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Invasive fungal infections in transplant recipients

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***Abstract*:** Invasive fungal infections are an important cause of morbidity and mortality in hematopoietic stem cell transplant and solid organ transplant recipients. Evolving transplant modalities and techniques, complex and extensive immunosuppressant strategies, and the increased use of broad spectrum antifungal prophylaxis has greatly impacted the epidemiology and temporal pattern of invasive fungal infections in the transplant population. The goal of this article is to provide an up-to-date review of the most commonly encountered invasive fungal infections seen in transplant recipients, including epidemiology, risk factors, clinical features, diagnostic dilemmas, management and their overall influence on outcomes.

***Keywords*:** transplant recipients, *Candida*, *Aspergillus*, *Mucor*, antifungal agents

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Introduction

Recent advances and improvements in medical therapeutics, chemotherapy, and organ transplantation methodology have substantially reduced the overall morbidity and mortality associated with transplantation. However, along with these improvements, a variety of opportunistic infections frequently caused by relatively avirulent organisms have emerged. Critically ill, immunocompromised patients, especially those who have undergone transplants, are the prime targets for these opportunistic fungal infections, primarily due to *Candida* and *Aspergillus* spp. This increase is multifactorial in origin and reflects increased recognition as well as a growing population of patients at risk.

Candidiasis

Candida spp. are ubiquitous fungi and are the most common fungal pathogens that affect humans [Vazquez and Sobel, 2011; Pfaller and Diekema, 2007]. The growing problem of systemic candidiasis reflects the enormous increase in the pool of patients at risk and the increased opportunity that exists for *Candida* spp. to invade tissues normally resistant to invasion. *Candida* spp. are true opportunistic pathogens that exploit recent technological advances to gain access to the circulation and deep tissues. *Candida* spp. are the most common cause of fungal infection affecting immunocompromised patients and are currently the fourth most common pathogen recovered from blood cultures [Pfaller and Diekema, 2007].

Epidemiology

Candida spp. produce a wide spectrum of diseases, ranging from superficial mucocutaneous disease to invasive illnesses, such as hepatosplenic candidiasis and systemic candidiasis [Vazquez and Sobel, 2011; Pfaller and Diekema, 2007]. Management of invasive candidiasis remains severely hampered by delays in diagnosis and the lack of reliable diagnostic methods that allow detection of both fungemia and tissue invasion by *Candida* spp. [Pappas, 2006; Pappas *et al.* 2003].

Over 165 species of *Candida* exist in nature; only a few species, however, are recognized causes of disease in humans (Table 1) [Vazquez and Sobel, 2011; Pfaller and Diekema, 2007; Pappas *et al.* 2003]. *C. albicans* and *C. glabrata* account for approximately 70–80% of *Candida* spp. isolated from patients with candidemia and invasive candidiasis. *C. glabrata* has recently become important because of its increasing incidence worldwide, and it is intrinsically less susceptible to azoles and amphotericin B (AmB) [Pfaller and Diekema, 2007; Morgan, 2005; Colombo *et al.* 2006]. *C. krusei* is also important because of its intrinsic resistance to most azoles, including ketoconazole, fluconazole, and itraconazole. In addition, it is less susceptible to AmB. Another

important *Candida* spp. is *C. lusitaniae*; although not as common as some *Candida* spp., it is of clinical significance because it is frequently resistant to AmB, although it remains susceptible to azoles and echinocandins. *C. parapsilosis* is the second to third most common *Candida* spp. recovered from blood cultures and has become an important species to consider in hospitalized patients with vascular catheters. Additionally, *in vitro* susceptibility studies have shown a reduced susceptibility to echinocandins compared with the other *Candida* spp. [Eiland *et al.* 2008]. *C. tropicalis* is also considered an important cause of candidemia in patients with cancer (leukemia) and in those who have undergone hematopoietic stem cell transplantation (HSCT).

Candida spp. contain their own set of well recognized virulence factors. Although not well characterized, several virulence factors may contribute to their ability to cause infection [Yang, 2003]. As with most fungal infections, host defects play a significant role in the development of candidal infections. Numerous host defects have been associated with candidal infections. Risk factors associated with candidemia and systemic candidiasis include granulocytopenia, HSCT, solid organ transplants (SOTs) (kidney and liver), total parenteral hyperalimentation, solid neoplasm, corticosteroids, broad-spectrum antibiotics, prolonged intensive care unit stay, prolonged hospitalization, mechanical ventilation for over 3 days, pancreatitis, severe trauma, recent surgery (especially gastrointestinal tract), central venous catheters, and hemodialysis [Vazquez and Sobel, 2011; Pappas, 2006].

Clinical manifestation

Infections due to *Candida* spp. can manifest in a wide spectrum of clinical syndromes as described below (Table 2) [Vazquez and Sobel, 2011; Pappas, 2006]. The clinical presentation can vary depending on the type of infection, the organ involved and the degree of immunosuppression.

Systemic candidiasis may be divided into two different categories: candidemia without organ involvement and disseminated candidiasis (organ infection by *Candida* spp.). Deep organ infections due to *Candida* spp. are generally observed as part of the disseminated candidiasis syndromes, which may be associated with either single- or multiorgan involvement. The patient's history commonly reveals the following: several days of fever that is unresponsive to broad-spectrum antimicrobials (frequently the only marker of infection), prolonged intravenous catheterization, and several key risk factors. Physical examination is remarkable for the following: fever, macronodular skin lesions (approximately 10%), candidal endophthalmitis (approximately 5%), and occasionally septic shock. Disseminated candidiasis is frequently associated with multiple deep organ infections or may involve single organ infection (Table 2).

Diagnosis

Unfortunately, findings from laboratory studies are either negative or nonspecific [Vazquez and Sobel, 2011; Pappas, 2006]. Clinicians are required to act definitively and early based on a high index of suspicion. Patients who remain febrile despite broad-spectrum antibiotic therapy, with either neutropenia or other risk factors and persistent leukocytosis, should be suspected of

Table 1. *Candida* spp. Why should they be identified?

Candida species	Distribution (%)	Comments
C. albicans	50–60	
C. glabrata	15–25	Less susceptible to all antifungals
C. parapsilosis	10–20	Frequently catheter-related, less susceptible to echinocandins
C. tropicalis	6–12	Generally susceptible to all antifungals
C. krusei	1–3	Intrinsically resistant to fluconazole and itraconazole; less susceptible to AmB
C. guilliermondi	<1	Resistant to AmB
C. lusitaniae	<1	Resistant to AmB
C. dubliniensis	<1	Primarily recovered in patients with HIV

Vazquez and Sobel [2011].
HIV, human immunodeficiency virus.

having systemic candidiasis. Cultures of nonsterile sites, although not useful for establishing a diagnosis, frequently demonstrate a high degree of candidal colonization. However, these positive cultures may be useful for initiating antifungal therapy in patients who are febrile and are unresponsive to broad-spectrum antimicrobials. It is important to always consider positive results from these sites significant and definitive evidence of infection. To be effective, appropriate antifungal therapy should be provided early and empirically in such high-risk patients [Morrell *et al.* 2005].

Table 2. Manifestations of invasive candidiasis.

- Fever unresponsive to broad-spectrum antimicrobials, frequently the only marker of infection, especially if:
  - prolonged intravenous catheterization
  - a history of several major risk factors
  - possibly associated with multiorgan infection
- Physical examination is remarkable for the following:
  - macronodular skin lesions (~10–20%)
  - candidal endophthalmitis (~5%)
  - occasionally, septic shock (hypotension, tachycardia, tachypnea)
  - multiorgan dysfunction, depending on the site affected

Vazquez and Sobel [2011].

