

MONOGRAPH

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The Value of Prospective Epidemiologic Surveys

Invasive fungal infections impose an enormous cost, both in morbidity and mortality and in health care expenditures. Even a decade ago, invasive candidiasis was estimated to cause up to a 49% increase in mortality, anywhere from 3 to 30 days increased length of hospital stay per episode of care, excess costs close to \$100,000, and an average total cost of approximately \$45,000 per private insurance patient (Rentz et al, 1998).

Avoiding development of invasive mycoses in a compromised population may be difficult. *Aspergillus* and other molds are endemic, making complete avoidance of exposure nearly unattainable. Disruption of natural barriers, neutrophil dysfunction, deficits in cell-mediated immunity, and various metabolic defects also predispose individuals to development of an invasive fungal infection. The susceptible patient populations include, but are not limited to, individuals who are immunocompromised for any reason, those who are in the intensive care unit (ICU), and the neonatal/pediatric population.

Diagnosis of the infections has traditionally been through either of the traditional gold standards: blood culture or biopsy and tissue culture. Traditional blood cultures, however, have a sensitivity of only about 50%, increasing to 70% with use of the latest and most sensitive blood culture techniques, such as fungal isolators and radiometric assays. Biopsy and tissue culture may be of limited use because the patients most at risk for invasive fungal infections are also those at highest risk for complications following invasive procedures. Use of a serologic assay for β -D-glucan, a component of the fungal cell wall, provides another diagnostic tool for candidiasis, fusariosis, trichosporonosis, and aspergillosis that is both highly sensitive and specific in single and in multicenter trials (Table 1; Obayashi et al, 1995; Odabasi et al, 2004; Ostrosky-Zeichner et al, 2005).

Table 1. Use of β -D-glucan Assay to Diagnose Candidemia

Author	Population	Sampling	Sensitivity, %	Specificity, %	PPV,%	NPV, %
Obayashi ^a	Febrile patients	Single	90	100	59	97
Odabasi ^b	AML/MDS	Multiple, 2+	65	96	57	97
Ostrosky-Zeichner ^c	Hospitalized patients	Single	64	92	89	93

a. Obayashi et al. *Lancet*. 1995;345(8941):17-20.

b. Odabasi et al. *Clin Infect Dis*. 2004;39:199-205.

c. Ostrosky-Zeichner et al. *Clin Infect Dis*. 2005;41:654-659.

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; AML, acute myelocytic leukemia; MDS, myelodysplastic syndrome.

A significant challenge in the management of invasive fungal infections is deciding who should receive treatment and when precisely that treatment should begin. Figure 1 illustrates an algorithm that may be useful as the clinician makes these decisions. Prophylaxis is the earliest intervention, and is appropriate for individuals who have no evidence of infection but who are at very high risk for becoming infected; these individuals include patients in the ICU with several risk factors, those receiving induction chemotherapy, or neonates in the neonatal intensive care unit (NICU). Preemptive therapy comes into play for individuals who are currently asymptomatic, but who have several diagnostic indicators of infection. Empiric therapy is appropriate for patients who, although diagnostic indicators do not confirm infection, have the signs and symptoms of candidemia, are at high risk of infection, and are receiving antibiotics, or are neutropenic, febrile, and unresponsive to antibiotics. Obviously, therapy options are clearer when there is obvious disease.

