the release of this CME/CPE activity, the following non–FDA-approved off-label uses of the following antifungal agents are discussed in this educational activity: amphotericin B deoxycholate and lipid formulations of amphotericin B as well as aerosolized delivery of these agents as prophylaxis for invasive fungal infections; fluconazole for the treatment of invasive aspergillosis; itraconazole as prophylaxis for invasive fungal infections and the treatment of coccidioides infections; voriconazole as prophylaxis for invasive fungal infections; and micafungin for primary and salvage treatment of invasive aspergillosis, as well as coccidioides infections.

Antifungal Therapy: Focus on Prophylaxis

Historically, invasive fungal infections (IFIs) have been associated with a high mortality rate, and outcomes have been poor. This emphasizes the importance of prophylactic strategies. The high mortality rate associated with fungal infections is due in part to difficulties of diagnosis and treatment, which result in infections that are all too frequently diagnosed at an advanced stage and prone to rapid progression. Early risk assessment and diagnosis, as well as appropriate treatment, are required for successful clinical outcomes. Diagnosis is further complicated by the fact that there are few signs and symptoms for systemic fungal infections, and immunosuppression masks the typical clinical markers of systemic infection. Often sputum and blood cultures are negative and invasive diagnostic procedures are associated with greater risk in patients that are hypoxic and/or thrombocytopenic.[1]

Principles of Antifungal Use

Prophylactic, empiric, preemptive, and therapeutic use represent viable options for the prevention and treatment of IFIs. Prophylactic use is the universal administration of antifungal therapy to all at-risk patients to prevent IFIs. Empiric use is the administration of antifungal therapy to patients at high risk of IFIs, such as patients with persistent neutropenic fever. Preemptive antifungal therapy is given when IFIs are suspected and the patient has radiographic and/or laboratory data that support the diagnosis. Therapeutic use is the administration of antifungal therapy for the treatment of proven fungal infections.[2] Though empiric, preemptive, and therapeutic use are essential strategies for the treatment of probable and proven IFIs, the optimal strategy may well be focusing on preventing infections in the first place.[3] Therefore, the following discussion will highlight the current clinical approach to prophylaxis for IFIs.

Potential Patient Groups for Prophylaxis

Antifungal prophylactic strategies vary by clinical condition; however, solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients are the patient subgroups that most often receive routine antifungal prophylaxis. Another potential subgroup of patients for routine antifungal prophylaxis includes patients receiving care in the intensive care unit (ICU). However, conflicting evidence exists regarding antifungal prophylaxis in the ICU. The most comprehensive assessment of the issue of routine antifungal prophylaxis concerns a meta-analysis of nine studies showing benefit from azole prophylaxis in the ICU. There was, however, wide variability in the design of the separate studies, and most were conducted prior to changes in the epidemiology of *Candida* species.[4] Prior to the implementation of routine antifungal prophylaxis in the ICU, data are required to define the population that would receive the most benefit from prophylaxis and the long-term effects on fungal epidemiology.

Transplant Recipients and the Risk for Infection

A central component in preventing and treating infections caused by a wide variety of pathogens, including fungi, is assessing patient risk. In transplant patients, the range of organisms capable of causing infections is quite extensive. Simply, they can be classified as true pathogens, "sometime" pathogens, or non-pathogens. True pathogens are obvious and include the usual bacterial and viral organisms. "Sometime" pathogens are those that normally reside on mucocutaneous surfaces and are usually not clinically significant until injury introduces these pathogens to internal tissues and invasive infections. "Non-pathogens" are those common environmental organisms typically controlled by the host's innate immunity that generally only cause disease in significantly immunocompromised patients. Examples of these opportunistic infections include aspergillosis and candidiasis. Transplant patients are at risk for all three types of infection.[5] The risk of infection in transplant patients is determined by three factors, as shown in Table 1. These factors are: pathogen exposure, organism virulence, and the "net state of immunosuppression," which describes the additive effect of antirejection medications, immunomodulatory viral infections, and co-morbid disease states. The risk of developing IFIs varies by organ system transplanted as does the causative fungal pathogen.[6] Table 2 indicates the incidence of IFIs depending upon the organ transplanted.

Table 1. Factors for Assessing Infection Risk in the Transplant Patient

Factor 1: Exposure

- Environment
  - Community acquired
  - Nosocomial
- Donor/allograft
  - Prior infections (e.g., herpes viruses, tuberculosis, fungal pathogens)
- Endogenous
  - Prior exposures (e.g., herpes viruses, tuberculosis, fungal pathogens)

Factor 2: Organism virulence

- Organism ability to cause infection at a given site (e.g., adherence factors, growth factors)

Factor 3: State of immunosuppression[7]

- Immunosuppressive regimen
  - Dose, duration, and temporal sequence
- Underlying immune deficiency (e.g., autoimmune disease)
- Lack of integrity of mucosal barrier
  - Catheters, epithelial surfaces
- Devitalized tissue, fluid collections
- Neutropenia, lymphopenia
- Metabolic conditions
  - Uremia, malnutrition, diabetes mellitus, alcoholism with cirrhosis
- Infection with immunomodulating viruses
  - Cytomegalovirus (CMV), Epstein-Barr virus, hepatitis B & C viruses, HIV

Table 2. Incidence of IFIs by Type of Organ Transplant[8]

Type of Transplant	Incidence of IFIs, %	Proportion of IFIs, %	
		Aspergillus	*Candida*
Kidney	1.4 – 14	0 – 10	90 – 95
Heart	5 – 21	77 – 91	8 – 23
Liver	7 – 42	9 – 34	35 – 91
Lung & heart/lung	15 – 35	25 – 50	43 – 72
Small bowel	40 – 59	0 – 3.6	80 – 100
Pancreas	18 – 38	0 – 3	97 – 100

The Temporal Etiology of Infection

In both SOT and HSCT, immunosuppressive regimens designed to prevent rejection have become standardized so as to confer the greatest period of immunosuppression in the first few months post-transplant and to allow for tapered immunosuppression over time given the absence of organ rejection or graft-versus-host disease (GVHD). The time course of the incidence of different infections reflects the level of immunosuppression and the corresponding risk of infection.

Understanding the spectrum of infection risk and relevant antifungal prophylactic strategies for SOT and HSCT recipients is useful. A knowledge of temporal etiology helps determine a differential diagnosis for the patient with an infectious disease syndrome, as well as serving as a guide for infection control strategies and a means for cost-effective preventive strategies.[5]

Solid Organ Transplantation

In the SOT patient, the spectrum of infection risk or "timetable of infection" (see Figure 1) may be divided into three distinct periods: the first month following transplant; one to six months following transplant; and more than six months following transplant.[2, 5, 7]

First month post-transplant

In the first month following SOT, there are three categories of infection. These include unresolved infection, which is present in the patient prior to surgery and may in fact be exacerbated by the surgery; infections derived from the donor organ, including through its procurement, transport, and implantation; and nosocomial infection acquired in the same manner as non-immunocompromised patients undergoing comparable surgery.[5] *Candida* is the most common fungal pathogen and most often causes bloodstream, urine, or intra-abdominal infection.

One to six months post-transplant

At this stage, opportunistic infections are more common due to prolonged, high-level immunosuppression, the lasting effects of induction agents, and maintenance immunosuppressive drugs. Organisms causing opportunistic infections include fungal pathogens in three distinct categories: yeasts (e.g., *Cryptococcus*, *Candida*), molds (e.g., *Aspergillus*, *Zygomycetes*), and endemic pathogens (e.g., *Histoplasma*).

More than six months post-transplant

Patients who have experienced a good outcome with SOT, where there is no organ dysfunction and no treatment for organ rejection, have about the same risk of infection as that of the general population. There is a persistent low-level risk for invasive fungal pathogens.

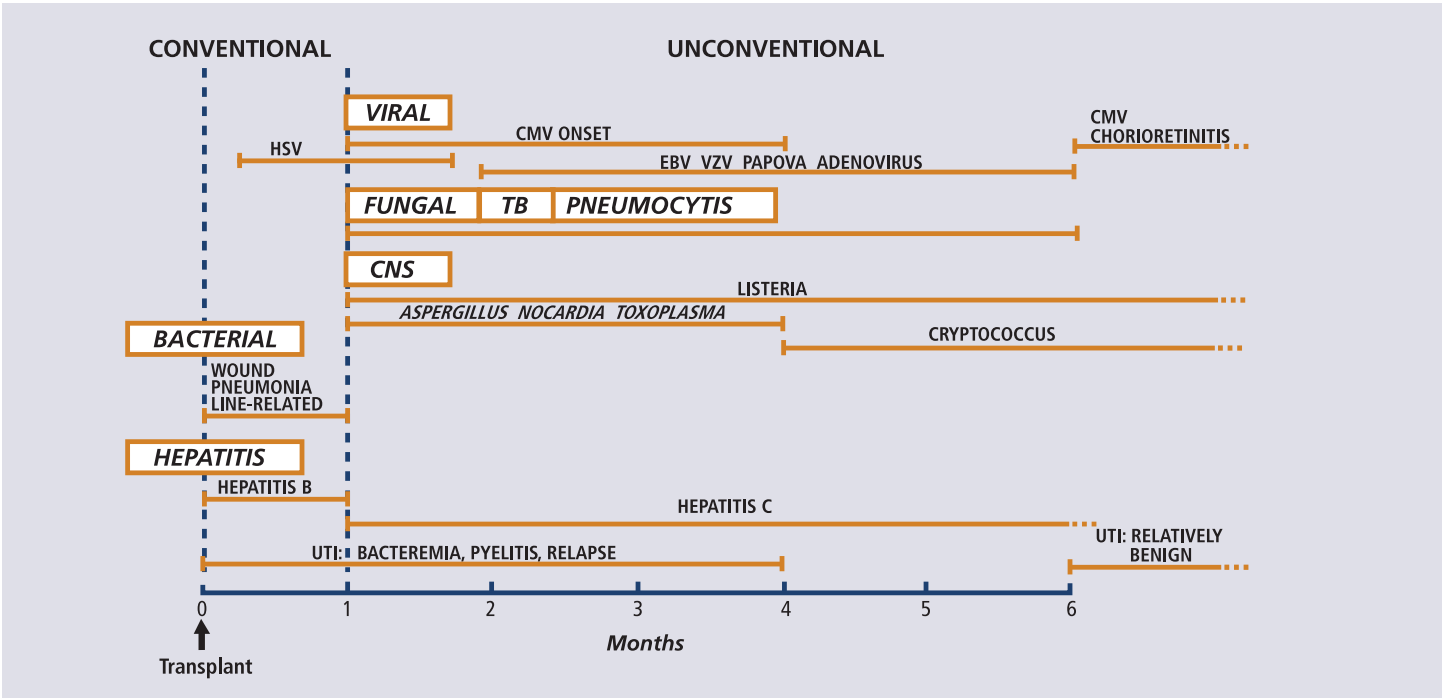

Figure 1: Timetable of infection after solid organ (renal) transplantation. HSV, herpes simplex virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; VZV, Varicella (Herpes) Zoster virus; Papova, papovaviruses (BK and JC); TB, tuberculosis. Reprinted with permission from Marty et al. *Transpl Int*. 2006; 19:2-11.

Delineation of risk factors for fungal infection can identify candidates for targeted prophylaxis during the most vulnerable period immediately after transplantation and also at later times. Risk factors vary in their contribution to the development of fungal infection and the pathogenesis varies according to the pathogen and allograft. Table 3 outlines patient risk factors, possible prophylactic strategies, and treatment considerations by type of organ.