Recently, a newer diagnostic assay detecting the presence of 1-3 β-D-glucan (BG) Fungitell Assay (Associates of Cape Cod Incorporated, East Falmouth, MA, USA). in serum has been used as a diagnostic aid [Alexander and Pfaller, 2006; Odabasi et al. 2004]. β-D-glucan is a major component of the fungal cell wall of a wide variety of fungi and can be detected by its ability to activate factor G of the horseshoe crab coagulation cascade. This assay has a sensitivity of 75–100% and a specificity of 88–100% (Table 3). However, it is a broad-spectrum assay that can also detect *Aspergillus*, *Fusarium*, *Acremonium*, and *Saccharomyces* spp. [Odabasi *et al.* 2004].

Table 3. Characteristic features of biomarkers currently used for the diagnosis of invasive fungal infections.

	Biomarkers	
Test features	1,3 β-D-glucan (BG)	Galactomannan (GM)
Method	Biological cascade based assay	Anti-GM monoclonal antibody
Results interpretation	Negative < 60 pg/ml Intermediate 60–79 pg/ml Positive > 80 pg/ml	Negative < 0.5 index Positive > 0.5 index
Clinical applications	Useful for early detection	Useful for the early detection of invasive aspergillosis in adults
FDA approval	Serum	Serum, BAL
Clinical significance in diagnosis of IFI	Sensitivity: 77% (67–84%) Specificity: 85% (80–90%)	Serum: sensitivity 41% (59–83%), specificity 93% (92–94%) BAL: sensitivity 85% (72–92%), specificity: 88% (78–92%)
Major caveats		
Cross reactivity	*Pneumocystis jiroveci*, *Coccidioides immitis*, *Histoplasma encapsulatum*, *Candida* spp., *Acremonium*, *Fusarium* spp., *Trichosporon* spp., *Aspergillus* spp.	*Aspergillus* spp., *Fusarium* spp., *Paecilomyces*, *Penicillium* spp., *Alternaria* spp., *Histoplasma encapsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*
False positives	Semisynthetic β lactam antibiotics Hemodialysis with cellulose membranes Bacteremia Transfusion given through cellulose membranes Exposure to gauze Intravenous imunoglobulins and albumin	Semisynthetic β lactam antibiotics Mucositis or GI tract GVHD Multiple myeloma Plasmalyte used in BAL Cotton swabs
False negatives	Concomitant use of antifungals	Concomitant use of antifungals

Odabassi *et al.* [2004]; Alexander and Pfaller [2006]; Mennick-Kersten *et al.* [2004].
BAL, bronchoalveolar lavage; FDA, US Food and Drugs Administration; GI, gastrointestinal; GVHD, graft *versus* host disease; IFI, invasive fungal infection.

The BG assay does not detect infections caused by *Cryptococcus neoformans* or *Mucor* spp.

Management

The treatment of *Candida* infections varies substantially and is based on the anatomic location of the infection, the patients' underlying disease and immune status, the patients' risk factors for infection, the specific species of *Candida* responsible for infection, and in some cases, the susceptibility of the strain to the different antifungal drugs [Vazquez and Sobel, 2011; Pappas *et al.* 2009]. In January 2009, the Infectious Disease Society of America and the Mycosis Study Group published updated practice guidelines for the treatment of candidemia and candidiasis [Pappas *et al.* 2009].

Antifungal agents. Three major classes of systemic antifungal agents are available for the treatment of invasive fungal infections (IFIs): polyenes, azoles, and echinocandins [Sucher *et al.* 2009; Moen *et al.* 2009; Miceli and Chandrasekar, 2012; Kauffman, 2006; Sable *et al.* 2008]. Systemic agents with anti-*Candida* activity include AmB deoxycholate (AmB-d), fluconazole, voriconazole, caspofungin, micafungin, anidulafungin, lipid formulations of AmB (LFAmB) and flucytosine (Table 4).

Polyenes include AmB-d and the LFAmB (AmB lipid complex, liposomal amphotericin B, and amphotericin B colloidal dispersion formulations) [Moen *et al.* 2009]. AmB was considered the gold standard of antifungal treatment for over 50 years. Unfortunately, its use is limited due to significant adverse events such as infusion-related reactions and nephrotoxicity. Lipid formulations of AmB were developed to overcome the limitations associated with the use of AmB-d. In general, LFAmB are better tolerated due to their different molecular structures. In fact, patients can be treated with larger doses of AmB without experiencing the typical side effects of AmB-d [Miceli and Chandrasekar, 2012]. The antifungal spectrum of activity, common drug–drug interactions, and side effects are shown in Table 4.

The activities of these antifungal agents against *Candida* are predictable and vary with species (Table 5). The drug of choice for candidemia or invasive candidiasis depends on the infecting species and the clinical setting. *C. albicans* is the most susceptible species. *C. parapsilosis* tends to have higher minimum inhibitory concentrations (MICs) *in vitro* and is less susceptible to echinocandin agents [Pappas *et al.* 2009; Kauffman, 2006; Sable, 2008]. *C. glabrata* is less susceptible to all antifungals and approximately 10–15% are intrinsically resistant to fluconazole. *C. krusei* isolates have the highest fluconazole and flucytosine MICs of any of the species. In addition, it is also resistant to itraconazole and AmB [Pfaller and Diekema, 2007; Morgan, 2005; Colombo *et al.* 2006] (Table 5).

Until recently, the use of AmB and fluconazole was the standard therapy for all forms of candidiasis [Charlier *et al.* 2006]. The primary difference between the newer guidelines and the prior guidelines has to do with the upfront use of echinocandins in patients with candidemia and suspected candidiasis who have moderate to severe infections, patients with infections due to *C. glabrata* and *C. krusei*, and those who have a history of prior azole exposure [Pappas *et al.* 2009; Vazquez and Sobel, 2006; Chandrasekar and Sobel, 2006; Kuse *et al.* 2007; Reboli *et al.* 2007; Cornely *et al.* 2007; Sobel and Revankar, 2007].

In the non-neutropenic adult patient with candidemia or invasive candidiasis, most infections are due to the presence of an intravascular catheter in up to 70% of patients [Pappas *et al.* 2003, 2009]. Removal of all intravascular catheters appears to shorten the duration of candidemia and has been associated with reduced mortality [Pappas *et al.* 2009; Andes *et al.* 2012].

Candidemia requires treatment in all patient populations. In most situations, either fluconazole or an echinocandin are the drug of choice in the management of candidemia and disseminated candidiasis. The options listed should be considered depending on the history of a prior exposure to antifungals, the probability of fluconazole resistance, the presence of comorbid conditions, and the clinical status of the patient. Fluconazole (loading dose of 800 mg, then 400 mg daily) or an echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily) are recommended as initial therapy for most adult patients [Pappas *et al.* 2009]. However, an echinocandin is preferred in patients with moderate to severe illness, in patients who have a recent azole exposure, and in patients infected with a non-*albicans Candida* spp. [Pappas *et al.* 2009; Sobel and Revankar,

Table 4. Summary of systemic antifungal agents currently available.