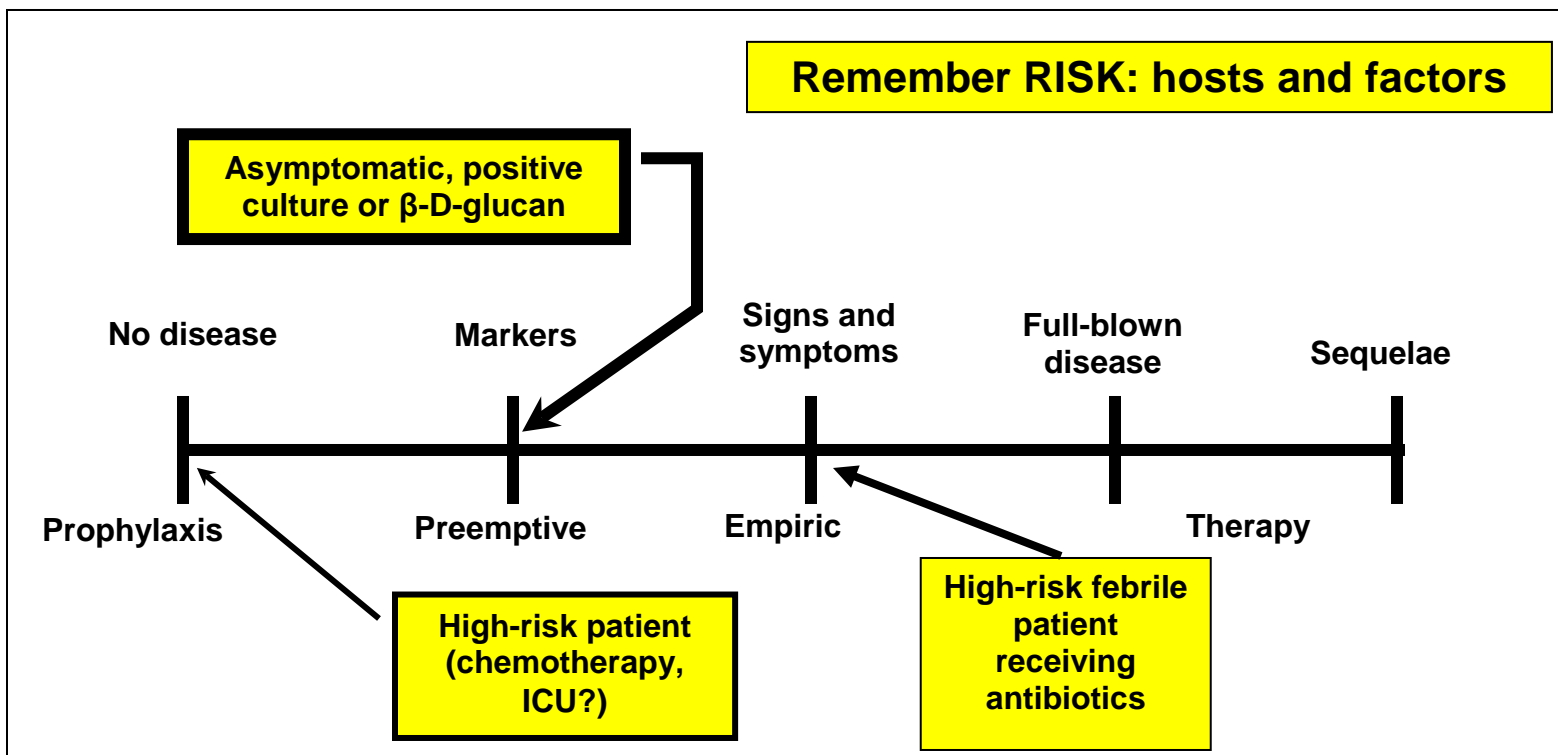


Figure 1. Candidemia Management: Whom to Treat and When

Several investigators have proposed rules that also provide some direction as to patient selection and timing of treatment. In a multicenter trial in the United States and Brazil, Ostrosky-Zeichner and colleagues (2007) determined that ICU patients at highest risk of invasive candidiasis were those receiving any systemic antibiotic or those with a central venous catheter, who also had at least 2 additional factors: total

parenteral nutrition (TPN), dialysis, major surgery, pancreatitis, administration of steroids, or other immunosuppression. In an earlier study of ICU patients with peritonitis, the presence of 4 additional risk factors, including intraoperative cardiovascular failure, previous antimicrobial therapy, female gender, and peritonitis originating in the upper gastrointestinal tract, was identified with an increased risk of yeast isolation in the peritoneal fluid (Dupont et al, 2003), an identification which might suggest a benefit to prophylactic treatment in this patient population. A third rule, the León rule, was developed through logistic regression analysis of data from a multicenter surveillance study for *Candida* in the ICU. In this model, points were assigned to determine predictors of proven candidal infection: multifocal colonization (+1), surgery (+1), sepsis (+2), and administration of TPN (+1). A composite score >2.5 conferred a relative risk of candidemia 7 times greater than that seen if the rule was not met (León et al, 2006).

Choosing antifungal prophylactic treatment must be done with care. Meta-analysis of data from several single-center trials of fluconazole as prophylactic treatment for *Candida* and other mycoses in surgical ICU patients did show an overall reduction in the incidence of invasive candidiasis without any shift in susceptibility. However, the strategy did not improve survival and the results indicated the need to choose patients carefully to achieve a benefit from prophylaxis (Shorr et al, 2005).

Empiric therapy is another strategy. In a prospective, multicenter trial, patients who met the inclusion criteria (ie, surgery within 2 months, colonization with *Candida* spp, risk factors for *Candida* infection, and persistent fever despite antimicrobial therapy with ≥ 3 agents or fever for longer than 7 days) and had a positive assay for β -D-glucan received empiric therapy with fluconazole for at least 7 days. Figure 2 indicates that when more than 3 sites were colonized with *Candida* in conjunction with a positive test for β -D-glucan, there was a 60% chance that the patient would respond to fluconazole. Therefore, there was a correlation between colonization, the presence of β -D-glucan, and response to antifungal agents (Takesue et al, 2004).

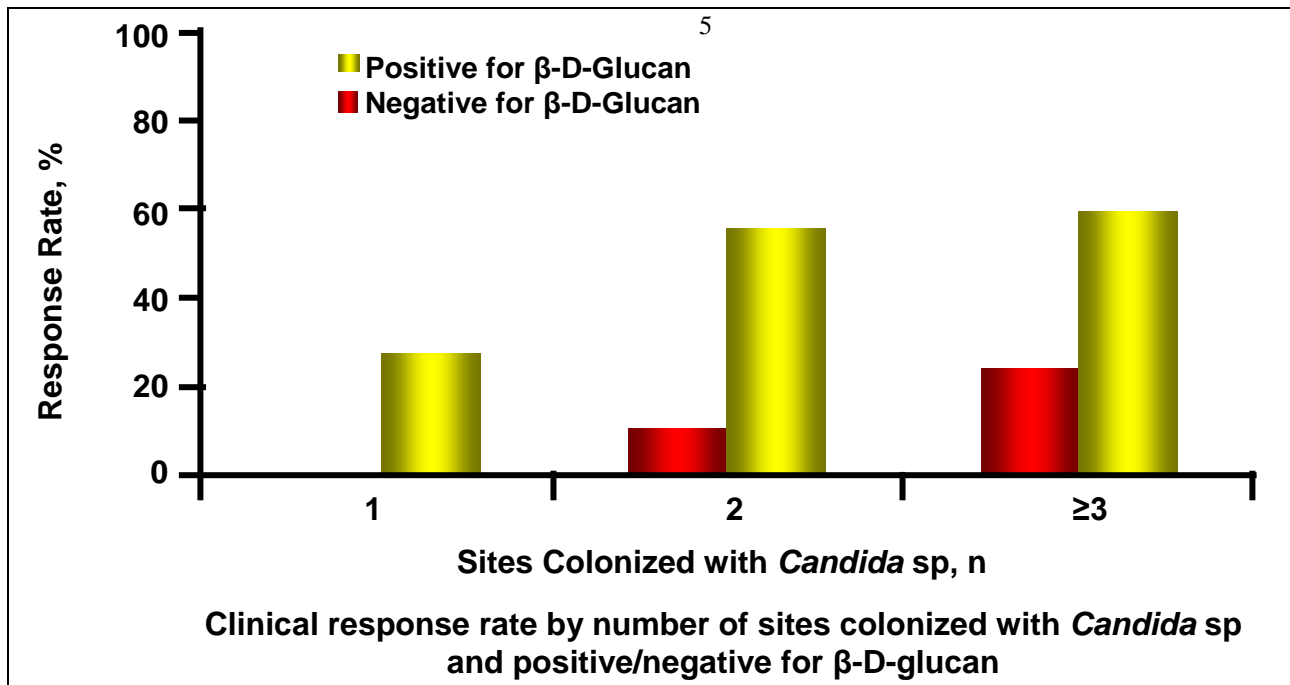


Figure 2. β-D-glucan and Colonization as Triggers for Empiric Therapy
 Takesue et al. *World J Surg.* 2004;28(6):625-630.