Table 3. Patient Risk Factors and Treatment Considerations by Organ Type[2]

Organ type	Risk factors	Therapeutic options and considerations
Kidney	• Universal prophylaxis not recommended	• For asymptomatic persistent candiduria, fluconazole may be used for eradication

Heart	• In the absence of invasive disease, preemptive therapy should be considered during periods of increased risk:
	  • Enhanced immunosuppression
	  • Therapy with antilymphocyte antibodies
	  • CMV infection
		• Isolation of *Aspergillus* from a respiratory specimen is highly suggestive of invasive disease

Liver	• Pre-transplant fulminant hepatic failure • Primary allograft failure or severe dysfunction • Retransplantation • Acute renal failure or hemodialysis • High perioperative transfusion requirement • Use of OKT3 monoclonal antibody preparations • United Network for Organ Sharing (UNOS) status 1 or 2a	• Consider antifungal prophylaxis in patients at high risk for aspergillosis • Lipid formulations of amphotericin B (LFAB) 2.5-5 mg/kg/day • Fluconazole may be used in patients at risk for invasive candidiasis or low-risk patients for a short duration
Lung	• Preoperative isolation of *Aspergillus* species from respiratory cultures • Donor bronchus cultures positive for *Candida* or other fungal isolates • Hyperacute rejection • Acute graft failure or severe dysfunction • Severe lung dysfunction from lung injury or reimplantation response • Bronchial ischemic or poorly vascularized bronchial segments • Early isolation of *Aspergillus* from respiratory culture • Anastomotic dehiscence • CMV infection • Retransplantation	• In high-risk recipients, an antifungal with activity against *Aspergillus* should be considered • Aerosolized ABLC, aerosolized AmBd, itraconazole, or voriconazole[9] • Duration of prophylaxis should extend through anastomotic remodeling (4-8 months)
Small bowel	• Graft rejection • High-level immunosuppression • Gastrointestinal translocation • Transplantation of a colonic segment • CMV infection • Multivisceral transplantation	• Fluconazole is sufficient for the prevention of *Candida* infections • Consider LFABs in patients with known isolates of non-*albicans Candida* and/or patients undergoing simultaneous liver transplantation
Pancreas	• Enteric drainage • Older donor age • Older recipient age • Vascular graft thrombosis • Retransplantation • Long preservation time	• Consider fluconazole for patients a high-risk of fungal infections • Duration determined by reduction of risk factors • Consider local fungal epidemiology and utilize an alternative agent if there is a high incidence of fluconazole resistance

Hematopoietic Stem Cell Transplant

There are two important factors that determine complications due to infections in HSCT patients. The first concerns the rate at which bone marrow and the immune system revitalize, and the second concerns whether or not significant GVHD has developed in the HSCT patient. Advancement in nonmyeloablative conditioning regimens minimizes the period and intensity of neutropenia and mucositis. However, the overall risk of complications from infections especially due to opportunistic pathogens is not reduced. The same environmental exposures and vascular access risk factors that are important in SOT patients are also important in HSCT recipients.[5]

As with SOT, there is a delineated timetable of infection associated with HSCT (see Figure 2). The time period after transplantation may be divided into three discrete phases.[5]

Phase 1 is associated with profound neutropenia and mucositis. It begins with the conditioning regimen and extends until engraftment occurs. Possible risk of infectious disease falls into two basic categories. The first is possible residual infection from pretransplant exposure. Invasive aspergillosis represents the best example of this, and the risk of *Aspergillus* infection increases with the duration of neutropenia. The second category of risk is a new infection, particularly a bloodstream infection caused by bacterial organisms or *Candida* species. This type of infection is generally related to compromised mucocutaneous membranes.

Phase 2 encompasses that period of time between engraftment and 100 days post-transplant. The highest incidence of herpesvirus reactivation, especially CMV, is seen in Phase 2. If engraftment is delayed, then the risk of invasive aspergillosis increases significantly.

Phase 3 occurs more than 100 days post-transplant, when the risk of infection is determined primarily by the presence of GVHD. In the absence of GVHD, common infections include those caused by varicella zoster virus, *Streptococcus pneumoniae*, respiratory viruses, and CMV. In the presence of GVHD and its treatment, there is significant risk of infection with CMV, *Pneumocystis jiroveci*, invasive fungi, and other opportunistic organisms.

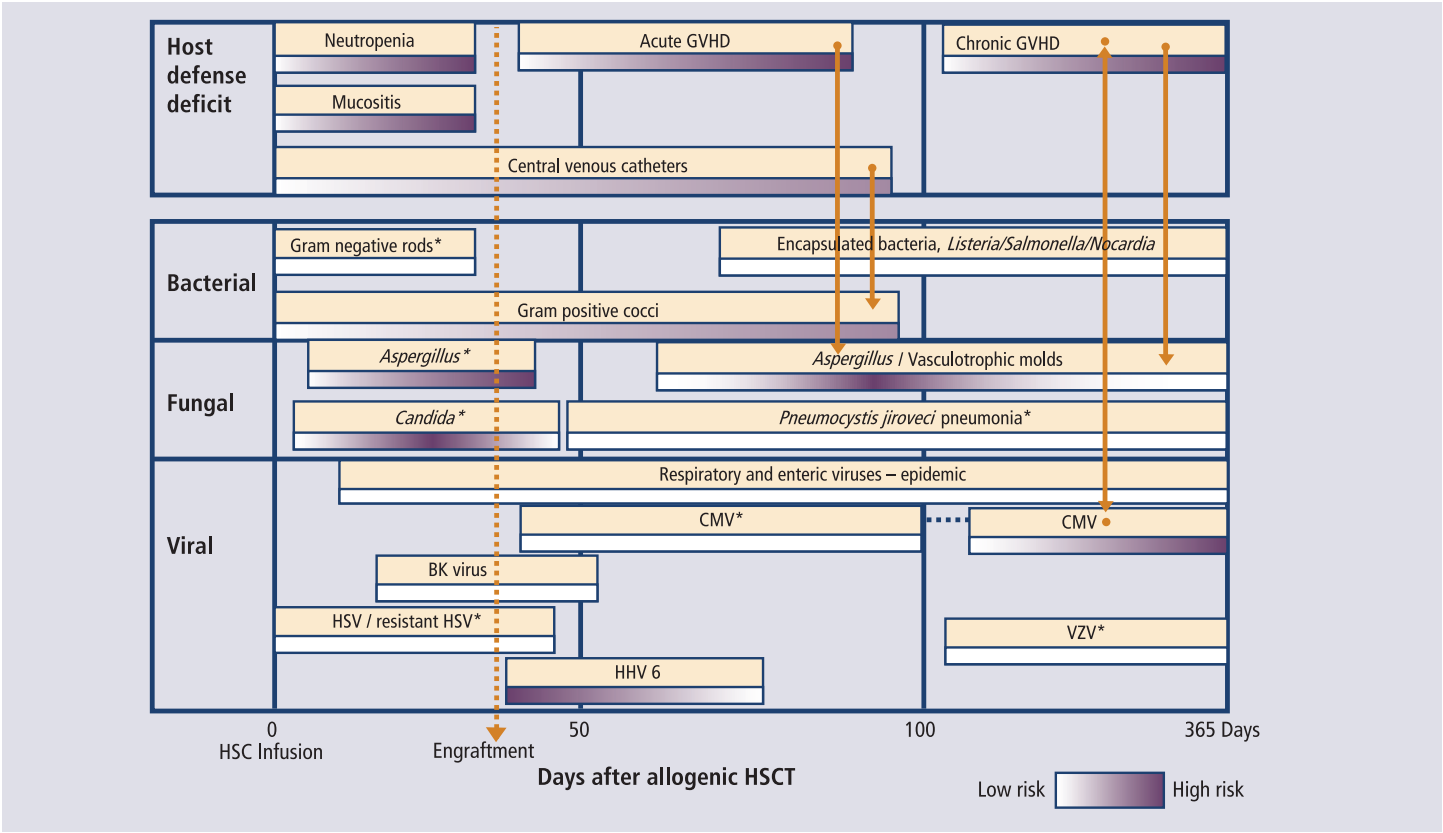

Figure 2: Timetable of infection after HSCT. Infections are depicted in relation to the changing pattern of host immunological condition over transplantation. The risk density is represented by the bar underlying a specific pathogen(s). *Highlights microorganisms for which an established antimicrobial strategy is commonly used in clinical practice. HHV6, human herpesvirus-6. Reprinted with permission from Marty et al. *Transpl Int*. 2006;19:2-11.

IFIs in HCST

In summary, there are two distinct peaks in the incidence of IFIs in patients receiving HSCT-the period of pre-engraftment prior to transplantation and late post-transplantation. In the presence of severe, persistent granulocytopenia during pre-engraftment, residual infections commonly caused by *Aspergillus* or new *Candida* infections are prevalent IFIs for HSCT recipients during this time period. As the duration of granulocytopenia increases, the incidence of angioinvasive fungal infections due to *Aspergillus*, *Scedosporium*, and *Fusarium* increases significantly, thus underscoring the role of granulocytes in preventing these infections. Preventative strategies include systematic use of protective gear (e.g., gloves and masks) by healthcare workers; HEPA filtration and positive pressure ventilation in patient rooms; and prophylactic antifungal therapy. The second period associated with increased risk and incidence of IFIs is late (>100 days) post-transplantation and is closely linked with the incidence of GVHD requiring more intense and prolonged immunosuppressive therapy. Invasive aspergillosis is the most prevalent IFI associated with HSCT complicated by GVHD.

Options for Prophylactic Therapy in HSCT

The number of antifungal agents is steadily increasing, which warrants a reevaluation of strategies employed to prevent infection in at-risk patients. Clinical evidence supports the use of specific antifungal agents as prophylactic therapy in HSCT.

Fluconazole

There are many studies in the literature that show the benefits of fluconazole prophylaxis, now used as standard preventative therapy in transplantation patients. The rate of mucosal and systemic fungal infections has dropped[10, 11], and the chances for survival have improved.[11] A concern with routine fluconazole use is its decreased activity against *C. glabrata* and lack of activity against *C. krusei* and molds, including *Aspergillus* species.

Itraconazole

Two randomized, controlled studies have compared fluconazole with itraconazole oral solution[12,13], since the oral solution was found to have more reliable bioavailability than the oral capsules. Study results showed that there was a decreased incidence of invasive aspergillosis in the itraconazole arms. However, the survival rate tended to be worse among those patients receiving itraconazole due to high amounts of toxicity.

Voriconazole

Currently, one randomized clinical trial is underway to compare fluconazole with voriconazole. Data are pending.

Posaconazole

A randomized, controlled study compared the efficacy of posaconazole with fluconazole for prophylaxis in HSCT recipients with GVHD.[14] While patients were receiving study medications in the GVHD study, there were fewer breakthrough IFIs including invasive aspergillosis in the posaconazole group compared with the fluconazole group.[14] A second study compared posaconazole with fluconazole or itraconazole in high-risk patients with neutropenia as a result of acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS).[15] Study findings showed that there was a decreased incidence of IFIs and fewer breakthrough fungal infections, including aspergillosis, in the neutropenic patients receiving posaconazole prophylaxis, showing improved overall survival.[15] No difference in safety and tolerability was detected in either study among the three agents.[14, 15]

Micafungin

A randomized, controlled trial compared micafungin with fluconazole for prophylaxis in neutropenic patients undergoing HSCT.[16] During prophylaxis and for 4 weeks following the end of treatment, the micafungin group experienced fewer fungal infections. A similar rate of breakthrough candidemia existed in both groups, and the fluconazole arm showed a trend toward increased aspergillosis. There was no difference in mortality between the two groups.

Options for Treating Invasive Fungal Infections

Historically, amphotericin B deoxycholate (AmBd) has been the antifungal medication of choice for the treatment of invasive fungal infections due to its broad spectrum of activity. However, toxicities such as nephrotoxicity and infusion-related reactions have limited its use.