Agent	Spectrum of Activity[$]	Expected Clinical resistance[‡]	Interactions	Adverse events	Precautions
Azoles					
Fluconazole	Most yeast Dimorphic fungi	*Candida krusei* Molds Dematiaceous fungi	*Fluconazole increases plasma concentration of*: phenytoin, theophylline, tolbutamide, glyburide, glipizide, cyclosporine, terfenadine, astemizole, cisapride, tacrolimus and warfarin	*Most common*:nausea, vomiting, diarrhea, allergic reactions *Rare*: clinical hepatitis and cholestasis and fulminant hepatitis	Dose adjustment recommended for renal insufficiency Avoid during breastfeeding Pregnancy: category C
Itraconazole	Most yeast Dimorphic fungi Molds: most *Aspergillus* spp. Dematiaceous fungi	*Candida krusei*, *Aspergillus lentulus*, *Aspergillus terreus*, *Fusarium solani*, *Rhizopus* spp., *Mucor* spp., *Scedosporium apiospermum*, *Scedosporium prolificans*	*Itraconazole increases plasma concentrations of*: digoxin, quinidine, carbamazepine, rifabutin, pimozide, long-acting barbiturics, cisapride; cyclosporine, tacrolimus, sirolimus *Decrease plasma concentrations of itraconazole*: carbamazepine, phenytoin, rifampin *Other interactions*: calcium channel blockers (edema) statins (rhabdomyolysis) quinidine, pimozide and cisapride (QT prolongation, torsades de pointes, ventricular tachycardia and sudden cardiac death reported)	*Most common*: nausea, vomiting, diarrhea, and abdominal discomfort. *Rare*: hypertension, hypokalemia, edema	Use with caution in patients with liver failure Avoid if GFR is <30 ml/min Pregnancy: category C
Voriconazole	Yeast Dimorphic fungi Molds: most *Aspergillus* spp. Dematiaceous fungi	*Aspergillus lentulus*, *Rhizopus* spp., *Mucor* spp.	*Voriconazole increases plasma concentrations of*: quinidine, pimozide, cisapride, sirulimus, ergot alkaloids, astemizole, warfarin, tacrolimus, cyclosporine, digoxin, phenytoin, midazolam, terfenadine *Decrease plasma concentrations of voriconazole*: carbamazepine, rifampin, long-acting barbiturics, phenytoin, rifabutin *Other interactions*: sulfonylureas (hypoglycemia), cisapride (cardiac arrhythmias)	*Most common*: skin rash, liver enzymes and elevation, transient visual disturbances *Uncommon*: total bilirubin and alkaline phosphatase	IV formulation: IV vehicle can accumulate if GFR <50 ml/min Pregnancy: category D

(continued)

Table 4. Continued.

Agent	Spectrum of Activity[$]	Expected Clinical resistance[‡]	Interactions	Adverse events	Precautions
Posaconazole	Yeast Dimorphic fungi Molds: *Aspergillus* spp., *Fusarium solani*, *Mucor* spp., *Rhizopus* spp. Dematiaceous fungi	*Scedosporium prolificans*, *Scedosporium apiospermum*	*Posaconazole increases plasma concentrations of*: ritonavir, atazanavir, midazolam, cyclosporine, tacrolimus, sirolimus *Decrease plasma concentrations of posaconazole*: rifabutin, cimetidine, efavirenz *Other interactions*: sirulimus (QT prolongation), contraindicated	*Most common*: nausea, vomiting, diarrhea, abdominal discomfort and liver enzymes elevation	Pregnancy: category C
Polyenes					
Conventional amphotericin B and lipid formulations[*]	Most yeast Dimorphic fungi Molds: *Aspergillus fumigatus*, *Aspergillus lentulus*, Mucor spp., *Rhizopus* spp., *Fusarium* spp.	*Candida lusitaniae*, *Candida guillermondii*, *Candida rugosa*, *Trichosporon* spp., non-*fumigatus Aspergillus* (*A. terreus*, *A. ustus*), *Scedosporium apiospermum*, *Scedosporium prolificans*	*Increased risk of nephrotoxicity with*: nephrotoxic antibiotic agents; nephrotoxic immunosuppressant agents; cyclosporine and IV pentamidine *Increased risk of toxicity with*: neuromuscular blocking agents and digitalis glycosides	*Most common*: infusion related toxicities (hypoxia, chills, local thrombophlebitis), vomiting, anemia; nephrotoxicity *Rare*: hypersensitivity reaction, transient elevation of liver enzymes, acute liver failure Note: lipid formulations of amphotericin B are associated with reduced nephrotoxicity and infusion-related reactions	Avoid concomitant use of nephrotoxic agents, neuromuscular blockers and digitalis glycosides Pregnancy: category B
Echinocandins					
Caspofungin	*Candida spp.* Dimorphic fungi *Aspergillus* spp.	*Aspergillus lentulus*, *Fusarium* spp. *Mucor* spp. Dematiaceous fungi	*Caspofungin decreases plasma concentrations of*: tacrolimus (by 20%) *Increases plasma concentrations of caspofungin*: cyclosporine (by 35%) *Decrease plasma concentrations of caspofungi*:	*Most common*: phlebitis, elevated liver enzymes Rare: skin rash, facial edema, pruritus, sensation of warmth	Reduced dosage should be used in patients with moderate liver insufficiency Pregnancy: category C

(continued)

Table 4. Continued.

Agent	Spectrum of Activity[$]	Expected resistance[‡]	Clinical	Interactions	Adverse events	Precautions
				rifampin, phenytoin, dexamethasone, efavirenz, nelfinavir, carbamazepine *Other interactions*: additive/synergistic antifungal activity with concomitant used with polyenes or azoles		
Micafungin				*Micafungin increases plasma concentrations of*: sirulimus and nifedipine	*Most common*: nausea, vomiting, headaches, elevated liver enzymes *Rare*: pruritus, skin rash and flushing	Usually well tolerated Pregnancy: category C
Anidulafungin				No clinically relevant drug–drug interaction reported	Most common: nausea, vomiting, diarrhea, dyspepsia, elevated liver enzymes, rash and hypokalemia *Rare*: pruritus, skin rash, urticaria, flushing and hypotension	Usually well tolerated Pregnancy: category C

GFR, glomerular filtration rate; IV, intravenous.

Table 5. General patterns of susceptibility of *Candida* species.

Candida species	Fluconazole	Itraconazole	Voriconazole	Amphotericin B	Echinocandins
C. albicans	S	S	S	S	S
C. tropicalis	S	S	S	S	S
C. parapsilosis	S	S	S	S	S-I
C. glabrata	S-DD to R	S-DD to R	S	S-I	S
C. krusei	R	S-DD to R	S	S-I	S
C. lusitaniae	S	S	S	S to R	S
C. kefyr	S	S	S	S	S
C. guilliermondii	S	S	S	S-R	S-I
C. dubliniensis	S	S	S	S	S

Vazquez and Sobel [2011]; S, susceptible; S-DD, susceptible dose-dependent; R, resistant; I, intermediately susceptible.

2007; Andes *et al.* 2012]. In a recently published study by Andes and colleagues, a quantitative review of 1915 patients who were randomized into several clinical trials evaluating the treatment of invasive candidiasis were reviewed. Although numerous variables were evaluated, only two treatment-related factors, use of an echinocandin and the removal of the central venous catheter, were associated with an improved survival rate and greater clinical success [Andes *et al.* 2012]. However, patients who are infected with susceptible *Candida* spp. and are clinically stable can be readily transitioned to oral fluconazole or voriconazole to complete the recommended 14-day course after the blood cultures have been cleared. Initial therapy with an echinocandin is also preferred in patients infected with either *C. glabrata* or *C. krusei.* In patients who have initially received fluconazole and are clinically improving, and whose follow-up culture results are negative, continuing use of an azole is reasonable [Pappas *et al.* 2009]. For infections due to *C. parapsilosis*, initial treatment with fluconazole is recommended nonetheless if a patient has initially received an echinocandin and is clinically improved, continued use of an echinocandin is reasonable. If an echinocandin is not available and either *C. glabrata* or *C. krusei* are suspected, initial therapy with voriconazole 6 mg/kg twice daily followed by 3 mg/kg twice daily is reasonable [Kullberg *et al.* 2005]. Other alternatives may also include AmB-d 0.5–1.0 mg/kg daily or LFAmB 3–5 mg/kg daily.