Other studies of empiric antifungal therapy have yielded mixed results. In one study where only 5.7% of patients received antifungal treatment within 12 hours following the first positive blood culture, delay of empiric treatment for more than 12 hours resulted in a 33.1% hospital mortality rate, compared with a mortality rate of 11.1% with prompt treatment (Morrell et al, 2005). However, in a more recent large, multicenter trial of empiric fluconazole therapy in high-risk ICU populations, only 36% of patients treated with fluconazole had a successful outcome (determined by a composite end point) compared with 38% of the patients in the placebo group. Based on their findings, the authors concluded that, while fluconazole was safe, it was not recommended for empiric therapy and should therefore be used only for documented infections (Schuster et al, 2008).

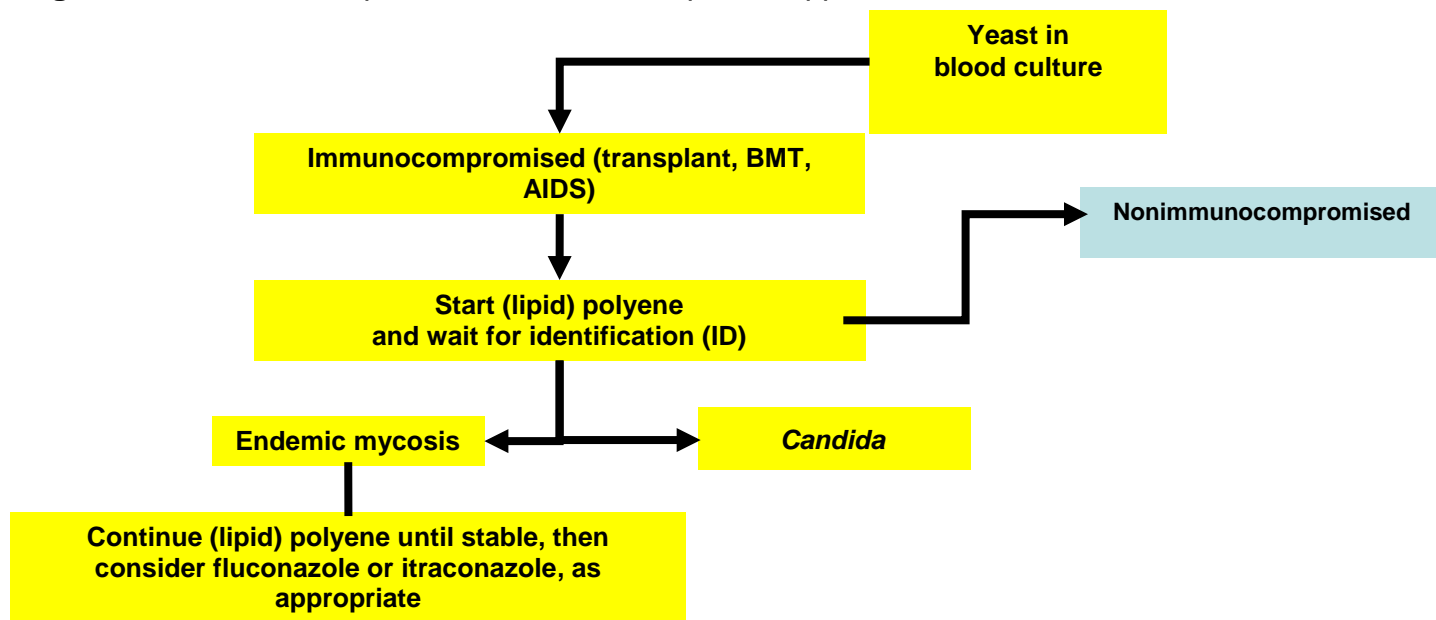
Once an invasive mycosis such as candidiasis has been identified and the diagnosis has been confirmed through repeated cultures and imaging, the source of the infection should be determined to guide the clinician's management strategy. Since the infection is quite possibly nosocomial, information on treatment susceptibilities for common local strains will help with choice of therapy. Susceptibility testing, particularly for *Candida glabrata* or *Candida krusei*, also should be considered. In addition, prosthetic devices should be removed, if possible, to eliminate possible sources of biofilm-related contamination. Finally, all options for antifungal therapy should be considered, including the polyenes, the azoles, and the echinocandins.

An algorithmic approach, outlined in Figures 3A and 3B, has been proposed that can be used when yeast has been identified in the blood culture (Ostrosky-Zeichner & Pappas, 2006). The first decision point is whether the patient is immunocompromised,

an important discrimination because yeasts other than *Candida* may be present in immunocompromised patients. If the patient is immunocompromised, therapy with a broad-spectrum agent, such as a polyene or lipid polyene, is recommended until the organism is identified. *Candida* may then be treated as if the patient is not immunocompromised. *Cryptococcus* or an endemic mycosis are better treated with the original broad-spectrum agent or with itraconazole or fluconazole, depending upon strain susceptibility.