Recently, there have been advances in the antifungal armamentarium including the introduction of three lipid-based formulations of amphotericin B (LFABs) from 1995 to 1997: amphotericin B lipid complex (ABLC); amphotericin B colloidal dispersion (ABCD); and liposomal amphotericin B (L-AmB), which many believe should replace AmBd as the gold-standard antifungal agent.[17]

Fluconazole, introduced in 1990, provided a safe, oral therapy against candidiasis and cryptococcosis.[18, 19] Itraconazole, marketed two years later, provided similar anti-*Candida* activity and improved activity against organisms such as *Blastomyces*, *Histoplasma*, and *Aspergillus*.[20] Voriconazole, which demonstrated superior efficacy compared with AmBd against invasive aspergillosis, was introduced in 2002.[21] In 2006, posaconazole was approved by the Food and Drug Administration (FDA) and has an antifungal spectrum similar to itraconazole with up to twofold more activity against *Zygomycetes*.[22] The echinocandins, which have a novel site of action, were first introduced with caspofungin in 2001. Micafungin and anidulafungin were FDA approved in 2005 and 2006, respectively, and as a class they possess a broad anti-*Candida* spectrum.[23]

As the number of treatment options against invasive fungal infections has increased, there have been shifts in fungal epidemiology as well. The frequency of invasive fungal infections has increased over the past 20 years. This is directly related to an expanding immunocompromised population, including bone marrow and SOT recipients, patients undergoing major surgery, patients with HIV infection, malignancy or advanced age, patients receiving immunosuppressive therapy, and premature infants.[24]

The most frequently occurring fungal pathogens are the *Candida* species. *Candida albicans* remains the most common *Candida* species causing infection, but the rate of infections secondary to non-*albicans Candida* is increasing.[24, 25] Non-*albicans* species such as *C. glabrata* and *C. krusei* are concerning due to decreased fluconazole susceptibility.[23, 24] Among mold pathogens, *Aspergillus* species remain an important cause of invasive disease in immunocompromised hosts, especially among patients with hematological malignancy or after bone marrow transplantation. Invasive aspergillosis is associated with significant morbidity and mortality rates of over 50%.[24] Equally concerning are non-*Aspergillus* molds, which are increasing in frequency.[26, 27] Marr et al. reported that the three most common non-*Aspergillus* molds in stem cell transplant recipients are *Fusarium*, *Scedosporium*, and *Zygomycetes*[26], which are also associated with high mortality rates. In addition to yeasts and molds, geographically restricted dimorphic fungi, *Blastomyces*, *Coccidioides*, and *Histoplasma*, are capable of causing invasive disease, especially among immunocompromised hosts.

Despite advances in antifungal treatment options, the best use and timing of these agents are unclear. A significant challenge in the treatment of fungal infections is that there are limited data available regarding the efficacy of antifungal medications. Randomized, controlled trials are rare, and much of the information used to guide treatment decisions is from anecdotal reports.

The four cases that follow address the subtleties of clinical diagnosis and treatment for representative yeast, mold, and endemic fungal infections.

Featuring Cases From the Clinic: Yeasts, Molds, and Endemics

Invasive Candidiasis

Candida species are the most common cause of fungal infections and may range in presentation from mucocutaneous disease to invasive, life-threatening illness. This section will discuss the epidemiology, associated risk factors, clinical presentation, and pharmacologic management of invasive _Candida_ infections.

Epidemiology

Candidemia is the fourth leading cause of nosocomial bloodstream infections after coagulase-negative staphylococci, *Staphylococcus aureus*, and Enterococcus species[28] and is associated with high mortality.[29] Among *Candida* species, *C. albicans* remains the most common species causing invasive infection, although the incidence of infections caused by non-*albicans Candida* is increasing.[23, 24] In the microbiology laboratory, *C. albicans* can be easily differentiated from other *Candida* species by its characteristic germ tube production after incubation at 37°C for 2-3 hours (see Figure 3). Though the susceptibility of *Candida* to the currently available antifungal agents can be predicted if the species of the infecting isolate is known (Table 4), individual isolates do not necessarily follow the general pattern. The concept of "susceptibility–dose/delivery dependent" (S-DD) indicates that maximization of dosage and bioavailability are critical to successful therapy (Table 5). In the case of fluconazole, data for both humans and animals suggest that S-DD isolates may be treated successfully with a dosage of 12 mg/kg per day.[23]

Table 4. General Patterns of Susceptibility of *Candida* species[23]

***Candida* species**	**Fluconazole**	**Itraconazole**	**Voriconazole**	**Flucytosine**	**AmBd**	**Candins**
C. albicans	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S (to I?)
C. glabrata	S-DD to R	S-DD to R	S to I	S	S to I	S
C. krusei	R	S-DD to R	S to I	I to R	S to I	S
C. lusitaniae	S	S	S	S	S to R	S

S = susceptible; I = intermediate; S-DD = susceptible dose-dependent; R = resistant

Table 5. Interpretative Breakpoints for Isolates of *Candida* species

	MIC range, µg/mL		
	Susceptible	Intermediately susceptible	Resistant
Fluconazole	≤8	16 – 32 (S-DD)	>32
Itraconazole	≤0.125	0.25 – 0.5 (S-DD)	>0.5
Flucytosine	≤4	8 – 16	>16

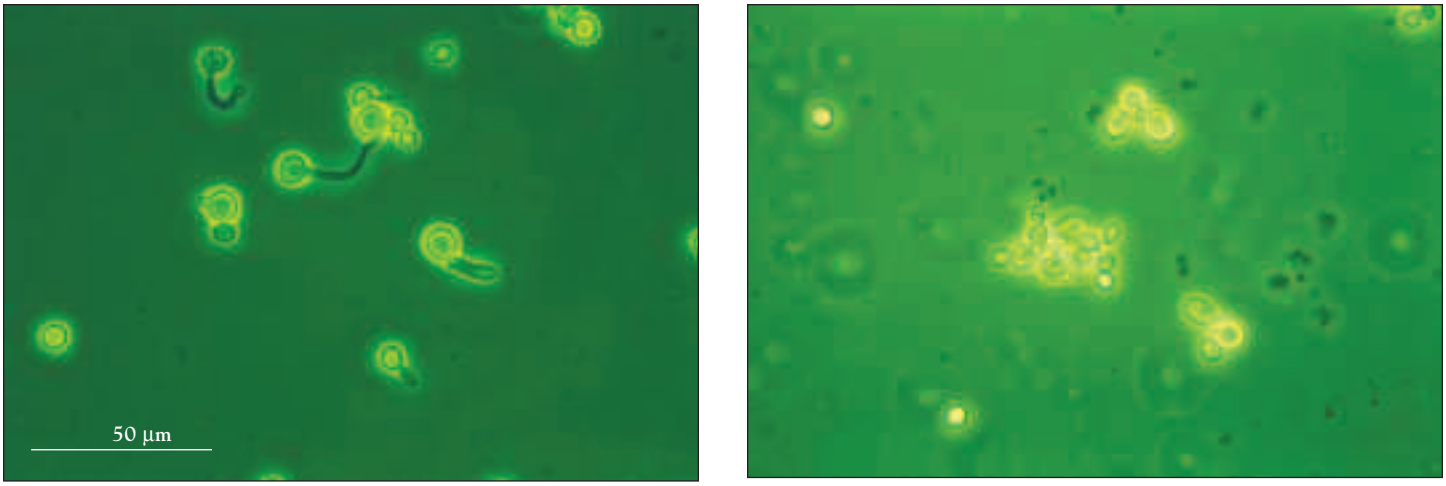

Figure 3. *Candida albicans*, with characteristic germ tubes at left. Non-*albicans Candida*, germ-tube negative at right. Source: Mycology Online http://www.mycology.adelaide.edu.au

Who Is at Risk for Invasive Candidiasis?

Candida species are symbiotic organisms that are a component of normal flora and may be found in the mouth, colon, vagina, and on the skin. In general, patients are at increased risk of developing invasive infection when the skin barrier is penetrated, for example through surgery or the use of intravascular catheters. Infection may also develop after exposure to broad-spectrum antimicrobial agents or in the presence of an immunocompromising condition.

Risk Factors for Invasive Candidiasis

- Hematologic malignancy
- Neutropenia
- Gastrointestinal surgery
- Prematurity (neonates)
- Age >70 years
- Presence of vascular catheters
- Exposure to broad-spectrum antibiotics
- Renal failure
- Prolonged ICU stay
- Receipt of parenteral nutrition
- Mucosal colonization with *Candida* species

Clinical Presentation

Invasive candidiasis may present as an acute or subacute illness. The clinical manifestations are non-specific, and often a fever refractory to broad-spectrum antibiotics may be the primary sign of infection. The various sites for infection are listed in the box below.

Sites of Invasive Candidiasis

- Bloodstream
- Urine
- Intra-abdominal
- Central nervous system (CNS)
- Heart
- Kidney
- Eye
- Bone

Case 1: Invasive Candidiasis following Laparotomy and Gastrectomy

A 57-year-old male with a past medical history of esophageal reflux and a 35-pack per year smoking history was admitted to the hospital with acute abdominal pain lasting 3-4 hours. The patient was diagnosed with an acute peptic ulcer perforation, and an exploratory laparotomy was performed. A periperforation intraoperative swab was sent for culture. The next day *Candida albicans* was identified.

Assessing the Patient's Risk

This patient's primary risk factor for invasive candidiasis was the abdominal surgery. Most likely he had an intravascular catheter and may have received systemic antibiotics which would have also contributed to his risk for systemic *Candida* infection.

The Decision to Treat

The first decision is whether or not to treat based solely on an intraoperative swab culture, which would depend on clinical status and suspicion of fungal infection. The availability of azole antifungals has lowered the threshold for antifungal therapy.

Weighing Benefits Against Risks

When weighing the benefits of antifungal therapy against the potential risks and disadvantage of treatment, there are three important questions for clinicians to address.

Question 1: Does the patient appear clinically ill? For example, is the patient febrile; is there an elevated WBC count; and is hemodynamic stability maintained?

Question 2: Is the patient immunocompromised?

Question 3: If the patient received antifungal therapy, do the benefits of treatment outweigh the potential risk of drug toxicity and resistance?

Choosing Optimal Antifungal Therapy

If the decision is made to treat, there are several factors to consider when deciding on first-line therapy. If the *Candida* species is known, drug choice should be based on general susceptibility patterns (Table 4). Local fungal epidemiology and the results of antifungal drug susceptibility testing, if performed, should be taken into account. Patient-specific considerations include severity of illness, immunosuppressed status (e.g., HIV infection, immunosuppressive medications), and the patient's recent history of fungal infections and/or antifungal medication exposure. In addition, drug specific concerns include nephrotoxicity with amphotericin B, hepatotoxicity and insufficient urinary concentrations with the echinocandins and azoles (except fluconazole), and drug interactions with the azoles.

Given the identification of *C. albicans*, antifungal therapy with fluconazole was initiated. Tissue biopsy of the gastric ulcer revealed gastric carcinoma for which a gastrectomy and an esophageal-jejunal anastomosis were performed. Eight days after gastrectomy and one day after fluconazole discontinuation, the patient developed signs of sepsis and peritonitis with a confirmed anastamotic leak.

Is Empiric Antifungal Therapy Indicated?

Given the patient's recent fluconazole exposure, there is potential for fluconazole resistance as evidenced by selection of non-*albicans Candida* species. In light of the patient's worsening status, broadening antifungal coverage with an echinocandin or amphotericin B agent might be considered. This would empirically cover for *Candida* species with decreased fluconazole susceptibility. Regardless of the antifungal agent chosen, therapy should be altered if necessary and narrowed, if possible, based on culture and susceptibility data.

Case 2: Invasive Candidiasis following Gastric Bypass Surgery

A 48-year-old female underwent laparoscopic gastric bypass surgery (Roux-en-Y) for extreme obesity. Day 1 postoperatively, the patient developed fever, respiratory distress, hypotension, acute renal failure, and respiratory distress requiring mechanical ventilation. On physical exam, the patient was noted to have icteric sclerae, a distended abdomen with absent bowel sounds, and normal-appearing postsurgical incisions. The patient had a local anesthetic pump, two Jackson Pratt drains, and multiple intravenous (IV) and intra-arterial (IA) lines. A gram stain of a tracheal aspirate revealed many WBCs, mixed upper respiratory flora, and rare yeast. The culture grew beta-lactamase positive *Haemophilus influenzae*. Urinalysis showed <5 WBC and urine culture grew >10^5 colonies of C. *glabrata*. Blood cultures were negative and an abdominal CT was not performed due to size limitations

Assessing the Patient's Risk

This patient had the following risk factors for the development of intra-abdominal candidiasis: gastrointestinal surgery, vascular catheters, broad-spectrum antibiotics, renal failure, prolonged ICU stay, and mucosal colonization with *Candida* species.