Management of invasive candidiasis in patients with neutropenia may include an echinocandin, LFAmB 3–5 mg/kg/day or voriconazole (6 mg/kg administered intravenously twice daily for two doses, then 3 mg/kg twice daily) [Pappas *et al.* 2009]. Fluconazole 400 mg/day may also be an alternative.

Successful therapy for serious systemic *Candida* infections requires starting antifungal therapy as early as possible. Therapy should be initiated as soon as adequate cultures have been obtained. Despite the newer advances in the diagnosis and newer antifungals, mortality rates for candidemia and disseminated candidiasis have not improved markedly over the past decade and remain in the range of 30–40%.

Antifungal prophylaxis of invasive candidiasis in patients who are in the high-risk group is currently recommended in several situations, which include patients with chemotherapy-induced neutropenia: fluconazole 400 mg daily, posaconazole 200 mg three times per day, or caspofungin 50 mg daily is recommended during induction chemotherapy for the duration of neutropenia [Viscoli *et al.* 1999; Husain *et al.* 2006; Ullmann and Cornely, 2006; van Burik *et al.* 2004]. In HSCT recipients, primarily those with allogeneic transplants, fluconazole 400 mg daily, or posaconazole 200 mg three times daily, or micafungin 50 mg daily is recommended during the period of neutropenia. In SOT recipients, fluconazole 200–400 mg daily or LFAmB 1–2 mg/kg daily for at least 7–14 days is recommended as postoperative prophylaxis for high-risk liver, pancreas, and small bowel transplant recipients.

Posaconazole has been shown to be effective prophylaxis against IFIs in high-risk patients with neutropenia and HSCT recipients, but its role as empirical therapy for candidiasis has not been established.

Empiric therapy. Empiric use of antifungal agents in patients who are febrile is widespread without much supporting data [Pappas, 2006, Leleu *et al.* 2002]. A major pitfall has been in

Table 6. Distribution of fungal pathogens causing invasive fungal infections in transplant recipients.

	Type of transplantation						
IFI pathogen	HSCT (%)	Kidney (%)	Liver (%)	Lung (%)	Pancreas (%)	Heart (%)	Intestine (%)
Aspergillus	43–64	11–14	7–11	44–63	5–10	23–25	0
Mucorales	5–8	1–2	2–3	2–3	0	2–3	0
Fusarium	2–3	0	0	<1	0	0	0
Other mold	3–7	2–3	0–2	9–20	3–5	2–7	0
Candida	22–28	49–61	68–79	23–24	76	49–65	85

Neofytos *et al.* [2009]; Kontoyiannis *et al.* [2010]; Pappas *et al.* [2010].
IFI, invasive fungal infection; HSCT, hematopoietic stem cell transplantation.

establishing the definitive diagnosis of invasive candidiasis in the setting of negative blood cultures. It appears reasonable to initiate empiric antifungal therapy in selected patients with known risk factors. Echinocandins with their broad spectrum of activity and improved efficacy may be preferable, although less expensive fluconazole may also be an alternative. Some criteria for initiating empiric antifungal therapy include patients with known risk factors for candidiasis, patients who are febrile and on broad-spectrum antibiotics for over 96 h, and patients with multifocal *Candida* colonization.

Invasive mold infections

Invasive mold infections (IMIs) have become an important cause of morbidity and mortality in HSCT and SOT recipients. Evolving transplant modalities and techniques, immunosuppressive strategies, and the use of antifungal prophylaxis has impacted the epidemiology and temporal pattern of IFIs in this population [Neofytos *et al.* 2009; Kontoyiannis *et al.* 2010; Pappas *et al.* 2010].

Epidemiology

Although *Candida* spp. remain the most common cause of IFIs in transplant recipients, molds account for approximately 40% of IFIs in the transplant population [Kontoyiannis *et al.* 2010; Pappas *et al.* 2010]. Recently, the Transplant-Associated Infection Surveillance Network (TRANSNET) reported prospectively collected data between 2001 and 2006, on 983 IFIs in 875 HSCT recipients and 1208 IFIs in 1063 SOT recipients [Kontoyiannis *et al.* 2010; Pappas *et al.* 2010]. The distribution of fungal pathogens causing IFIs in the HSCT and SOT populations identified in this large multicenter study is shown in Table 6. In this report IMIs occurred mostly in HSCT recipients and accounted for 57% of IFIs among HSCT recipients, and 27% in SOT recipients, whereas *Candida* infections predominated in the SOT population. The comparative increased frequency of molds causing IFIs in the HSCT population is likely the consequence of greater numbers of human leukocyte antigen (HLA)-mismatched or unrelated HSCTs being performed, with a higher risk for graft *versus* host disease (GVHD), requiring more intense immunosuppression, as well as the widespread use of anti-*Candida* prophylaxis [Park *et al.* 2011]. *Aspergillus* spp. accounted for the majority of mold infections, 76% among HSCT recipients and 81% among SOT recipients [Kontoyiannis *et al.* 2010; Pappas *et al.* 2010]. *Aspergillus fumigatus* was the predominant *Aspergillus* spp., followed by *A. terreus*, *A. niger* and *A. flavus*. *Mucorales* was the next most common mold infection and occurred in 14% and 10% in HSCT and SOT recipients, respectively [Kontoyiannis *et al.* 2010; Pappas *et al.* 2010; Park *et al.* 2011]. Among the *Mucorales*, *Rhizopus*, *Mucor* and *Rhizomucor* were the most common species recovered. The other non-*Aspergillus* molds recovered primarily in the HSCT population included *Fusarium* and *Scedosporium* [Park *et al.* 2011]. Several studies have also reported the emergence of *Fusarium* and *Scedosporium* in the transplant population [Campo *et al.* 2010; Nucci *et al.* 2003; Ben-Ami *et al.* 2009; Rodriguez-Tudela *et al.* 2009; Musk *et al.* 2006; Farina *et al.* 2006; Lamaris *et al.* 2006; Husain *et al.* 2003, 2005; Maertens *et al.* 2000]. *F. solani* was the predominant *Fusarium* spp., whereas *S. apiospermum* and *S. prolificans* were the most common *Scedosporium* spp. [Park *et al.* 2011].

Non-*Aspergillus* molds have been increasing in transplant recipients and have implications for therapy since they exhibit a variable susceptibility

profile to the commonly used antifungals. For example, the *Mucorales* are intrinsically resistant to voriconazole yet remain susceptible to AmB and posaconazole. *Fusarium* spp. have variable susceptibilities to antifungals, as such *F. solani*, which tends to be resistant to azoles and have higher MICs than the polyenes [Nucci and Anaissie, 2007]. The triazoles voriconazole and posaconazole appear to have superior *in vitro* activity against *Scedosporium* spp. than AmB.