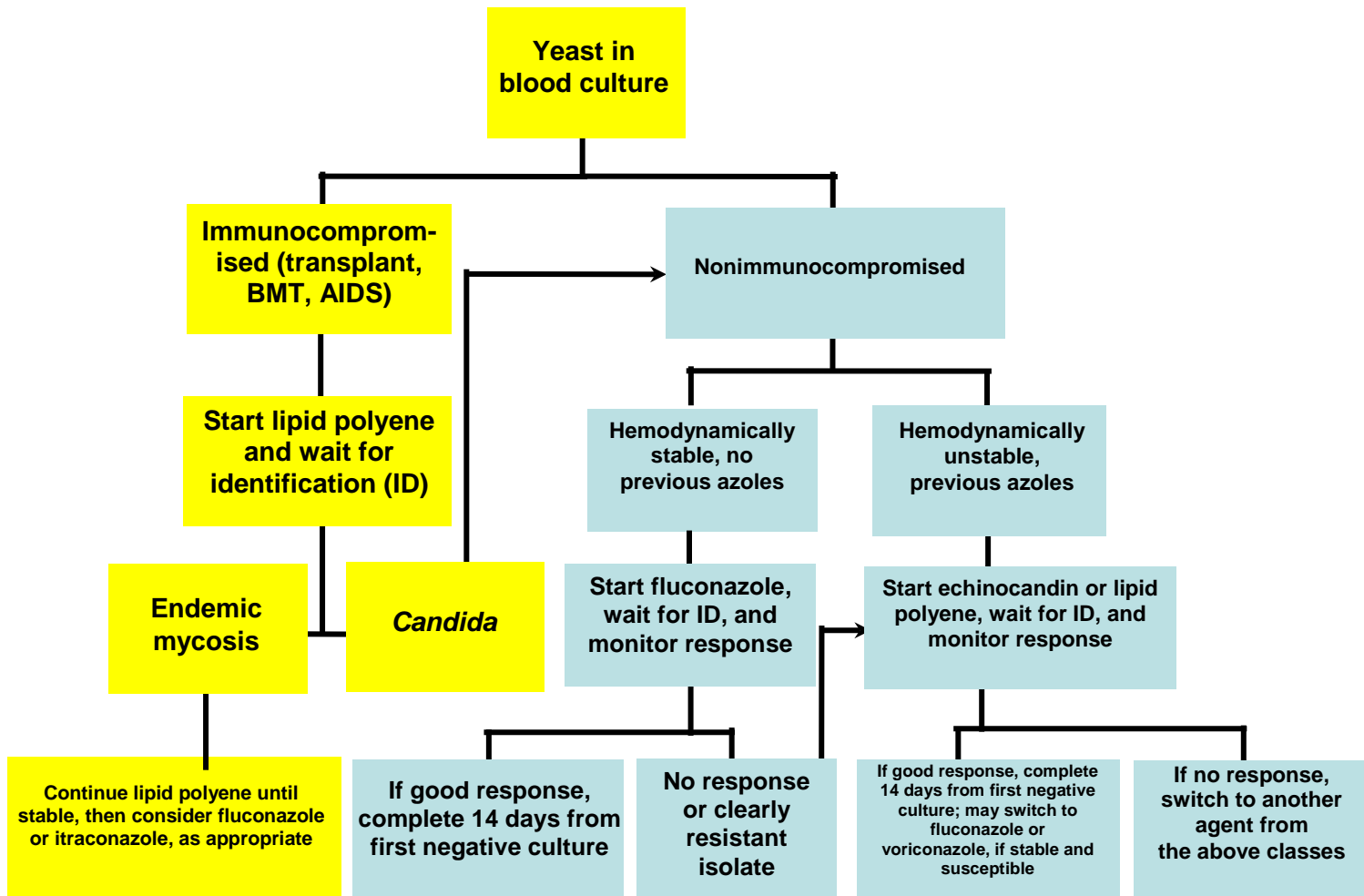
If the patient is not immunocompromised and *Candida* is present, patients who are hemodynamically stable, have not been previously treated with azoles, and are in an ICU which has a low incidence of azole resistance, fluconazole therapy is recommended. If the patient does not meet these criteria, or if *C. glabrata* or *C. krusei* are frequently identified in patients in that particular ICU, therapy with echinocandin or a lipid polyene is recommended. In all cases, changing therapy as needed is appropriate once the organism and susceptibility have been identified.

Figure 3A. Immunocompromised Patients: Proposed Approach



Ostrosky-Zeichner L, Pappas PG. *Crit Care Med.* 2006;34(3):857-863. BMT indicates bone marrow transplant.

Figure 3B. Nonimmunocompromised Patients: Proposed Approach



Ostrosky-Zeichner L, Pappas PG. *Crit Care Med.* 2006;34(3):857-863. BMT indicates bone marrow transplant.

The therapies available depend on the organism (eg, *Candida*, *Cryptococcus*, or other) and its susceptibility. The echinocandins (ie, anidulafungin, micafungin, and caspofungin) act against *Candida* and *Aspergillus* by inhibiting synthesis of 1,3- β -D-glucan in the fungal cell wall (Sucher et al, 2009). Amphotericin B, fluconazole, itraconazole, and voriconazole are other treatment options (Pappas et al, 2004). These antifungal agents provide a wide variety of therapeutic options, but early and accurate diagnosis is still critical for successful management of invasive fungal infections.

The Changing Epidemiology of *Candida* and *Aspergillus*

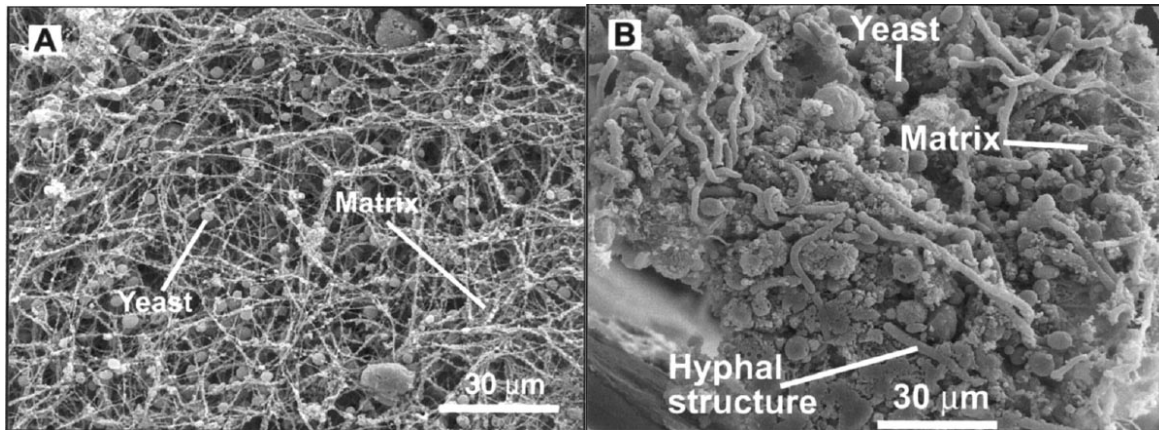
Cumulative data from 1995 to 2002 demonstrated the importance of *Candida* in the general hospital population, but more particularly in ICU and NICU patients. *Candida* sp. were the cause of 9.0% of bloodstream infections in the general population, 10.1% of the infections in ICU patients, and 7.9% of infections in neonates (Wisplinghoff et al, 2004). *Candida parapsilosis* predominated in neonatal patients, while the incidence of *C. glabrata* increased steadily with each decade of age (Malani et al, 2001).

Over time, the incidence of *C. krusei* infection has increased, emerging when prophylactic fluconazole is used. Although it is generally resistant to fluconazole and amphotericin B, *C. krusei* can be treated successfully with posaconazole, voriconazole, and the echinocandins (Pfaller et al, 2008a). *Candida parapsilosis* has remained susceptible to both the azoles and the echinocandins (Pfaller et al, 2008b), while most of the remaining common *Candida* sp. (eg, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. guilliermondii*) have not shown any decreasing susceptibility to the echinocandins (Pfaller et al, 2008c). Of the rare species, 95% were susceptible to all of 7 systemically active antifungal agents tested, including the azoles, amphotericin B, and the echinocandins (Diekema DJ et al).