The Decision to Treat

Initial antimicrobial therapy included cefepime, metronidazole, and vancomycin. Given the lack of pyuria, the decision was made not to start antifungal therapy.

The local anesthetic pump was removed and the intravascular catheter tip grew >15 colonies of yeast for which IV fluconazole was started. Given the patient's lack of fluconazole exposure and a chronic immunocompromising condition, fluconazole was reasonable initial therapy.

One week postoperatively, a 1300 ml hematoma was evacuated. The hematoma culture revealed C. *albicans* and C. *tropicalis*; antimicrobials were altered to tigecycline and caspofungin. Although C. *albicans* and C. *tropicalis* are generally susceptible to fluconazole, antifungal therapy was changed to caspofungin for its broader anti-*Candida* spectrum. The gastrografin swallow study was negative.

Important Attributes of "Ideal" Antifungal Agents

- Broad-spectrum coverage
- Oral and intravenous formulations
- Few drug-drug interactions
- Good tolerability profile

Two weeks after bypass laparoscopy, brownish fluid was noted to be draining from the incision site. Culture of the fluid revealed C. *albicans*, C. *tropicalis*, C. *glabrata*, and C. *krusei*, for which ABLC was added. Unfortunately, due to multiple and severe post-operative complications, the patient expired one week later. An autopsy was performed and gastric contents were noted throughout the peritoneal cavity. A 700-gm intraperitoneal hematoma in the left paracolic gutter and marked peritoneal adhesions were noted. No intestinal perforation or anastamotic leak was identified.

"The biggest challenges in the treatment of fungal infections are early and accurate diagnosis and the selection and timing of appropriate therapy."

–Jack Sobel

Therapeutic Considerations in the Treatment of Invasive Candidiasis

Invasive candidiasis can be a serious, life-threatening complication among postsurgical, immunocompromised, and critically ill hospitalized patients. Initial antifungal therapy should be based on fungal epidemiology, the patient's history of infection and/or antifungal medication exposure, severity of illness, and immunosuppressed status until the *Candida* species and drug susceptibility data are available. Table 6 (below) provides a summary of pharmacologic management of invasive candidiasis based on IDSA 2004 guidelines.

Table 6. Summary of Recommended Pharmacologic Treatment*[23]

	Therapy		
Condition	**Primary**	**Alternative**	**Duration**
Candidemia			
Non-neutropenic adults	AmBd 0.6–1 mg/kg/day or FLU 400–800 mg/day or CAS	AmB 0.7 mg/kg/day + FLU 800 mg for 4–7 days, then FLU 800 mg/day	14 days after last positive blood culture and resolution of signs and symptoms
Children	AmBd 0.6–1 mg/kg/day or FLU 6 mg/kg q12h	CAS	14–21 days after resolution of signs and symptoms and negative repeat blood cultures
Neonates	AmBd 0.6–1 mg/kg/day or FLU 5–12 mg/kg/day	CAS	14–21 days after resolution of signs and symptoms and negative repeat blood cultures
Neutropenia	AmBd 0.7–1 mg/kg/day or LFAB 3–6 mg/kg/day or CAS	FLU 6–12 mg/kg/day	14 days after last positive blood culture and resolution of signs and symptoms and resolved neutropenia
Chronic disseminated candidiasis	AmBd 0.6–0.7 mg/kg/day or LFAB 3–5 mg/kg/day	FLU 6 mg/kg/day or CAS	3–6 months and resolution or calcification of radiologic lesions
Urinary candidiasis	FLU 200 mg/day or AmBd 0.3–1 mg/kg/day	5-FC 25 mg/kg q6h	7–14 days
Osteomyelitis and arthritis	AmBd 0.5–1 mg/kg/day x 2–3 weeks, then FLU	FLU 6 mg/kg/day	6–12 months
Intra-abdominal candidiasis	AmBd or FLU		Based on clinical response (approximately 2–3 weeks)
Endocarditis	AmBd 0.6–1 mg/kg/day (or LFAB 3–6 mg/kg/day) plus 5-FC 25–37.5 mg/kg q6h	FLU 6–12 mg/kg/day or CAS	Minimum of 6 weeks after valve replacement
Meningitis	AmBd 0.7–1 mg/kg/day plus 5-FC 25 mg/kg q6h	FLU (follow-up therapy or long-term suppressive therapy)	Minimum of 4 weeks after resolution of signs and symptoms
Endophthalmitis	AmBd 0.7–1 mg/kg/day or FLU 6–12 mg/kg/day		6–12 weeks after surgery

*These guidelines were published prior to the FDA approval of voriconazole and anidulafungin for the treatment of candidemia and invasive candidiasis.[30, 31] In addition, micafungin 100 mg/day has been shown to be equivalent to caspofungin.[32] Posaconazole has demonstrated in vitro activity against *Candida* species as well[6], but is not approved by the FDA for this indication. Updated IDSA invasive candidiasis guidelines are expected in summer 2007.
FLU=fluconazole, CAS=caspofungin

Aspergillosis

Aspergillus is a ubiquitous mold that exists in all parts of the world.[33] There are more than 185 species and about 20 of these are pathogenic in humans. The most common species include *A. fumigatus*, *A. flavus*, and *A. niger*. *Aspergillus* is frequently found in soil and plants, but it may also be present indoors. *Aspergillus* may be identified by colony color and size and, as shown in Figure 4, by its conidial heads.

Clinical Presentation

Invasive aspergillosis is the most common invasive mold infection. Associated with severe immunosuppression, aspergillosis can occur in patients undergoing high-dose chemotherapy followed by bone-marrow transplantation or in patients undergoing solid organ transplantation. *A. fumigatus* and *A. flavus* are the most common species associated with infection; however, reports of infection caused by other species have also been documented. Exposure is universal, occurring via inhalation, but *Aspergillus* is an opportunistic pathogen and rarely causes infection in nonimmunocompromised hosts. The most common manifestation of infection is pneumonia, but *Aspergillus* may cause infection in almost every organ including the CNS, skin, and sinuses.

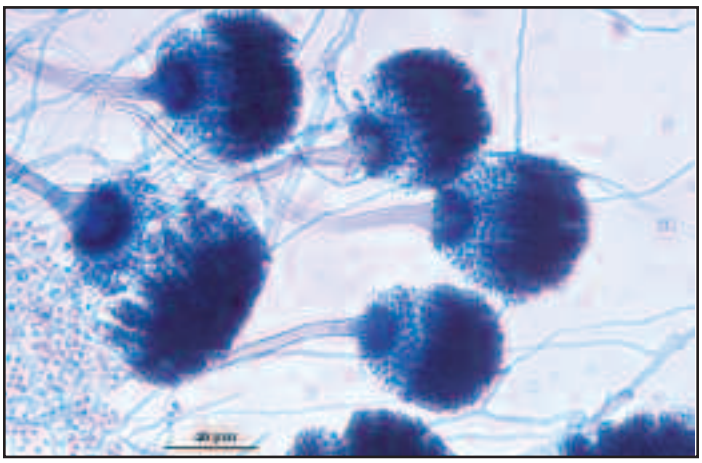

Figure 4: Microscopic morphology of *Aspergillus fumigatus* shows typical columnar, uniseriate conidial heads. Source: Mycology Online http://www.mycology.adelaide.edu.au

Aspergillosis After Stem Cell Transplantation

Patients receiving stem cell transplantation are at high risk of invasive aspergillosis. The incidence of infection is higher among allogeneic (vs. autologous) HSCT recipients as shown in Figure 5. Proven or probable invasive aspergillosis is present in 10%–12% of these patients. Onset of disease is bimodal (see Figure 6), where the first peak in incidence occurs during the initial neutropenia at a median of Day +16.[34] The second peak coincides with the development of GVHD and is observed at a median of Day +96. Patient risk factors for invasive aspergillosis following HSCT include neutropenia, age >40 years, underlying myelodysplasia, GVHD, receipt of corticorsteroids, and donor mismatch.

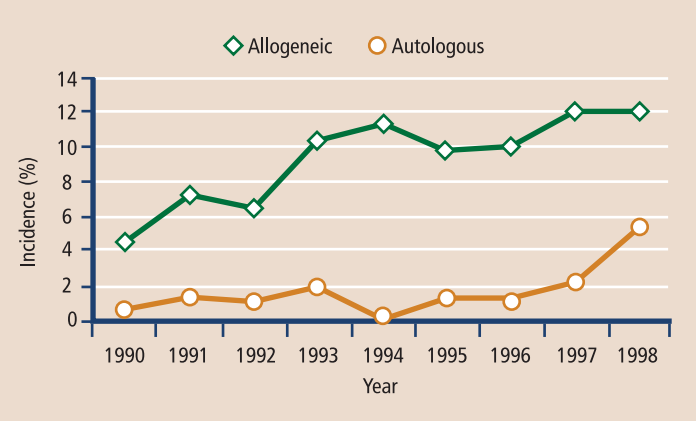

Figure 5: The incidence of proven or probable invasive aspergillosis by year of transplantation at Fred Hutchinson Cancer Research Center, Seattle, Washington.[26]

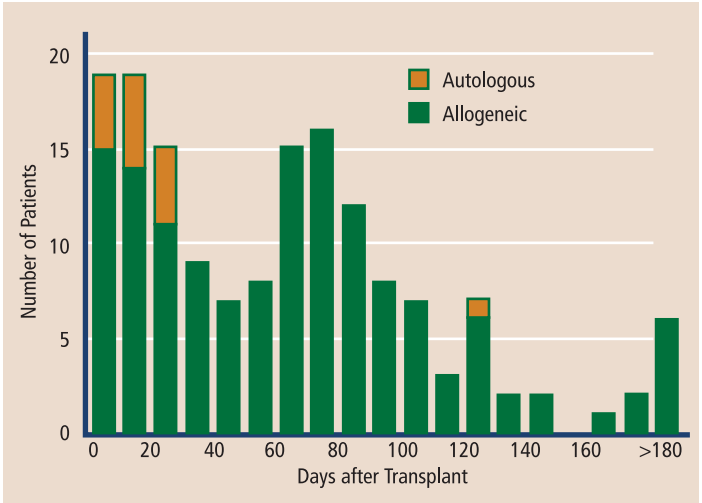

Figure 6: Time from transplant to diagnosis of invasive aspergillosis. Reprinted from Wald et al. *J Infect Dis* 1997;175:1459-99. ©1997 The University of Chicago. All rights reserved.

Diagnosis of Aspergillosis in Cancer Patients

Making a definitive diagnosis of invasive mold infections, including aspergillosis, is difficult due to lack of noninvasive, yet specific, diagnostic tests. For IFIs most commonly seen in immunocompromised cancer patients, three levels of probability are proposed, as shown in Table 7. These diagnostic criteria categorize potential mold infections as "possible," "probable," or "proven."