In the SOT population, the highest rate of IFIs was seen in small bowel transplants, followed by heart–lung, liver, pancreas, heart, and kidney transplants [Kontoyiannis *et al.* 2010]. Allogeneic HSCT recipients, especially unrelated or mismatched transplants, had a fivefold greater risk for IFIs compared with autologous HSCT recipients [Pappas *et al.* 2010]. Despite a slight increase in the incidence of all IFIs during 2002–2005, there was no significant increase in the incidence of mold infections in either the SOT or HSCT populations over the past decade. In contrast, there appears to be a comparative increase in the incidence of mucormycosis [Park *et al.* 2011; Kontoyiannis and Lewis, 2006; Petrikkos *et al.* 2012]. This increase may be a consequence of a greater number of at-risk patients undergoing HSCT or SOT, the use of more aggressive immunosuppressive treatments for GVHD and rejection, and possibly the increased use of voriconazole for antifungal prophylaxis or for empiric therapy [Kontoyiannis *et al.* 2006; Petrikkos *et al.* 2012; Trifilio *et al.* 2007; Spellberg *et al.* 2012; Xhaard *et al.* 2012, Lanternier *et al.* 2012].

The comparative distribution of IMIs varies among the type of organ transplanted (Table 6). Overall, invasive aspergillosis (IA) and other mold infections predominated among HSCT recipients. Among SOT recipients IA was most common in lung transplant recipients, accounting for 44% of all IFIs compared with 23%, 14%, 11%, and 5% in heart, kidney, liver, and pancreas transplant recipients respectively [Pappas *et al.* 2010].

The timing of IFIs after HSCT and SOT has also been evaluated in several prospective multicenter studies (Table 7) [Neofytos *et al.* 2009, 2010; Kontoyiannis and Lewis, 2006; Park *et al.* 2011]. The median time to the diagnosis of IA in HSCT recipients is 82–99 days compared with 184–400 days in SOT recipients [Neofytos *et al.* 2009; Kontoyiannis and Lewis, 2006; Park *et al.* 2011]. Mucormycosis, fusariosis and other IMIs tend to occur even later after transplantation (Table 7). The shift of IA and other IMIs in HSCT patients to the late post-transplant period has been noted in several studies [Park *et al.* 2011; Ben-Ami *et al.* 2009]. Similarly, the late occurrence of IMIs caused by *Aspergillus* and non-*Aspergillus* molds in SOT recipients has also been reported [Husain *et al.* 2005; Singh *et al.* 2003, 2006]. In HSCT recipients, the shift in IMIs from early in the neutropenic pre-engraftment period to later during the period of GVHD

Table 7. Incidence, timing and outcomes of invasive fungal infection after transplantation.

Incidence, timing and outcomes of IFI	HSCT	SOT
1-year incidence of IFI (average of studies) (%)		
Aspergillus IFI	1.6	0.7
Mucorales IFI	<0.3	0.2
Other mold IFI	<0.3	0.2
Candida IFI	1.1	1.9
Median time to IFI after transplant (days)		
Aspergillus IFI	99	184
Mucorales IFI	135	312
Fusarium IFI	123	–
Other mold IFI	–	467
Candida IFI	61	103
12-month survival after IFI (%)		
Aspergillus IFI	25.4	59
Fusarium IFI	6.3	–
Other mold IFI	28	61
Candida IFI	33.6	66

Neofytos *et al.* [2009]; Kontoyiannis *et al.* [2010]; Pappas *et al.* [2010].
IFI, invasive fungal infection; HSCT, hematopoietic stem cell transplantation; SOT, solid organ transplantation.

may be the consequence of the increasing use of reduced intensity nonmyeloablative conditioning regimens and peripheral blood stem cells, resulting in shorter periods of neutropenia as well as the use of antifungal prophylaxis during the early post-HSCT period [Park *et al.* 2011; Nucci and Anaissie, 2009].

Risk factors

Several studies have examined the risk factors associated with the development of IMIs in transplant recipients (Table 8). In HSCT recipients, the duration of profound neutropenia remains an important risk factor for early onset IMIs. The use of cord blood as the source of donor cells is also an additional risk factor for early IA [Park *et al.* 2011]. However, GVHD and its treatment are the key factors that contribute to the increased risk for late-onset IMIs. The increased use of unrelated and HLA mismatched donors, prolonged corticosteroids, immunomodulators, such as infliximab and alemtuzumab may also increase the risk of IA [Park *et al.* 2011; Safdar *et al.* 2010]. Prolonged neutropenia and the prolonged use of corticosteroids have also been associated with an increased risk of IMIs due to *Mucorales*, *Fusarium*, and *Scedosporium* in HSCT recipients [Neofytos *et al.* 2009; Kontoyiannis and Lewis, 2006; Park *et al.* 2011; Dignani and Anaissie, 2004; Nucci and Anaissie, 2006; Nucci, 2003].

In SOT recipients, the risk factors for IMIs are strongly associated with end-organ failure,

Table 8. Risk factors for invasive mold infections in transplant recipients.

Type of transplant	Risk factors associated with invasive mold infections caused by			
	Aspergillus	***Mucorales***	***Fusarium***	***Scedosporium***
HSCT	Older age Allogeneic HSCT MUD and MMRD HSCT T-cell depleted graft Cord blood grafts Neutropenia Severe GVHD Corticosteroid Alemtuzumab, infliximab CMV disease TLR4 haplotype in donor	Neutropenia Severe GVHD Corticosteroids Older age Diabetes mellitus CMV disease Malnutrition Myelodysplasia Voriconazole exposure	Neutropenia Severe GVHD Corticosteroids Myeloma	Neutropenia Severe GVHD Corticosteroids
SOT				
Kidney	Corticosteroids Antirejection therapy Renal failure requiring dialysis	Renal failure Diabetes mellitus Liver transplant with iron overload		
Liver	Retransplant Renal failure requiring dialysis Reoperation Prolonged ICU stay Corticosteroids CMV and HHV 6 infection	Voriconazole exposure Caspofungin exposure		
Lung	*Aspergillus* colonization Single-lung transplant Anastomotic complications Graft ischemia Antirejection therapy CMV disease			
Heart	*Aspergillus* colonization Renal failure requiring dialysis Reoperation CMV disease			

Park *et al.* [2011]; Petrikkos *et al.* [2012]; Trifilio *et al.* [2007], Spellberg *et al.* [2012]; Safdar *et al.* [2010]; Fortún *et al.* [2012]; Silveira and Husain [2007]; Singh *et al.* [2003]; Husain [2009]; Ibrahim *et al.* [2011].
CMV, cytomegalovirus; GVHD, graft *versus* host disease; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; MUD, matched unrelated donor; MMRD, mismatched related donor; TLR4, toll-like receptor 4; SOT, solid organ transplantation.

especially renal or hepatic insufficiency [Nucci, 2003; Fortún *et al.* 2012; Silveira and Husain, 2007]. A study from Spain reported a 29-fold higher risk of IA in liver transplant recipients who required retransplantation and a 24-fold higher risk in patients requiring dialysis after transplantation [Fortún *et al.* 2012]. Lung transplant recipients who have documented prior colonization with *Aspergillus* or those with anastomotic complications have a greater risk of post-transplant *Aspergillus* tracheobronchitis or pulmonary IA. Renal transplant recipients receiving prolonged corticosteroids or antirejection therapy with sirolimus were also reported to be at higher risk of developing IA. A higher risk of mucormycosis was also reported in SOT recipients with diabetes and prior exposure to either voriconazole or caspofungin [Petrikkos *et al.* 2012]. An understanding of the specific risk factors in the various types of SOT and HSCT and the identification of high-risk transplant recipients is essential to guide effective empiric and preventive antifungal strategies [Neofytos *et al.* 2009; Singh *et al.* 2003; Silveira and Husain, 2007].