The increased risk for and persistence of candidemia in patients with indwelling medical devices may be due to the ability of some *Candida* species (including *C. parapsilosis*) to form biofilms on biomedical substrates (Lattif et al 2009). The relative activities of antifungal agents against *C. albicans* and *C. parapsilosis* in biofilms varied; the mean inhibitory concentrations for voriconazole and posaconazole were high (≥ 256 mg/L and >64 mg/L, respectively), but comparatively low for caspofungin and anidulafungin (≤ 1 mg/L and ≤ 2 mg/L respectively) (Katragkou et al, 2008). In a rat in vivo model, upregulation of 2 fluconazole efflux pumps, CD1 and CD2, was observed in the biofilm-associated cells (Figure 4) (Andes et al, 2004).

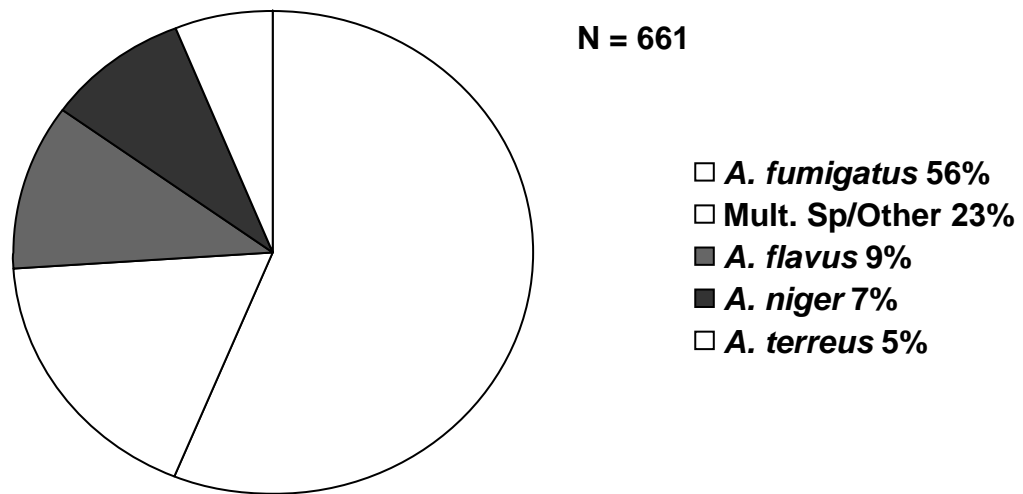
The incidence of invasive *Aspergillus* infections has also increased, particularly among ICU patients with chronic obstructive pulmonary disease (Samarakoon & Soubani, 2008) and in patients with significant immune dysfunction. *Aspergillus fumigatus* is the most common invasive pathogen, followed by *A. flavus*, *A. niger*, and *A. terreus* (Figure 5).

Figure 4. Scanning Electron Microscopy Image of in vivo *C. albicans* Biofilm After 24 Hours of Development



A, View of intraluminal surface of biofilm. B, View of biofilm cross-section. (Andes et al, 2004.) Reprinted with permission.

Figure 5. Distribution of *Aspergillus* spp in the TRANSNET Population, 2001 to 2006



TRANSNET indicates Transplant-associated Infection Surveillance Network.

Applying Principles of the 2008 and 2009 Infectious Diseases Society of America Guidelines to Clinical Practice

Currently, a wide range of antifungal agents is available for treatment of *Candida* sp. that are either approved by the US Food and Drug Administration (FDA) or nearing approval. These agents include amphotericin B, either as amphotericin B deoxycholate or as a lipid formulation; fluconazole administered singly, after amphotericin B, or in combination with amphotericin B; amphotericin B plus flucytosine; caspofungin; anidulafungin; micafungin; and voriconazole.

Approval of some of these agents has been complicated by difficulties associated with the assessment of data from clinical trials. First, the agents themselves are a cause for concern because of associated toxicity and variations in susceptibility. Second, individuals with candidiasis constitute a very heterogeneous population, with varied risk factors, a wide variety of underlying disorders, and multiple comorbidities associated with high mortality rates. Third, diagnosis through the gold standard blood culture and tissue culture of biopsies is insensitive, although the addition of a serologic assay for β -D-glucan has the potential to improve sensitivity and specificity. Fourth, candidemia is not caused by a single entity, but rather by multiple species with variable susceptibility to the available antifungal agents. Furthermore, the data may be compromised by pervasive use of empiric therapy with antifungal agents or by prophylactic use of these agents. Finally, the enrollment criteria and defined endpoints may be outdated.

Despite these difficulties, randomized trials have demonstrated the efficacy of the various antifungal agents. For example, in a direct comparison of intravenous (IV) therapy with anidulafungin versus IV fluconazole in adult patients with invasive candidiasis, treatment was successful in 75.6% of patients treated with anidulafungin versus 60.2% of patients receiving fluconazole. Fluconazole-treated patients had a mortality rate of 31%, compared with 23% of the patients treated with anidulafungin. In this study, anidulafungin was determined to be noninferior to fluconazole for the treatment of invasive candidiasis (Reboli et al, 2007).

Also, a large, international trial (Pappas et al, 2007; Table 2) compared IV caspofungin — the first FDA-approved echinocandin — with 2 different doses of micafungin (100 mg/d and 150 mg/d). Micafungin at 100 mg/day was adequate for therapy, with a success rate of approximately 75%, compared with a 70% success rate for caspofungin. Mortality rates were 29% for micafungin (100 mg/d) and 26% for caspofungin. The mortality rate for micafungin used at 150 mg/day was 33%, which was not significantly different from that for the 100-mg daily dosage.

Table 2. Comparison of Micafungin With Caspofungin (Pappas et al, 2007)

	Micafungin	Micafungin	Caspofungin
Dose, mg/d	100	150	50 ^a
Patients, n	191	199	188
Candidemia, %	85	84	86
MITT success, %	75	68	70
Mortality, %	29	33	26

^a The initial dose of caspofungin was 70 mg, followed by a 50-mg daily dosage.
Abbreviation: MITT = modified intent-to-treat.