Table 7. Diagnosing and Categorizing Invasive Mold Infections

Possible	Probable	Proven[35]
Presence of at least one host factor criterion **+** one microbiological criterion **or** one major clinical criterion **or** 2 minor clinical criteria from a site consistent with infection	Presence of at least one host factor criterion **+** one microbiological criterion **+** one major criterion **or** 2 minor clinical criteria from a site consistent with infection	Pathologic evidence of hyphae from needle aspiration or tissue biopsy with evidence of tissue damage **or** Positive culture result from a normally sterile site consistent with infection, with supportive clinical or radiological evidence

The following host factors, microbiological criteria, and clinical criteria are important considerations in determining possible, probable, and proven invasive mold infections:

Host factors

- Neutropenia (ANC <500 cells/mm^3 for >10 days)
- Persistent fever for >96h refractory to broad-spectrum antibiotics
- Body temperature >38 or <36 °C and one of the following: prolonged neutropenia, recent/current use of immunosuppressive agents, history of proven or probable invasive fungal infection during previous neutropenia, or symptomatic AIDS
- GVHD

Microbiological criteria

- Positive result of culture for mold from any of the following sites: sputum, bronchoalveolar lavage fluid samples, or sinus aspirate specimen
- Positive findings of cytologic/direct microscopic evaluation for mold from any of the following sites: bronchoalveolar fluid samples, sinus aspirate specimen, or sterile body fluids (e.g., cerebrospinal fluid [CSF])
- Positive result for *Aspergillus* antigen in specimens of bronchoalveolar lavage fluid, CSF, or ≥2 blood samples

Clinical criteria

Two levels of evidence, major and minor, were incorporated into the clinical features that characterize clinical criteria for invasive aspergillosis. Table 8 presents these criteria by site of infection.

Table 8. Clinical Criteria for Diagnosing *Aspergillus* Infections

	LRT	Sinonasal	CNS
Major Criteria	• Presence of halo sign, air-crescent sign, or cavity within area of consolidation on CT	• Radiographical evidence of sinus invasive infection	• Radiological evidence of CNS infection
Minor Criteria	• Symptoms of lower respiratory tract infection (cough, chest pain, hemoptysis, dyspnea) • Pleural rub • New infiltrate not fulfilling major criterion • Pleural effusion	• Upper respiratory symptoms (nasal discharge, stuffiness) • Nose ulceration or eschar of nasal mucosa or epistaxis • Periorbital swelling • Maxillary tenderness • Black necrotic lesions or perforation of hard palate	• Focal neurological symptoms and signs (focal seizures, hemiparesis, cranial nerve palsies) • Mental status changes • Findings of meningeal irritation • Abnormalities in CSF chemistry and cell count

Additional Diagnostic Aids

Radiographic findings

Chest CTs are often used in the diagnosis of IFIs as well to measure the clinical response to these infections. Brodoefel and colleagues reviewed 310 serial chest CT scans in 40 consecutive patients diagnosed with pulmonary aspergillosis.[36] The investigators reported that regardless of the antifungal therapy employed, 90% of patients had increased size and number of pulmonary lesions until the 9th day of antifungal therapy. Patients who developed cavitation took 2.5 times longer to achieve radiographic response than those without cavitation, however; cavitation was associated with positive outcome (OR 8.4, CI 1.07–176).

Serum galactomannan antigen test

Detection of *Aspergillus* galactomannan in serum with the Platelia *Aspergillus* enzyme immunoassay (EIA) may be useful for diagnosing invasive aspergillosis. The galactomannan antigen test has been shown to be most sensitive in patients undergoing allogeneic HSCT and in neutropenic adults with leukemia when serial tests are performed. This test is less sensitive in SOT recipients and in patients who have received prior antifungals. The rate of false-positivity is increased in children; in patients on concomitant piperacillin/tazobactam when a cutoff of 0.5 is used to define positive (current cutoff in the United States and Europe); and in lower-risk patients undergoing repeated testing.

Marr and colleagues found that the serum galactomannan antigen test becomes positive sooner, and sensitivity is highest, in patients not on antifungal therapy (see Figure 7).[37] The ability to confirm diagnosis by this test will occur later and less often in patients on antifungals. If the galactomannan antigen test is used, it should be obtained serially with the intent of catching the peak prior to the initiation of empiric antifungals.

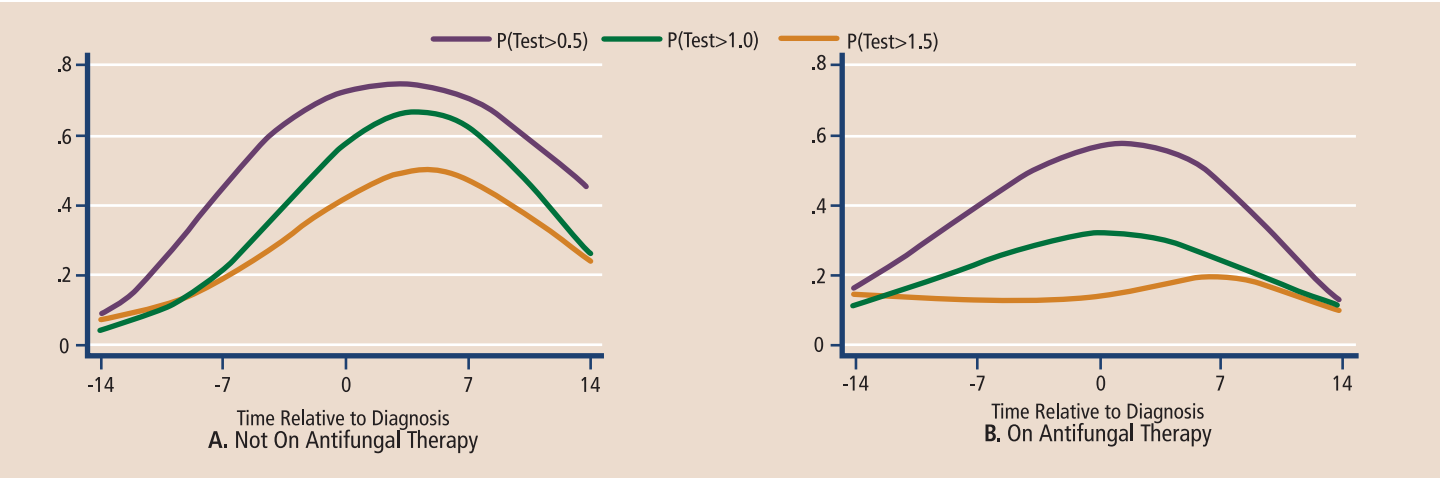

Figure 7: Sensitivity of the galactomannan EIA, plotted as a function of time relative to diagnosis, using multiple index cutoff values for patients not receiving (A) and patients receiving (B) antifungal therapy. Positivity was defined as an assay result greater than the index cutoff value. Sensitivity was modeled using generalized estimating equation logistic regression models, allowing time to diagnosis to impact the shape flexibly with cubicspline functions.[38]

Treatment of Invasive Aspergillosis

Historically, AmBd and its lipid formulations have been considered the optimal pharmacologic treatment for invasive aspergillosis.[39] In 2002, Herbrecht et al. reported the results of their study in which voriconazole was compared to AmBd for primary therapy of invasive aspergillosis. It was shown that patients who were randomized to voriconazole had better response rates, improved survival, and fewer severe adverse events (see Figure 8).[21]

Caspofungin was studied for salvage therapy in patients refractory or intolerant to initial therapy; investigators reported a complete or partial response rate of 45%.[40] Micafungin was studied alone or in combination with other antifungal agents for primary or salvage treatment of pulmonary aspergillosis; a 36% complete or partial response rate was found,[41] Posaconazole and anidulafungin have demonstrated in vitro activity against *Aspergillus* spp., but no controlled clinical trials have been conducted.[22, 25] There have been some reports of salvage patients with aspergillosis treated with posaconazole.[41a]

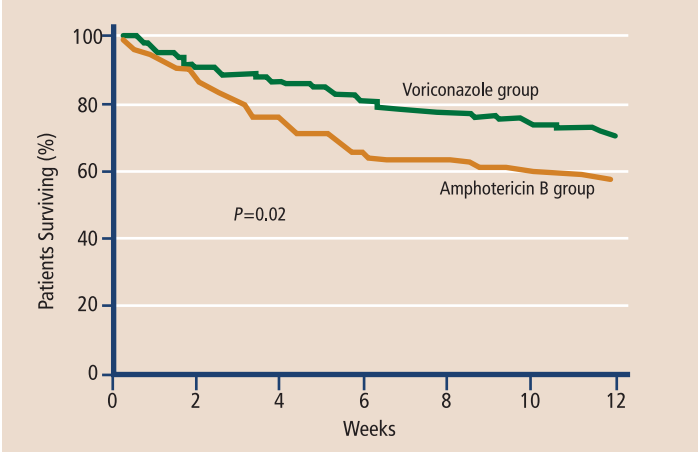

Figure 8: Survival curves for the modified intention-to-treat population according to treatment group. The *P* value was calculated by the log-rank test. Herbrecht R, et al. *N Engl J Med* 2004;347:408-15.

The combination of voriconazole and caspofungin for salvage therapy was compared with an historical cohort of voriconazole alone.[42] The combination group had improved 3-month survival; however, this study was limited by lack of randomization and a prospective control group. When considering combination antifungal therapy, clinicians should weigh the potential for increased efficacy with the risk of increased toxicities and costs.

Amphotericin B exhibits higher MICs against *A. terreus* and should not routinely be used to treat this species.

Case 3: Possible Invasive Aspergillosis During Neutropenic Fever

A 73-year-old male with a history of insulin-dependent diabetes mellitus and acute myelogenous leukemia (AML) received a nonmyeloablative, T-cell–depleted allogeneic HSCT. On the day of transplantation, fluconazole prophylaxis was initiated. On Day +3 the patient had an absolute neutrophil count (ANC) of 51 cells/mm^3 and developed a temperature to 38.9°C. Empiric antimicrobial therapy was initiated with ceftazidime. On Day +4, blood culture results showed the presence of *P. aeruginosa* for which ceftazidime was continued. On Day +5, the ANC was 18 cells/mm^3 and the patient was febrile. Repeat blood cultures were negative, but due to persistent fever, antimicrobial therapy was modified to imipenem/cilastatin and vancomycin. Ceftazidime was discontinued. On Day +6, the patient's ANC had increased to 352 cells/mm^3; however, the patient was still febrile at 39°C.

Assessing the Patient's Risk

The patient's risk factors for invasive aspergillosis include neutropenia, allogeneic HSCT, and older age.

Choosing an Antifungal Agent

Based on the patient's persistent fever, empiric therapy was begun with voriconazole. On Day +8, the patient's ANC was >2500 cells/mm^3, but fever was still present to 39.3°C. A chest X-ray revealed a new 3 cm infiltrate and chest CT revealed a halo sign (shown in Figure 9A). For GVHD prophylaxis, cyclosporine was begun and cyclosporine levels were carefully monitored due to the inhibition of metabolism by voriconazole. On Day +18, the patient had low-grade fever to 38.2°C and chest CT revealed an air crescent sign (shown in Figure 9B).

"Initiation of antifungal therapy on the basis of a halo sign by chest CT is associated with a better response to treatment and improved survival."[43]

–John Bennett

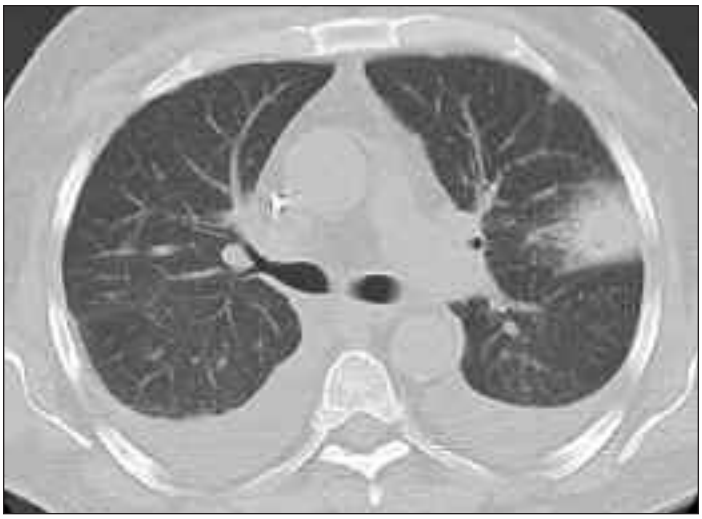

Figure 9A: The halo sign is a solid nodule filled with hemorrhage and edema fluid. The area around the edge of the nodule is less well demarcated and is called the halo sign. The halo sign is typically seen in neutropenic patients and represents hemorrhage and edema.