Clinical features

The clinical features of IMIs are frequently nonspecific. Although most IMIs cause pulmonary infection, infections may also involve the paranasal sinuses, the central nervous system (CNS), the skin, the gastrointestinal tract or occasionally they can become disseminated (Figure 1). Table 6 summarizes the frequency of the organ sites involved in IMIs in transplant recipients.

Aspergillus can cause a wide spectrum of disease in humans. Fever is a common, but nonspecific symptom [Nucci, 2003]. Involvement of the respiratory tract occurs in over 60% of patients, and thus, about 50% of the patients present with respiratory symptoms, including cough, dyspnea and pleuritic chest pain [Nucci, 2003]. Sinus infection can result in facial and orbital pain, along with localized edema. Infections of the CNS can present as altered mentation or focal neurological deficits. Given the angioinvasive nature of *Aspergillus* spp., the symptoms of lung and brain involvement can resemble either a pulmonary embolism or a stroke. In SOT recipients, IA tends to be localized to the lungs. The manifestations of IA in the lung and heart–lung transplant recipients are frequently different from the pulmonary infection in other transplants. Infections at the anastomotic site and ulcerative tracheobronchitis are the most common pulmonary infections reported. In addition, endobronchial stent obstruction, bronchial plugging and pneumonitis may also be seen [Singh and Husain, 2003; Husain, 2009]. Interestingly enough, both CNS and disseminated disease have declined in recent years [Singh and Husain, 2003]. The factors resulting in the lower incidence of CNS and disseminated disease are yet to be elucidated. Recent reports suggest that the current use of calcineurin and TOR (target of rapamycin) inhibitors in antirejection regimens may have a beneficial antifungal effect [Singh and Husain, 2003].

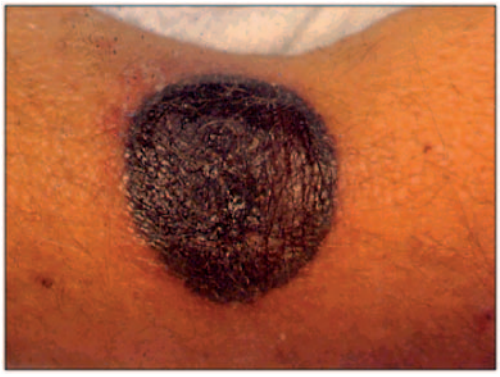


Figure 1. Cutaneous lesion of aspergillosis. Reproduced with permission from Dr Pranatharthi Chandrasekar.

Infections due to *Mucorales* often cause localized infections such as sinonasal, sino-orbital or rhinocerebral disease. Occasionally, involvement of the lung, gastrointestinal tract, skin and disseminated disease may be seen [Petrikkos *et al.* 2012; Lanternier *et al.* 2012]. Typical symptoms may include facial pain and swelling, orbital pain, proptosis, visual loss and opthalmoplegias. Given the propensity of *Mucorales* to cause invasion of the blood vessels, the infection is characterized by the development of necrotic lesions in the oral, nasal or sinus mucosa. The infection may progress rapidly and can invade the CNS, causing stroke-like symptoms [Kontoyiannis and Lewis, 2006; Lanternier *et al.* 2012; Ibrahim *et al.* 2011, 2012]. When dissemination to the skin occurs it is characterized by the development of rapidly progressive cutaneous necrosis.

Although IMIs caused by *Fusarium* and *Scedosporium* in HSCT recipients generally affect the lungs, unlike infections caused by

Aspergillus or *Mucorales*, dissemination to the skin structures occurs in up to 70% of cases. In the case of *Fusarium* spp., the propensity for dissemination via the bloodstream often results in high rates of isolation from blood cultures (~70%) [Nucci *et al.* 2004; Maertens *et al.* 2000; Nucci and Anaissie, 2006].

Diagnosis and management of mold infection

EORCT/MSG definitions. The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) have developed standard definitions for IFIs based on the level of probability in the diagnosis of IFIs occurring in immunocompromised patients [De Pauw *et al.* 2008]. Classically, IFIs have been divided into three categories: proven, probable, and possible based on host factors, clinical manifestations and mycological evidence.

Microbiologic criteria for the diagnosis of proven IFIs rely on direct tests (cytology, direct microscopy and culture) demonstrating the presence of fungal elements [De Pauw *et al.* 2008]. However, obtaining tissue samples or performing invasive procedures is not always feasible because of cytopenias or the poor clinical condition of these patients. Thus, the initiation of appropriate antifungal therapy is frequently delayed. The difficulty in establishing an early diagnosis is one of the primary reasons for the high mortality rates seen in IMIs [Chamilos *et al.* 2006; Rinaldi 1991; von Eiff *et al.* 1995].

Nonculture diagnostic assays such as the galactomannan (GM) and BG for the diagnosis of IFIs have been developed over the last two decades [Boudewijns *et al.* 2006; Mennik-Kersten and Verweij, 2006]. The advent of these indirect tests represents a major advance in the management of patients at risk for IFIs (Table 3).

Galactomannan assay. GM is an *Aspergillus*-specific polysaccharide residue that is incorporated into the cell wall during the initial phase of fungal growth. Eventually, GM is released into the circulation and possibly reused as a source of nutrient for further growth [Mennik-Kersten *et al.* 2004].

Table 9. Organ involvement in invasive mold infections among transplant recipients.

Organ involved	*Aspergillus* (%)	*Mucorales* (%)	*Fusarium* (%)	*Scedosporium* (%)
HSCT				
Lung	74–93	52	7	40
Sinus	4	21	7	NA
Central nervous system	4–6	14	NA	36
Skin	NA	9	36	38
Gastrointestinal tract	NA	2	NA	NA
Fungemia	NA	NA	28	25
Disseminated infection	13–16	10	75	69
SOT				
Lung	91	24–56		46
Sinus	NA	15–22		2
Central nervous system	7	14–16		25
Skin	NA	13–22	63	32
Gastrointestinal tract	NA	7–12	NA	NA
Fungemia	NA	NA	NA	16
Disseminated infection	11–22	9–26	22	55
Disseminated infection in specific SOT				
Kidney	9–36	9–13		
Liver	50–60	26–55		
Lung	15–20	11–25		
Heart	20–35	11–20		

Neofytos *et al.* [2009]; Kontoyiannis *et al.* [2010]; Pappas *et al.* [2010]; Park *et al.* [2011]; Nucci *et al.* [2004]; Petrikkos *et al.* [2012]; Rodriguez-Tudela *et al.* [2009]; Lamaris *et al.* [2006]; Nucci and Anaissie [2007]; Trifilio *et al.* [2007]; Lanternier *et al.* [2012]; Safdar *et al.* [2010]; Fortún *et al.* [2012]; Silveira and Husain [2007]; Singh *et al.* [2003]; Husain [2009]; Ibrahim *et al.* [2011].
Data tabulated and averages used from the studies.
HSCT, hematopoietic stem cell transplant; SOT, solid organ transplantation; NA, not available.

In the clinical setting, the detection of serum GM antigen has been shown to be a useful screening test for the early diagnosis of IA in patients at risk [Maertens *et al.* 2001; Pfeiffer *et al.* 2006; Sulahian *et al.* 2001]. Serum is the most frequently tested specimen and appears to provide the highest sensitivity (up to 95%, depending on the patient population and previous antifungal therapy) [Chamilos *et al.* 2006]. Galactomannan is water soluble and therefore can be detected in specimens other than serum, including bronchoalveolar lavage (BAL), cerebrospinal fluid, pleural fluid and urine [Klont *et al.* 2004]. Except for serum and BAL, the use of GM in other specimens remains investigational.