Echinocandins (ie, caspofungin, micafungin, and anidulafungin) appear to be efficacious and well-tolerated. These antifungal agents, which seem to be interchangeable in terms of efficacy, are probably the agents of choice for initial therapy for invasive candidiasis, although preliminary evidence shows resistance to echinocandins by some strains of *C. parapsilosis*. Echinocandins may not be indicated for central nervous system (CNS) infections, however, as there have been anecdotal reports of CNS relapses and breakthroughs. In the treatment of endocarditis, echinocandins are an adequate replacement for amphotericin B plus 5-flucytosine (Venditti, 2009).

Management of Invasive Candidiasis: The 2009 IDSA Guidelines

Deciding when to treat a patient is as important as deciding which antifungal agent to use as primary therapy. Early serodiagnosis employing a serologic assay for β -D-glucan or polymerase chain reaction (PCR) may help with this decision. Additional challenges for managing invasive candidiasis include the potential for prophylaxis or empiric therapy, as well as a possible role for adjunct immunotherapy to prevent or reduce colonization. To address these issues, an expert panel of the Infectious Diseases Society of America (IDSA) convened in 2009 and prepared updated clinical practice guidelines for the management of patients with invasive candidiasis and mucosal candidiasis (Pappas et al, 2009). These guidelines, summarized in Tables 3 through 5, addressed 15 questions and assigned grades to each recommendation based on the strength of the clinical evidence.

Table 3. Treatment of Candidemia in Non-neutropenic Patients: 2009 IDSA Guidelines

1. For unknown <i>Candida</i> species, either fluconazole or an echinocandin is appropriate initial therapy for most adult patients.
2. Echinocandins are favored for patients with moderately severe to severe disease or with recent azole exposure.
3. Fluconazole is recommended for patients with less severe disease and with no recent azole exposure.
4. Transition from an echinocandin to fluconazole may be appropriate for clinically stable patients with isolates (eg, <i>C. albicans</i>) that are likely to be susceptible to fluconazole.
5. An echinocandin is preferred as the initial therapy for patients who have a proven or suspected infection due to <i>C. glabrata</i> , and transition to fluconazole or voriconazole is not recommended without confirmation of isolate susceptibility.
6. Fluconazole is preferred as initial therapy for patients with proven or suspected infection due to <i>C. parapsilosis</i> .
7. Amphotericin B is an effective alternative to an echinocandin in areas where resources or availability is limited, but transition from amphotericin B to fluconazole is recommended for stable patients with an isolate susceptible to fluconazole.
8. Voriconazole is generally limited to transitional oral therapy for selected cases of invasive candidiasis (eg, <i>C. krusei</i>).
9. Intravenous catheters should be removed, if possible.
10. The recommended duration of therapy for candidemia is 2 weeks following documented clearance of <i>Candida</i> from the bloodstream and resolution of symptoms.

Table 4. Treatment of Candidemia in Neutropenic Patients: 2009 IDSA Guidelines

1. If the <i>Candida</i> species is unknown, an echinocandin or a lipid formulation of amphotericin B is recommended.
2. Patients with less severe disease and no recent exposure to azoles may be treated with fluconazole or voriconazole.
3. An echinocandin or a lipid formulation of amphotericin B is recommended as initial therapy for <i>C. glabrata</i> .
4. <i>Candida parapsilosis</i> infections are best treated with fluconazole or a lipid formulation of amphotericin B, while an echinocandin or voriconazole is recommended for an infection due to <i>C. krusei</i> .
5. Therapy should continue for 2 weeks following documented clearance of <i>Candida</i> from the bloodstream <i>and</i> resolution of symptoms attributable to candidemia <i>and</i> resolution of neutropenia.
6. Intravenous catheters should be removed, if possible.

Table 5. Recommended Empiric Therapy for Non-neutropenic Patients With Suspected Invasive Candidiasis: 2009 IDSA Guidelines

1. Fluconazole or an echinocandin is recommended. Echinocandins are recommended for patients at high risk for <i>C. glabrata</i> or <i>C. krusei</i> .
2. Amphotericin B or a lipid formulation may be used instead of fluconazole or an echinocandin if other antifungal agents are not tolerated or if access is limited due to cost.
3. Selection of non-neutropenic patients for empiric antifungal therapy should be based on clinical assessment of risk factors, serologic markers for invasive candidiasis, and/or culture data from nonsterile sites.
4. Since the duration of empiric antifungal therapy has not been explicitly determined, the clinician must balance the benefits delivered by treatment versus the potential risks of continued therapy.

In some instances, the changes from the 2004 IDSA clinical practice guidelines were minimal, such as recommendations for vulvovaginal candidiasis, CNS candidiasis, chronic disseminated candidiasis, *Candida* endocarditis/phlebitis/infected, *Candida* endophthalmitis, and mucosal candidiasis. Major changes included an increased emphasis on fluconazole and echinocandins as preferred therapy for either proven or suspected invasive candidiasis coupled with a de-emphasis of amphotericin B and lipid formulations of amphotericin B under most circumstances. Little distinction is made between the different echinocandins. In NICUs, it is recommended that fluconazole prophylaxis be limited to high-risk sites. In addition, the concept of step-down therapy is strongly encouraged, particularly in environments limited in resources. For some selected isolates (eg, *C. krusei*), voriconazole is recommended for step-down therapy.

The 2009 guidelines still present limited clinical data supporting empiric antifungal therapy in the non-neutropenic population. In general, the same fundamental principles for treating candidemia should be applied. The most appropriate use of empiric or prophylactic therapy should be determined using a combination of serologic markers (eg, β -D-glucan assay), surveillance cultures, and/or a “scoring system.” The duration of therapy was not specifically addressed; in general, however, therapy in stable patients without evidence of infection should be curtailed.

Management of Aspergillosis: The 2008 IDSA Guidelines

The 2008 IDSA guidelines addressed similar issues for the diagnosis and management of invasive aspergillosis. Treatment concerns included the use of single or combination antifungal therapy, appropriate antifungal agents, and duration of

therapy. The agents currently available for treatment of invasive aspergillosis include the azoles (eg, voriconazole, itraconazole, and possibly posaconazole), amphotericin B and its lipid formulations, and the echinocandins (ie, caspofungin, micafungin, and anidulafungin). Susceptibility patterns for some of these agents were analyzed for *Aspergillus* isolates recovered from patients enrolled in the Transplant-associated Infection Surveillance Network (TRANSNET). Most species were susceptible to itraconazole, voriconazole, posaconazole, and ravuconazole, with the exception of *Aspergillus calidoustus*, and one isolate of *A. fumigatus*. Amphotericin B also was effective, except for 68% of the *A. terreus* isolates (Baddley et al, 2009).