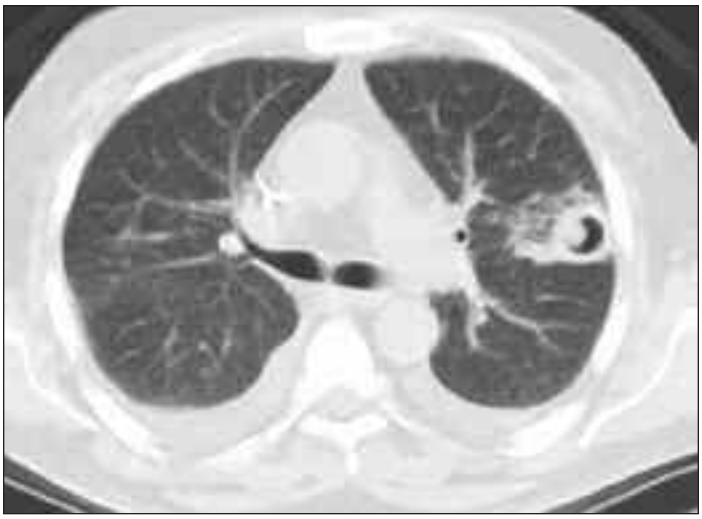

Figure 9B: The air crescent sign is a later finding and is a result of air between the infarcted lung and surrounding lung parenchyma. Images provided by Dr. Bennett and used with permission.

Modification of Therapy in Neutropenic Fever

After 3–5 days of persistent fever without an identified source, there are three treatment options to consider as illustrated in Figure 10.

Option 1. Continue the current antimicrobial regimen. This applies to clinically stable patients in whom the duration of neutropenia is expected to last no longer than 5 additional days (e.g., nonmyeloablative conditioning regimens).

Option 2. In patients in whom there is evidence of progressive or new disease such as abdominal pain or pulmonary infiltrates, consideration should be given to alteration of the empiric antimicrobial regimen.

Option 3. The third option is to consider broadening antifungal coverage for *Candida* and *Aspergillus* species; this should be considered in patients who remain febrile and profoundly neutropenic for ≥5 days despite adequate broad-spectrum antimicrobial therapy.

The 2002 IDSA guidelines indicate that amphotericin B deoxycholate (AmBd) or its lipid formulations (LFABs; amphotericin B lipid complex [ABLC], liposomal amphotericin B [L-AmB]) are the first-line treatment in this situation. Fluconazole should not be considered for empiric therapy if patients have symptoms or radiographic evidence of sinusitis or pneumonia, or if patients have received fluconazole for prophylaxis.

Other Therapeutic Options for Antifungal Therapy in Persistent Neutropenic Fever

Since the publication of the 2002 IDSA guidelines, caspofungin and voriconazole have been studied as empiric antifungal therapy for neutropenic fever. In a prospective, randomized, double-blind study, caspofungin was compared to L-AmB in patients with neutropenic fever for at least 4 days.[44] The primary endpoint was based on the composite score of 5 parts including successful treatment of baseline fungal infection, absence of breakthrough fungal infection during therapy or within 7 days of the completion of therapy, survival for 7 days after the completion of therapy, lack of study drug discontinuation for intolerance or refractory infection, and fever resolution.

Caspofungin was found to be equally efficacious to L-AmB and was granted FDA approval for neutropenic fever in 2004. Voriconazole was compared to L-AmB in a similarly designed study with the same composite endpoint.[45] Overall success was 26.0% and 30.6% (95% CI –10.6 to 1.6%) in the voriconazole and L-AmB groups, respectively; however, the 95% CI fell just outside the predefined lower limit of –10 percentage points.

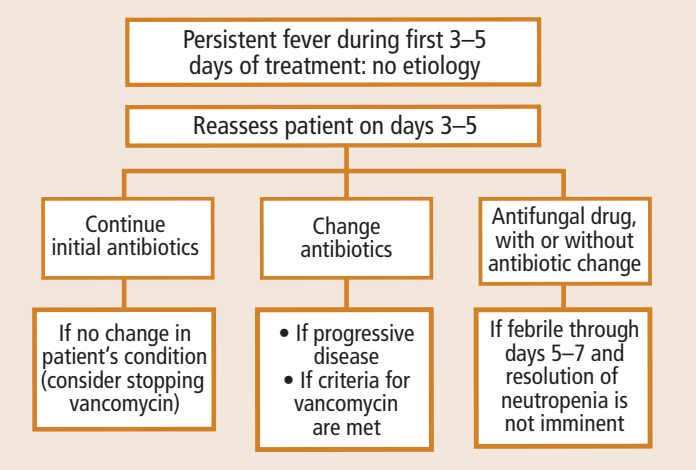

Figure 10: A guide to the treatment of patients who have persistent fever after 3 to 5 days of treatment and for whom the cause of fever is not known.[46]

Based on this lack of noninferiority, voriconazole is not FDA approved for empiric antifungal therapy in neutropenic fever. There were fewer breakthrough fungal infections among recipients of voriconazole (8 vs. 21, P=0.02). Based on this result, many clinicians use voriconazole for empiric antifungal therapy in neutropenic fever.

Several other agents that have not yet been studied for this indication may have activity. These include posaconazole, micafungin, and anidulafungin.

Summary of Therapeutic Considerations in the Treatment of Aspergillosis

According to the 2000 IDSA treatment guidelines for invasive aspergillosis, maximally tolerated doses of AmBd or LFABs for patients intolerant to AmBd should be used for first-line pharmacologic treatment.[39] Voriconazole was since found to have improved response rates and survival and fewer severe adverse events. Caspofungin was studied for salvage therapy and is FDA indicated for same.[40] Micafungin was studied alone or in combination with similar success as caspofungin.[41] Posaconazole and anidulafungin both have demonstrated in vitro activity.[22, 25] There are data to suggest the improved efficacy of combination therapy; however, the evidence is not conclusive.[42]

For empiric antifungal therapy in neutropenic fever, first-line therapy has traditionally been AmBd or an LFAB. Caspofungin and voriconazole were separately compared to L-AmB for this indication; caspofungin was found to be equally efficacious to L-AmB and was granted FDA approval. Voriconazole failed to show noninferiority; however, many clinicians use voriconazole for this indication because the overall success was similar and there were fewer breakthrough fungal infections in the voriconazole group.

Endemic Fungal Pathogens

Endemic fungal pathogens, such as *Histoplasma capsulatum*, *Coccidioides* spp., and *Blastomyces dermatitidis* can be difficult to diagnose and manage in the clinical setting. Clinical consequences of endemic mycoses include: pneumonia, disseminated forms (e.g., cutaneous and soft tissue, musculoskeletal, CNS, gastrointestinal, and other rare presentations).

Histoplasma capsulatum[47]

H. capsulatum is the etiologic agent of histoplasmosis in humans. Reportedly, *H. capsulatum* exists on every continent except Antarctica with the most endemic region being the Ohio and Mississippi river valleys.

At ambient temperature, *H. capsulatum* exists as mycelial phase as shown in Figure 11. Identifying characteristics include large, rounded, single-celled, tuberculate macroconidia formed on short, hyaline, undifferentiated conidiophores. Transformation to yeast occurs at temperatures of at least 35°C.

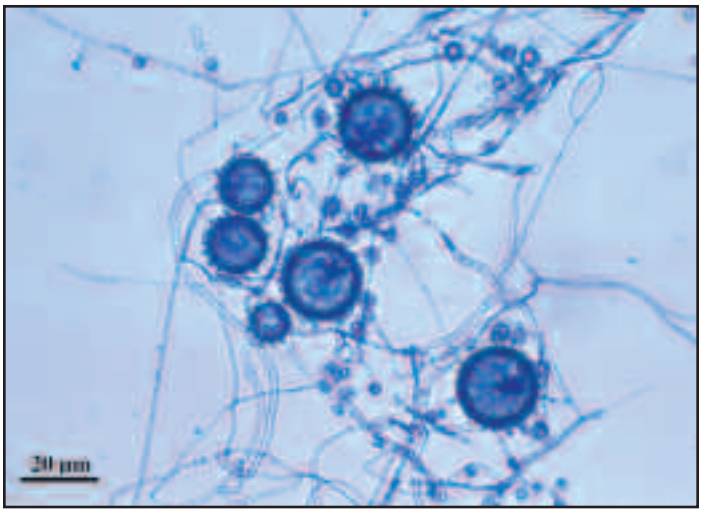

Figure 11: Microscopic morphology of the saprophytic or mycelial form of *H. capsulatum*. Source: Mycology Online http://www.mycology.adelaide.edu.au

Clinical Presentation

Histoplasmosis can take the form of an acute or chronic pulmonary infection. It may spread systemically through the bloodstream. However, disseminated histoplasmosis is uncommon in immunocompetent hosts. Table 9 below gives an overview of clinical features. Manifestations of *H. capsulatum* infection also include granulomatous mediastinitis, fibrosing mediastinitis, pericarditis, and, rarely, isolated focal organ involvement.

Treatment of Histoplasmosis

Infections caused by *H. capsulatum* are frequently self-limiting. Therefore, not all clinical manifestations require treatment with antifungal agents. Treatment guidelines according to the IDSA are shown below in Table 10.[48]

When treatment is indicated, an antifungal agent may be used. In the past, AmBd has been considered the first-line antifungal therapy in patients with serious disease.[48] For the treatment of mild-to-moderate pulmonary or disseminated histoplasmosis, oral itraconazole is the treatment of choice. Itraconazole is also frequently used as step-down therapy after an initial response to AmB in patients with severe histoplasmosis.

Table 9. Common Clinical Signs and Symptoms of Histoplasmosis

Acute pulmonary	Chronic pulmonary	Disseminated
• >90% of acute pulmonary infections are never diagnosed due to lack of symptoms or presence of mild symptoms • Besides age and underlying diseases (e.g., immune status) inoculum size determines if patient develops symptoms • Incubation period ranges from 7-21 days • Characterized by fever, chills, chest pain, and nonproductive cough	• Low-grade fever, productive cough, dyspnea, and weight loss • Characterized by the presence of cavitary lesions in the upper lobes • Isolation of organism	• May present as acute, subacute, or chronic infection • Laboratory abnormalities may include anemia, thrombocytopenia, leukopenia, elevated liver enzymes • Physical findings may include hepatosplenomegaly, lymphadenopathy, oropharyngeal ulcers, weight loss, fever, and symptoms suggesting Addison's disease • Disseminated infection may involve the CNS

Table 10. Indications for Antifungal Treatment in Patients with Histoplasmosis

Treatment indicated	Treatment not indicated
• Acute pulmonary histoplasmosis with hypoxemia	• Acute self-limited syndromes
• Acute pulmonary histoplasmosis for >1 month	• Acute pulmonary histoplasmosis, mildly ill
• Chronic pulmonary histoplasmosis	• Rheumatologic
• Esophageal compression and/or ulceration	• Pericarditis
• Granulomatous mediastinitis with obstruction and/or invasion of tissue	• Histoplasmoma
• Disseminated histoplasmosis	• Broncholithiasis
	• Fibrosing mediastinitis

Histoplasmosis in AIDS

In AIDS patients with moderate-to-severe disseminated histoplasmosis, L-AmB has been compared with AmBd in a randomized, double-blind trial. Investigators reported clinical success in 45/51 (88%) and 14/22 (64%) of patients treated with L-AmB and AmBd, respectively (P=0.014). Patients in the L-AmB arm were less likely to have fever at 14 days (13% vs 36%, P=0.09), although there was no difference in culture negativity at Day 14 or overall mortality.[49]

Coccidioides Species[50, 51]

Recently *Coccidioides* was split into two species: C. *immitis* and C. *posadasii*. C. *immitis* is found in California's San Joaquin valley region. C. *posadasii* is found in the desert southwest of the United States, Mexico, and South America. *Cocciodioides* spp. exist as mycelial phase at ambient temperature and may exist as a spherule at ≥37°C. Figure 12 shows arthroconidia, which are typically single-celled, hyaline, and may vary from rectangular to barrel-shaped. Here, alternate arthroconidia are separated from each other by a disjunction cell.