A recent meta-analysis study was conducted to determine the role of BAL-GM in the diagnosis of IA. In this study, BAL-GM sensitivity and specificity varied from 84% and 95%, respectively, depending on the population tested and the cutoff used [Zou *et al.* 2012]. BAL-GM may be used as an adjunctive tool in establishing the diagnosis of IA (see http://www.accessdata.fda.gov/cdrh_docs/pdf6/K060641.pdf and http://www.accessdata.fda.gov/cdrh_docs/pdf9/K093678.pdf). Typically, a serum GM value of at least 0.5 is considered positive. Using this suggested cutoff point, the reported sensitivity and specificity of the GM assay was 80.7% and 89.2% respectively [Chamilos *et al.* 2006]. Conversely, due to the lack of data, the threshold for positive BAL-GM remains under debate.

The use of serum GM is also an excellent tool for the early diagnosis of IA. Sulahian and colleagues showed that GM might be detected in serum as early as 5–8 days before the clinical manifestations of IA develop [Sulahian *et al.* 2001]. These results support the use of GM as a screening tool for patients at high risk of developing IA. In this setting, the detection of positive results, particularly in two consecutive serum samples, provides strong support for the diagnosis of IA [von Eiff *et al.* 1995; Mennick-Kersten and Verweij, 2006; Maertens *et al.* 2001]. Recently, some authors have also suggested that GM could serve as a surrogate marker of clinical response to treatment in patients with IA [Miceli *et al.* 2008; Park *et al.* 2011; Maertens *et al.* 2009; Boutboul *et al.* 2002]. Several studies showed that the titer of GM tends to decrease in cases that demonstrated a clinical response. Similarly, increasing GM titers were associated with poor outcomes [Park *et al.* 2011; Maertens *et al.* 2009; Boutboul *et al.* 2002; Woods *et al.* 2007; Segal *et al.* 2008]. False-positive reactions have also been reported in 1–18% of the tested samples and may be due to cross reactivity or false-positive GM (Table 3).

Radiographic imaging. Radiographs of the chest and sinuses have been used as a primary means of diagnostic assessment. However, they are frequently inadequate to establish a diagnosis. Initial chest computed tomography (CT) scan findings in IA are dominated by the nodule and its associated 'halo sign'. The main finding in IA is generally a pulmonary nodule greater than 1 cm in diameter, that is, the mancronodule. It is defined as a localized, space-occupying, ovoid, soft-tissue opacity that displaces rather than conforms to the shape of the preexisting aerated lung [Georgiadou *et al.* 2011]. More than 90% of patients with mycologically proven IA have at least one pulmonary nodule. The halo sign apparent on the CT scan is a modifier of the macronodule. It is defined as a perimeter of ground-glass lung opacity surrounding a pulmonary nodule. On initial CT scan, a study of patients with mycologically proven IA, about 33% have one or more macronodules with a halo sign. The 'air crescent sign' generally follows the halo sign approximately 1 week later (Figure 2).

Management

Despite the advances in the field and the advent of newer technologies, identification of fungal pathogens continues to be difficult and early diagnosis is not always possible [Georgiadou

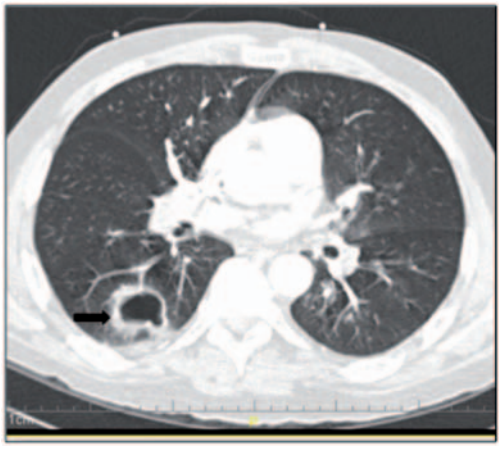
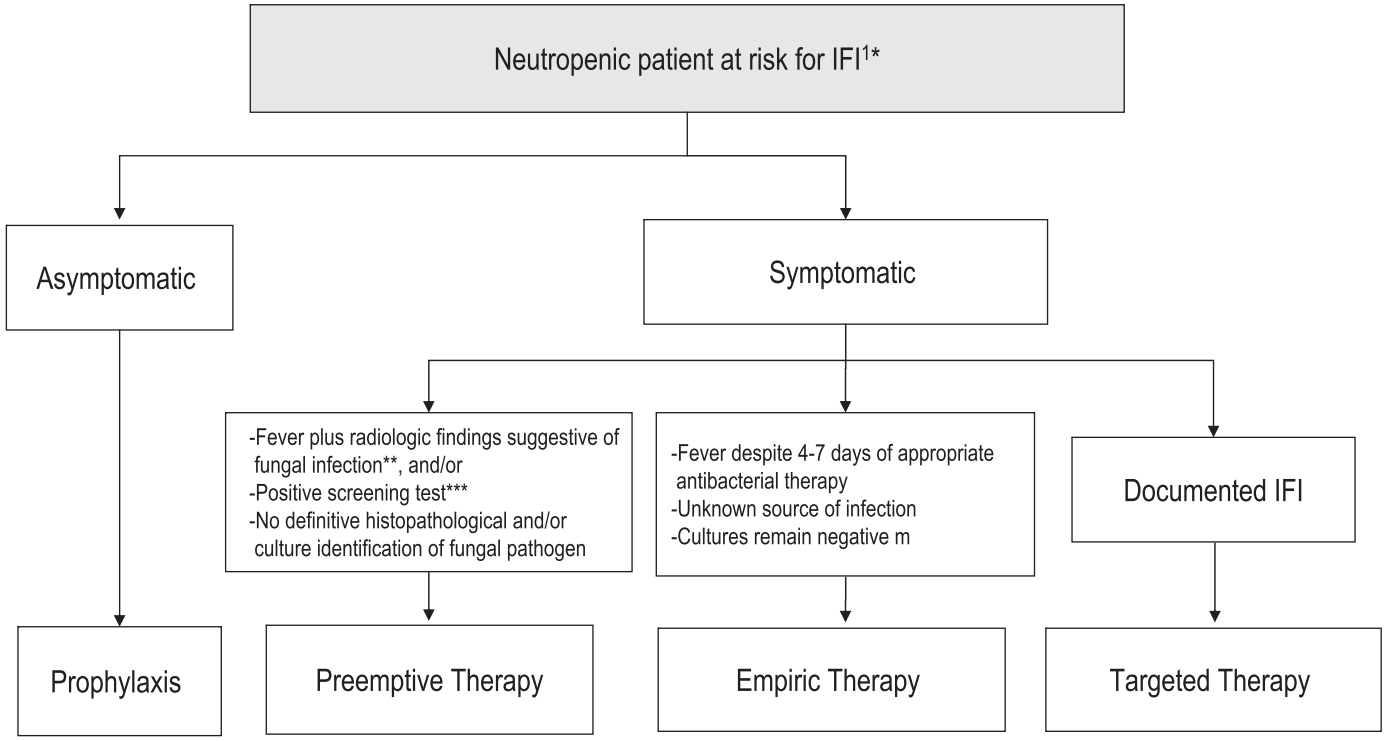


Figure 2. Computed tomography scan showing necrotic nodular infiltrate in a hematopoietic stem cell transplant recipient with pulmonary aspergillosis.

et al. 2011; Miceli and Lee, 2011; Revankar and Sutton, 2010]. Because early treatment is crucial in the management of these patients, initiation of empiric antifungal therapy is not uncommon when IFI is suspected [Walsh *et al.* 2008].