A prospective, randomized, global trial involving more than 20 countries and 150 sites is currently underway to determine the relative efficacy of voriconazole alone versus voriconazole plus anidulafungin in patients with proven or probable invasive aspergillosis following allogeneic stem cell transplantation for hematologic malignancies. At the conclusion of the trial, the primary end point (ie, mortality at 6 weeks for all patients) and secondary end points (ie, global response, mortality, time to death, safety, and tolerability) will have been determined. Studies comparing isavuconazole to voriconazole, and posaconazole plus an echinocandin to voriconazole, are currently on hold; a study investigating IV and parenteral formulations of ravuconazole is under development.

Specific diagnosis of an invasive *Aspergillus* infection can be challenging. A serum galactomannan assay for *Aspergillus* has been useful in patients who have undergone allogeneic stem cell transplantation or who have had prolonged neutropenia following hematologic malignancy (Pfeiffer et al, 2006). The assay had a sensitivity of 0.68 to 0.74 and a specificity of 0.88 to 0.90 in proven cases. Sensitivities were lower in probable cases and in patients treated with antifungal agents. Rising values were associated with a poor prognosis. Although this assay is useful, it is slow and expensive, a problem for patients who, following allogeneic stem cell transplantation, are at risk for invasive aspergillosis for 100 days or longer. Since voriconazole and the echinocandins are not highly toxic, empiric therapy may be more appropriate than routine galactomannan testing.

Table 6 presents a synopsis of the 2008 IDSA guidelines for management of invasive aspergillosis (Walsh et al, 2008). These guidelines emphasize use of voriconazole and do not currently recommend combination therapy. Immunotherapy also may be appropriate in some instances.

Table 6. Summary of the 2008 IDSA Guidelines: Treatment of Aspergillosis

- | |
|---|
| 1. High-dose voriconazole (6 mg/kg q 12 h) for 2 doses followed by a lower dose (4 mg/kg q 12 h) is recommended. |
| 2. Second-line therapies may include a lipid formulation of amphotericin B, caspofungin, or micafungin. |
| 3. Primary combination therapy is not recommended. |
| 4. Voriconazole levels should be monitored. |
| 5. The length of therapy should be determined by clinical and radiographic response, but will generally be at least 6 to 12 weeks. |
| 6. Selected patients may require salvage therapy with posaconazole. |
| 7. Azoles are preferred for all patients with <i>A. terreus</i> infections. |
| 8. Patients with critical lesions (eg, perivascular, hemoptysis) may require surgical therapy. |
| 9. Selected patients with neutropenia may require immunotherapy, including granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or granulocyte infusions. |
| 10. Antifungal therapy should be continued through periods of immunosuppression (eg, re-induction chemotherapy). |

New Directions in the Management of Invasive Fungal Infections in Neonatal and Pediatric Patients

Invasive fungal infections occur in 2% to 4% of very low birth weight infants, with mortality rates reported of up to 44% (Uko et al, 2006). The high costs associated with the morbidity and mortality related to invasive fungal infections, including neurodevelopmental sequelae (Benjamin et al, 2006) led to a series of studies assessing whether prophylaxis with antifungal agents was an appropriate method to decrease invasive fungal infections in infants weighing less than 1500 g at birth.

Invasive Candidiasis

Uko and colleagues (2006) reported that 13 of 206 (6.3%) infants whose birth weight was less than 1500 g developed invasive fungal infections with either *C. parapsilosis* or *C. albicans*. Only 2 of 178 (1.1%) infants treated prophylactically with fluconazole (3 mg/kg) developed invasive fungal infections. High-risk patients were specifically targeted for prophylactic therapy, and included all infants with a gestational age of less than 32 weeks or a body weight of less than 1500 g.

Prophylactic treatment of high-risk neonates with fluconazole has led to a shift in the demographics of infection. A study of prophylactic fluconazole therapy spanning 4 years in a NICU setting revealed an overall decrease in the incidence of invasive candidiasis, as well as a shift of infections to larger, more mature infants (Healy et al, 2008). Also, there was a significant decrease in the all-cause mortality rate at this center. There was no evidence of emergence of fluconazole-resistant *Candida* species or other fungi, despite the intensive use of prophylactic fluconazole treatment (Figure 6). Although the trial was not designed specifically to assess safety of prophylactic fluconazole and lacked a matched control group, development of cholestasis in 31% of the infants receiving fluconazole prophylaxis was observed as the only significant adverse effect. On multivariate logistic regression, however, the increased incidence of cholestasis was significantly associated with necrotizing enterocolitis and increasing days of TPN, but not with increasing number of doses on days of fluconazole.

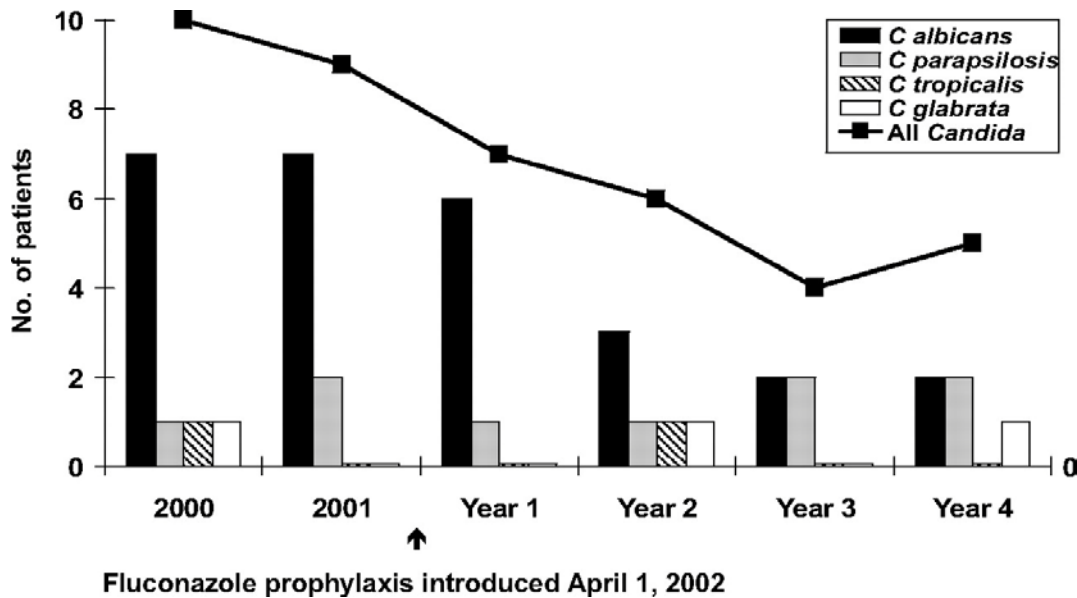


Figure 6. Distribution of invasive *Candida* species in infected infants of any birth weight before and after initiation of prophylactic fluconazole (Healy et al, 2008). Reprinted with permission.