C. *immitis*/C. *posadasii* is the causative agent of coccidioidomycosis in humans. Coccidioidomycosis is acquired through inhalation of dry arthroconidia. Respiratory infection typically occurs 7–21 days following exposure.

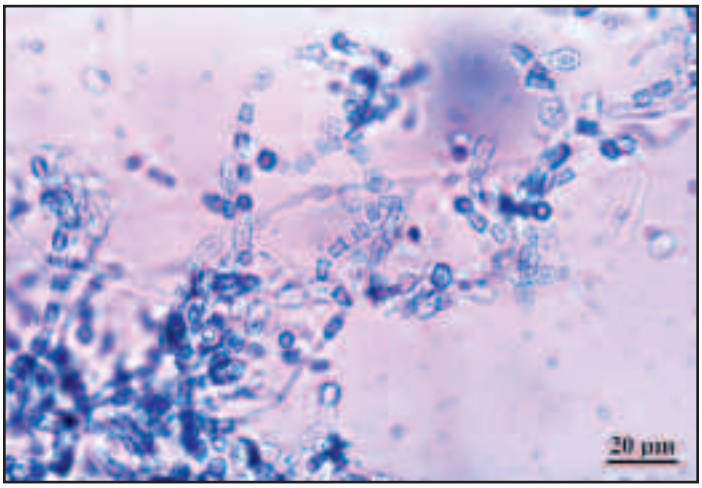

Figure 12: Microscopic morphology of C. *immitis*. Source: Mycology Online http://www.mycology.adelaide.edu.au

Clinical Presentation

In the early stages, respiratory infections caused by *Coccidioides* are difficult to diagnose. One-half to two-thirds are never diagnosed due to lack of symptoms or presence of mild symptoms. Following exposure, the incubation period ranges from 7–21 days. Possible symptoms include cough, chest pain, fever, fatigue, and dyspnea. On occasion, infection leads to the formation of pulmonary nodules and/or cavities.

In less than 1% of patients, infection spreads beyond the lungs. Extrapulmonary dissemination is more common, however, in immunocompromised patients. The most common site of dissemination is the skin. Clinical presentation ranges from superficial lesions to subcutaneous abscesses. Other sites of coccidioidomycosis include the bones, joints, and the CNS.

Treatment of *Coccidioides* Infection[51]

For patients with mild-to-moderate pulmonary or disseminated coccidioidomycosis, the preferred treatment is an oral azole. Fluconazole and itraconazole are most frequently used. When patients have severe pulmonary or disseminated disease, then amphotericin B is recommended, either conventional AmBd or L-AmB. Once patients with severe coccidioidomycosis achieve an initial response with AmB, an oral azole may be used as step-down therapy. For CNS infections, fluconazole is preferred. Therapy for coccidioidomycosis can be prolonged or even lifelong. Surgical management can also be useful in treating the pulmonary and extrapulmonary lesions that are sometimes features of the disease.

Blastomyces dermatitidis[52,53]

B. dermatitidis is native to North America, although cases have been reported in Africa, Central and South America, and Asia. In North America, the organism is found in the Midwestern United States and in Canadian provinces that border the Great Lakes. For those exposed to *B. dermatitidis*, infection results when inhaled conidia are converted to the yeast phase in the lung. At ambient temperature, *B. dermatitidis* exists in its mycelial phase and is transformed to the yeast phase at ≥35°C. Figure 13 shows a tissue section 8-15 μm in diameter with large, broad-base, unipolar budding yeast-like cells of *B. dermatitidis*.

Clinical Presentation

B. dermatitidis is the causative agent of blastomycosis in humans. Following exposure, the incubation period for blastomycosis ranges from 30–45 days. Acute infection presents with nonspecific symptoms that include myalgias, arthralgias, fever, and chills. Pulmonary symptoms include nonproductive cough, pleuritic pain, and shortness of breath.

In cases of chronic or progressive infection, the patient may develop chronic pneumonia, presenting with productive cough, hemoptysis, weight loss, fever, and night sweats. Extrapulmonary disease is generally seen on the skin and may manifest as verrucous or ulcerative lesions. Frequently, blastomycosis disseminates to the genitourinary and osteoarticular systems. The liver, spleen, lymph nodes, and CNS are less commonly involved.

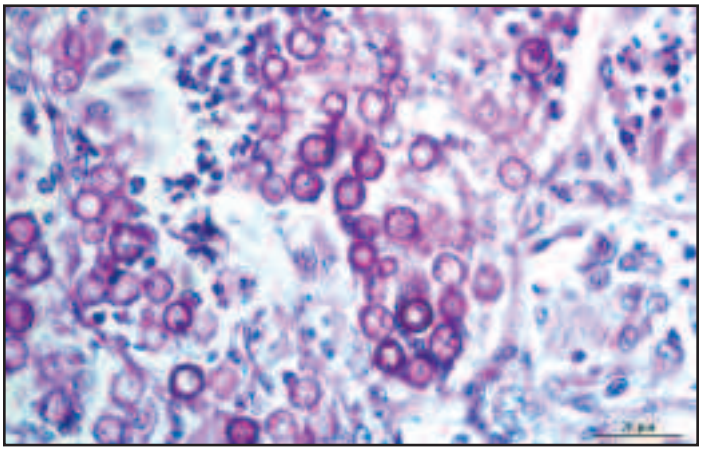

Figure 13: Microscopic morphology of *B. dermatitidis*. Source: Mycology Online http://www.mycology.adelaide.edu.au

Treatment of Blastomycosis[53]

All patients with blastomycosis should receive antifungal therapy. Itraconazole is the treatment of choice for mild-to-moderate pulmonary or disseminated blastomycosis. Patients with severe pulmonary or disseminated disease, and those with CNS infection, should be treated with either conventional or lipid-based AmB. Once an initial response has been achieved, itraconazole is used as a step-down therapy.

Case 4: Possible Histoplasmosis

A 67-year-old man with chronic obstructive pulmonary disease (COPD) and hypertension presented to a hospital in southeastern Arizona with fevers, night sweats, fatigue, and weakness that had been gradually worsening over the two months prior to admission. He complained of severe painful sores in his mouth and had lost 40 lbs. On physical exam, the patient appeared chronically ill, had orthostatic hypotension, and was febrile to 38.9°C. Several ulcerated lesions were present in his mouth (see Figure 14). Cardiovascular and lung exam were within normal limits. The liver was felt 3 cm below the right costal margin; the spleen was not felt. The patient reported living in Tennessee until seven years prior when he moved to Arizona for retirement. The patient reported no travel outside of the United States.

Diagnostic Considerations

The patient's presentation of mouth ulcers, weight loss, fevers, and adrenal involvement is most consistent with histoplasmosis or paracoccidioidomycosis. However, because he never lived in South America, paracoccidioidomycosis can be eliminated. He does live in the desert southwest and coccidioidomycosis must always be thought of; however, mouth ulcers and adrenal involvement in the absence of skin, bone, or central nervous system disease would be unlikely for disseminated coccidioidomycosis. Small cell lung cancer often infiltrates adrenal glands but should not cause mouth ulcers, and Hodgkin's disease could cause many of the symptoms, again with the exception of mouth ulcers. Thus, histoplasmosis fits best with his presentation, but the fact that he had not lived in the endemic area for many years made the diagnosis more difficult.

Radiographic Findings and Laboratory Results

A chest X-ray and chest CT showed a fine bilateral reticulo-nodular infilrate. The patient's pertinent laboratory values were as follows: WBC 3,100 cells/mcl, HgB 8.5 gm/dL, platelets 125,000/mm^3, sodium 125 mEq/L, potassium 4.9 mEq/L, aspartate aminotransferase (AST) 55 IU/L, alanine aminotransferase (ALT) 65 IU/L, alkaline phosphatase 290 IU/L, total bilirubin 2.3 mg/dL, and erythrocyte sedimentation rate (ESR) 98 mm/hr. As shown in Figure 15, an abdominal CT scan revealed enlarged adrenal glands.

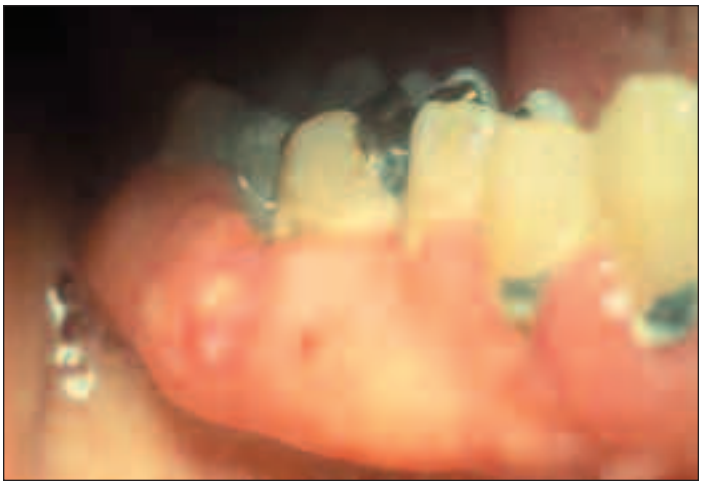

Figure 14: In addition to periodontal disease the patient presented with painful mouth ulcers. Image provided by Dr. Carol Kauffman and used with permission.

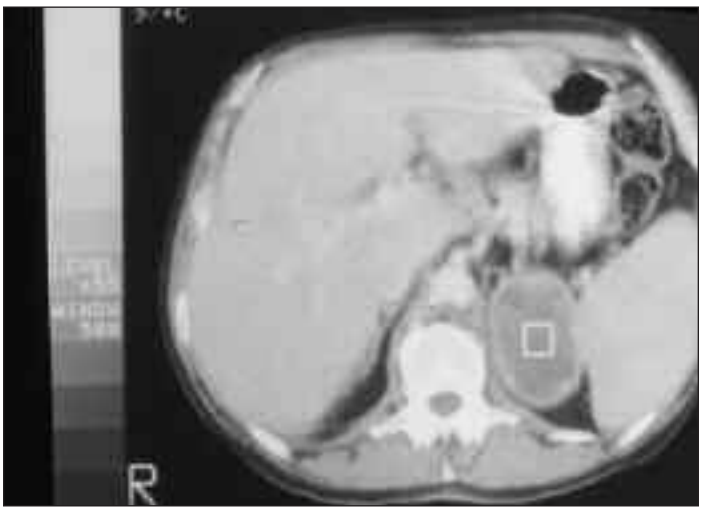

Figure 15: CT scan shows hepatosplenomegaly and an enlarged adrenal gland. Image provided by Dr. Carol Kauffman and used with permission.

Making a Clinical Diagnosis

Histoplasmosis can be diagnosed in one of two ways: a positive culture or histopathology from an affected site or positive blood cultures. Antigen detection is extremely helpful, but diagnosis should be confirmed with tissue biopsy.

For this patient, biopsy of the mouth ulcer reveals 2-4 micron budding yeasts consistent with *H. capsulatum* (see Figure 16). Additionally, a culture taken from the bone marrow biopsy yields *H. capsulatum*. *Histoplasma* urinary antigen is positive at 9.7 units.

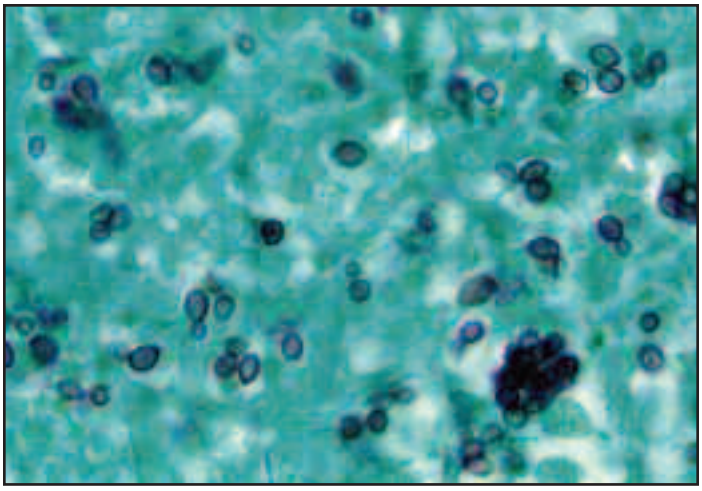

Figure 16: Tissue biopsy from mouth ulcers reveals 2-4 µm "budding yeast" consistent with a diagnosis of *H. capsulatum*. Image provided by Dr. Carol Kauffman and used with permission.