Strategies for the management of mold infections. Current strategies for the management of IFIs include prophylaxis, empiric, preemptive, and targeted therapy (Figure 3) [Ruhnke *et al.* 2012; Freifeld *et al.* 2011]. Antifungal prophylaxis involves the administration of an antifungal drug to high-risk patient populations before the onset of signs or symptoms of infection. In addition to neutropenia during the pre-engraftment period in HSCT recipients, these patients are at high-risk for mold infection as a consequence of severe cell-mediated immunodeficiency due to GVHD and its therapy (Table 8). Similarly, certain SOT recipients are also at high risk for mold infections (Table 8). Prophylaxis with anti-mold agents has been recommended in these select patient groups [Tomblyn *et al.* 2009; Singh *et al.* 2013]. In this setting, the antifungal agent is started despite the fact that adequate microbiological diagnosis of IFIs is unavailable [Freifeld *et al.* 2011]. Preemptive therapy is often initiated when non-specific radiographic signs are present or laboratory tests are suggestive of IMIs, in the absence of microbiological or histopathological confirmation of IFIs. Although preemptive antifungal therapy has been used successfully in patients with neutropenia who are febrile, there are no standard recommendations that fully support its use [Pasqualotto and Colombo, 2010; Kontoyiannis and Lewis, 2011; Lortholary *et al.* 2010]. Targeted therapy relies on treating microbiologically and histologically documented cases of IFIs [Ruhnke *et al.* 2012; Freifeld *et al.* 2011].

Specific management issues. Specific antifungals used for the treatment of IFI are summarized in Table 4. The management and prognosis of IA depends on the specific form of disease and the degree of immunosuppression. For over 50 years, AmB-d was the mainstay of antifungal therapy. Guidelines for the management of IA have been



References:
[1] Patient at risk for IFI include prolonged neutropenia after intense chemotherapy for hematologic malignancy, and high-risk HSCT and SOT recipients
*IFI: invasive fungal infection;
** Radiologic findings suggestive of IFI include high resolution computed tomography scan of the thorax showing new ≥1 cm single or multiple nodules with or without halo sign, lobar consolidation, wedge-shaped consolidative infarct.
***Screening tests include Aspergillus galactomannan, 1,3 beta-D-glucan, and /or PCR

Figure 3. Strategies for the Management of Neutropenic Patients at High Risk for Invasive Fungal Infections.

published by the Infectious Diseases Society of America [Walsh *et al.* 2008]. The current mainstay of therapy for IA is considered to be voriconazole. A randomized, multicenter study compared AMB-d with voriconazole as initial therapy for IA. This pivotal study demonstrated that initial therapy with voriconazole led to better responses and improved survival with fewer serious side effects, such as renal insufficiency and infusion-related toxicity [Pasqualotto and Colombo, 2010]. The appropriate dose of voriconazole is 6 mg/kg twice daily for 1 day, followed by 4 mg/kg twice daily.

A crucial factor in optimizing therapy in any patient with IA is the decrease or elimination of the immunosuppressant whenever possible. The recent literature suggests that if patients are diagnosed and treated early with appropriate antifungal therapy, the response rates may reach 50% or greater [Ruhnke *et al.* 2012].

Successful treatment of mucormycosis requires a high index of clinical suspicion for an early diagnosis [Kontoyiannis and Lewis, 2006; Ibrahim *et al.* 2011; Freifeld *et al.* 2011]. Mortality rates as high as 85% have been documented. Treatment requires reversal of the underlying condition, when possible; wide and extensive surgical removal of the affected tissue; and early antifungal therapy. Unfortunately, prospective randomized clinical trials have not been performed. Current recommendations include high-dose LFAmB at doses of 7–10 mg/kg/day [Kontoyiannis and Lewis, 2006]. The optimal duration of therapy is unknown, but a total dose of 2–6 g has been used in some cases.

In addition, posaconazole has demonstrated *in vitro* activity against many agents of mucormycosis and may be used as step-down therapy in patients who have responded to initial therapy with LFAmB. Voriconazole has not been shown to be active *in vitro*, and neither have the echinocandin group of antifungals.

The overall prognosis of the infection depends on several factors, including the site of infection, the rapidity of diagnosis, and the type and severity of immunosuppression. Although the overall mortality rate for mucormycosis is approximately 50%, the mortality rate for the rhinocerebral form is approximately 85%.

Patient survival in patients with infections due to *Fusarium* spp. include the variable susceptibility of the different *Fusarium* spp. and the immunocompromised state of the patient [Ibrahim *et al.* 2012]. *Fusarium* spp. are intrinsically resistant to many of the azoles, and occasionally, AmB. Early open-label clinical trials and compassionate clinical trials have demonstrated that voriconazole shows excellent activity against all *Fusarium* spp. [Lortholary *et al.* 2010; Herbrecht *et al.* 2004]. Voriconazole is used at a dose of 6 mg/kg every 12 h for two doses, followed by 4 mg/kg every 12 h. Utilization of voriconazole demonstrates an increased survival of approximately 40% compared with the historical 10% success rates seen with AmB. Studies using LFAmB at higher doses have also shown some promise. A report of the successful treatment of a *Fusarium* infection in a severely immunocompromised child demonstrated evidence of synergistic activity between AmB and rifampin when used together with granulocyte transfusions. Posaconazole has also shown activity against *Fusarium*. In a study of 23 patients with fusariosis, posaconazole demonstrated an overall success rate of 48% [Herbrecht *et al.* 2004]. As with all IFIs, the successful treatment depends on the host's immune response, the early diagnosis and the early initiation of appropriate antifungal therapy. If possible, immunosuppression should be stopped or reduced and by the correction of neutropenia with growth factors. Unfortunately, prognosis remains poor with disseminated disease but correlates with the resolution of neutropenia.

The successful management of invasive scedosporiosis also depends on the early diagnosis and the early initiation of appropriate antifungal therapy, as well as the correction of the host's immune status [Musk *et al.* 2006; Husain *et al.* 2005]. If possible, immunosuppression should be either discontinued or reduced and the neutropenia reversed. Although clinical studies have not yet been performed, voriconazole is the drug of choice in the treatment of infections due to *S. apiospermum* [Troke *et al.* 2008]. Successful outcomes have also been reported in several cases of *S. apiospermum* infection when posaconazole was used as salvage therapy [Troke *et al.* 2008; Cortez *et al.* 2008]. Combination antifungal therapy with AmB and caspofungin or voriconazole and caspofungin has also shown promise *in vitro* [Musk *et al.* 2006]. However, prognosis remains poor with disseminated disease, but correlates with the resolution of neutropenia [Cortez *et al.* 2008].

Conclusion

Invasive fungal diseases have become an infection of increasing importance in the transplant recipient. Recent advances in antifungal therapy, such as the echinocandins, voriconazole and posaconazole have made a significant impact on the selection of antifungals due to their broader spectrum of activity, their excellent safety profile, and their ease of use in these critically ill, severely immunosuppressed patients. Additionally, the earlier recognition of the high-risk patient and the known difficulty in establishing a definitive diagnosis warrant the use of early antifungal therapy in an attempt to decrease the exceedingly high morbidity and mortality associated with these infections.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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