Sensitivity of *Histoplasma* Urinary Antigen as a Diagnostic Tool

The sensitivity of *Histoplasma* urinary antigen is shown in Figure 17. For disseminated histoplasmosis, the urinary antigen test is more than 80% sensitive. For those patients with AIDS and disseminated histoplasmosis, it is more than 95% sensitive.[54] In pulmonary disease, the urinary antigen has optimal sensitivity for acute illness. Sensitivity decreases to 34% or less for sub-acute or chronic illness. This may be due to decreased fungal burden. Of note, there is cross-reactivity with blastomycosis, paracoccidioidomycosis, penicilliosis, and coccidioidomycosis.

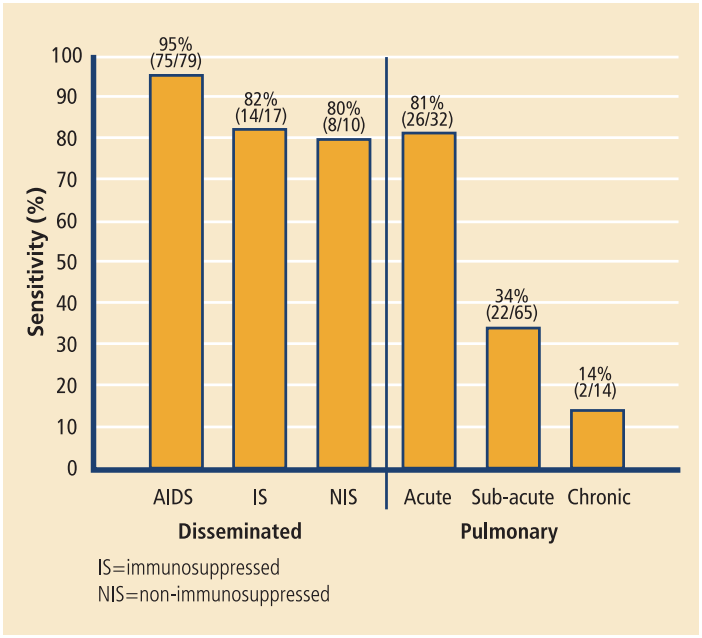

Figure 17: Sensitivity of *Histoplasma* urinary antigen. Reprinted from *Diag Microbiol Infect Dis* Vol. 43. Wheat LJ, Garringer T, Brizendine E, Connolly P. Diagnosis of histoplasmosis by antigen detection based upon experience at the histoplasmosis reference library; pp. 29-37 ©2002 with permission from Elsevier.

Summary

Invasive fungal infections remain a significant cause of morbidity and mortality among immunocompromised hosts. Changes in fungal epidemiology have been observed; rates of non-*albicans Candida* and non-*Aspergillus* molds are increasing. There have been multiple recent developments in the antifungal armamentarium including the extended spectrum azoles and the echinocandins. Further research will aim to define the optimal orchestration of these agents.

Invasive fungal infections due to *Candida* and *Aspergillus* species in high-risk patients are still a common cause of life-threatening infections. However, non-*albicans Candida* species and non-*fumigatus Aspergillus* species are showing an increased incidence as the cause of infections. Particularly dangerous non-*Aspergillus* molds, such as *Fusarium* and *Scedosporium* species and *Zygomycetes* are also emerging–due in part to voriconazole prophylaxis–with a higher prevalence in patients with leukemia and bone marrow transplantation (BMT).[24]

General risk factors remain an important consideration in the clinical diagnosis of IFIs due to yeasts, molds, and endemic species. For systemic *Candida* infection, these risks include the use of central venous catheters, total parenteral nutrition, recent surgery, and treatment with immunosuppressive regimens to manage transplant rejection. Invasive aspergillosis disproportionately affects patients with hematological disease and patients who have undergone BMT. The rarer fusariosis and zygomycosis have been reported most frequently in these same populations. A high index of suspicion for fungal infection and for atypical species is prudent when treating patients in these high-risk populations.[24] Geography, environmental exposure, and compromised immune status (especially among the elderly) remain prominent concerns in the diagnosis of endemic fungal infections.

There are three major strategies for the management of IFIs in the patient at risk, these include: (1) prevention through antifungal prophylaxis; (2) empiric therapy initiated after a prespecified period of persistent fever despite broad-spectrum antimicrobial treatment; (3) treatment for proven IFIs. The high mortality rate associated with fungal infections is due in part to difficulties of diagnosis and treatment, which results in infections that are all too frequently at an advanced stage, and prone to rapid progression. Therefore, early risk assessment and diagnosis, as well as timely and appropriate therapy, are critical for successful clinical outcomes. Therapeutic options for the treatment of IFIs have improved due to recent developments in the antifungal armamentarium including the extended spectrum azoles and the echinocandins. However, further research is required to define the optimal orchestration of these agents in the treatment of life-threatening infections.

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List of Abbreviations

ABCD	Amphotericin B colloidal dispersion
ABLC	Amphotericin B lipid complex
AmBd	Amphotericin B deoxycholate
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BMT	Bone marrow transplantation
BUN	Blood urea nitrogen
CI	Confidence interval
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
CT	Computed tomography
EIA	Enzyme immunoassay
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GVHD	Graft-versus-host disease
HgB	Hemoglobin
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplant
HSV	Herpes simplex virus
IA	Intra-articular
ICU	Intensive care unit
IFI	Invasive fungal infection
IV	Intravenous
L-AmB	Liposomal amphotericin B
LFAB	Lipid-base formulations of amphotericin B
MDS	Myelodysplastic syndrome
OR	Odds ratio
SOT	Solid organ transplant
SCr	Serum creatinine
UNOS	Unite Network for Organ Sharing
WBC	White blood cell count

CME/CPE Post Assessment

On the Case: Optimizing Outcomes for Fungal Infections
Featuring Cases from the Clinic

Release date: January 15, 2007 Expiration date: March 31, 2008

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Post Assessment

Please select the best answer for the following questions and mark your answer on the evaluation form.

1. **Infection caused by *Candida* species is most common during which post-transplantation period?**
   a) Pre-transplantation
   b) 0-1 month post-transplantation
   c) 1-6 months post-transplantation
   d) >6 months post-transplantation

2. **During what time period post-HSCT are patients at greatest risk of invasive aspergillosis?**
   a) Phase 1
   b) Phase 2
   c) Phase 3
   d) A and B
   e) A and C

3. **Which of the following azoles has an antifungal spectrum of activity comparable to itraconazole with additional in vitro activity against *Zygomycetes*?**
   a) Fluconazole
   b) Voriconazole
   c) Posaconazole

4. **What *Candida* species has decreased susceptibility to amphotericin B?**
   a) C. *tropicalis*
   b) C. *parapsilosis*
   c) C. *glabrata*
   d) C. *lusitaniae*
   e) C. *krusei*

5. **What antifungal class possesses the broadest spectrum against *Candida* species?**
   a) Polyenes
   b) Echinocandins
   c) Azoles
   d) A and B
   e) A and C

6. **Which of the following are risk factors for invasive *Candida* infections?**
   a) Gastrointestinal surgery
   b) Renal failure
   c) Receipt of parenteral nutrition
   d) Age >70 years
   e) All of the above

7. **A patient with persistent neutropenic fever has a worsening cough, shortness of breath, and is found to have a new infiltrate on chest CT. Induced sputum cultures reveal the presence of mold. How should this patient's infection be classified?**
   a) Proven invasive mold infection
   b) Probable invasive mold infection
   c) Possible invasive mold infection

8. **In which of the following populations is the serum galactomannan antigen test most useful?**
   a) Patients in whom serial tests are performed
   b) Patients who have received prior antifungals
   c) Patients on concomitant piperacillin/tazobactam
   d) Pediatric patients

9. Which antifungal agent was found to be superior to AmBd for the treatment of invasive aspergillosis?

a) Caspofungin
b) Voriconazole
c) Itraconazole
d) Posaconazole

10. Which fungal pathogen is most often found in the Ohio and Mississippi River valleys?

a) *Coccidioides immitis*
b) *Coccidioides posadasii*
c) *Histoplasma capsulatum*

11. Which of the following is the most common site of extrapulmonary Coccidioides infection?

a) CNS
b) Skin
c) Bone
d) Joints

12. Which of the following is the drug of choice for moderately severe-to-severe disseminated histoplasmosis in patients with AIDS?

a) AmBd
b) L-AmB
c) Itraconazole
d) Fluconazole

Activity Evaluation & Registration Information

On the Case: Optimizing Outcomes for Fungal Infections
Featuring Cases from the Clinic

ANSWER KEY

1_____ 2_____ 3_____ 4_____ 5_____ 6_____ 7_____ 8_____ 9_____ 10_____ 11_____ 12_____

Please check your professional title:

☐ Physician ☐ Pharmacist/PharmD

☐ Researcher/Scientist ☐ Nurse/Nurse Practitioner ☐ Other_____

Please evaluate the content of this educational activity.

Is the information timely/up-to-date?	☐ Yes	☐ No
Did the activity meet your expectations?	☐ Yes	☐ No
Is the content relevant to your area of professional interest?	☐ Yes	☐ No
Is the content useful to you in improving care of patients?	☐ Yes	☐ No
Is the activity free of commercial bias?	☐ Yes	☐ No

If no, why not? _____

Did the material presented in this activity meet the following educational objectives?

1. Identify patient and pathogen risk factors contributing to the development of fungal infections	☐ Yes	☐ No
2. List key clinical signs and symptoms as well as appropriate diagnostic tests for accurate diagnosis of fungal infections	☐ Yes	☐ No
3. Select appropriate therapeutic strategies for the treatment of fungal infections as well as understand the potential role of new and emerging treatment options	☐ Yes	☐ No
4. Assess the role of prophylactic and empiric therapy for the prevention and treatment of fungal infections	☐ Yes	☐ No

If you selected No for any answer above, please explain why not. _____

Please rate the overall activity using the scale below and check the appropriate box.

Value of topic	☐ Poor	☐ Fair	☐ Satisfactory	☐ Good	☐ Excellent
Content organization	☐ Poor	☐ Fair	☐ Satisfactory	☐ Good	☐ Excellent
Quality of activity	☐ Poor	☐ Fair	☐ Satisfactory	☐ Good	☐ Excellent

What one new thing did you learn? _____

How will you modify your practice performance as a result of participating in this activity?

_____

Assess your level of commitment to making the modification to your practice stated above:

Very committed	Committed	Somewhat committed	Not very committed	Do not expect to change practice
☐	☐	☐	☐	☐

What recommendations do you suggest to improve this activity? _____

_____

As you look ahead, what CME/CPE topic is your highest learning priority? _____

In order to assist us in measuring the outcomes of this educational activity, would you be willing to participate in a brief post-activity questionnaire? ☐ Yes ☐ No

If yes, please include your E-mail address here: _____

Registration/Credit Information

Name _____ Degree_____

Mailing Address _____

City_____ State_____ ZIP_____

Phone_____Fax_____E-mail _____

Time spent in the activity: _____ (Max. 1.5 hours)

(You will receive credit for only the actual amount of time you spent in the activity up to a maximum of 1.5 category 1 credit or 1.5 contact hours.)

By signing, I certify that I have completed this educational activity.

Signature: _____ Date: _____

Thank you for completing this CME/CPE activity. Please remember to detach the pages and fax front and back to 609-921-6428 or mail to the American Academy of CME, 186 Tamarack Circle, Skillman, NJ 08558

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