Invasive Aspergillosis: Treatment With Fluconazole and Amphotericin B

Invasive aspergillosis has become a major cause of morbidity and mortality in immunocompromised individuals, including those in the pediatric population. A multicenter retrospective review (from January 1, 2000 to July 1, 2005) of invasive *Aspergillus* in children showed immunosuppression and allogeneic stem cell transplant to be the major risk factors with an impact on survival (Burgos et al, 2008). In this population, the lungs were the site most often infected (59%), and nodules were the most frequent diagnostic radiologic finding (34.6%). Many children were treated with an antifungal agent prior to diagnosis (43.1% treated with fluconazole and 39.2% with liposomal amphotericin B). After diagnosis, 45.8% received at least 3 concomitant antifungal agents. No particular agent showed superiority in decreasing overall mortality.

Invasive Aspergillosis and Invasive Candidiasis: Treatment With Echinocandins

In addition to fluconazole and liposomal amphotericin B, the safety and efficacy of echinocandins have been recently investigated. Caspofungin safety was analyzed in 5 clinical registration studies and was shown to be well-tolerated in the pediatric population with few serious events or treatment discontinuations (Zaoutis T et al, 2009). A larger multicenter, prospective, open-label study of children with proven or probable invasive aspergillosis, proven invasive candidiasis, or proven esophageal candidiasis

evaluated the safety, tolerability, and efficacy of caspofungin used either as primary or as salvage monotherapy. Success, defined as either complete or partial response as shown by complete resolution or significant improvement of clinical and microbiologic findings, was achieved in 5 of 10 patients with invasive aspergillosis, 30 of 37 with invasive candidiasis, and 1 of 1 with esophageal candidiasis. Although drug-related clinical adverse events (27%) or laboratory adverse events (35%) were noted, there were no serious drug-related adverse events or discontinuations of caspofungin because of toxicity.

Diagnostic Assays

Accurate and prompt diagnosis of invasive fungal infections is as difficult in the pediatric population as it is in adults. The β -D-glucan assay for *Candida* and the galactomannan assay for *Aspergillus* have been useful in adults, but use in children required establishment of baseline levels in the pediatric population.

Smith and colleagues (2007) found that the mean β -D-glucan level in healthy children was higher than had been previously reported for healthy adult patients, but was still lower than that seen in adult patients with invasive candidiasis. Because of these increased baseline levels, the authors recommended that β -D-glucan levels be evaluated prospectively in a randomized clinical trial with pediatric patients at high risk for invasive candidiasis to determine whether the assay is of the same value in this population as it is in a similar adult population.

A similar study of the galactomannan assay for *Aspergillus* was performed prospectively in a pediatric population following hematopoietic stem cell transplantation. Serum samples were performed twice weekly during periods of high risk for infection (eg, neutropenia, graft-vs-host-disease). Specificity was 91.5% by patient and 98.4% by sample when false-positive results due to piperacillin/tazobactam therapy were excluded. This assay may help to provide early, noninvasive diagnosis of invasive aspergillosis in children at high risk for infection, and should be validated in a large-scale format.

Fungal Infection in the Immunocompromised Patient: Organ Transplant Recipients

Ample cited and anecdotal evidence support the concept that immunocompromised patients are at higher risk for invasive fungal infections than the general, immunocompetent population. Therefore, the Centers for Disease Control and Prevention (CDC) in conjunction with industry sponsored creation of the TRANSNET. Twenty-three transplant centers across the United States participated, with some beginning surveillance as early as March 2001. As part of the study, all cases of proven or probable invasive fungal infections in a transplant recipient, regardless of transplant date, were reported, and transplant logs were maintained at each site to supply demographic data. European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria were used for proven/probable infections, and difficult cases were reviewed for verification. Final data analysis occurred at the CDC and the University of Alabama at Birmingham. To date, 16,808 patients with solid organ transplants and 16,220 patients with hematopoietic stem cell transplants have been entered into the study. Of these 33,028 patients, 2,191 developed invasive fungal infections with 744 reported previously as descriptive cases, for a total of 1447 incident cases.

Aspergillosis predominated in patients who had received a hematopoietic stem cell transplant (Figure 7A), while candidiasis was predominant in patients following a solid organ transplant (Figure 7B). *Candida glabrata* (34%) was the most common invasive *Candida* species in hematopoietic stem cell transplant recipients, while *C. albicans* (46%) was most common in those who had received a solid organ transplant. Cryptococcosis was common in kidney transplant recipients.

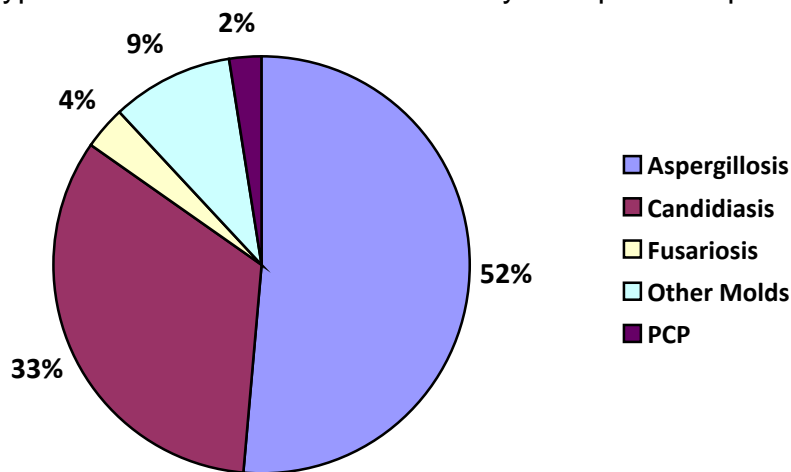


Figure 7A. Organisms Associated With Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Patients. PCP indicates pneumocystis pneumonia.

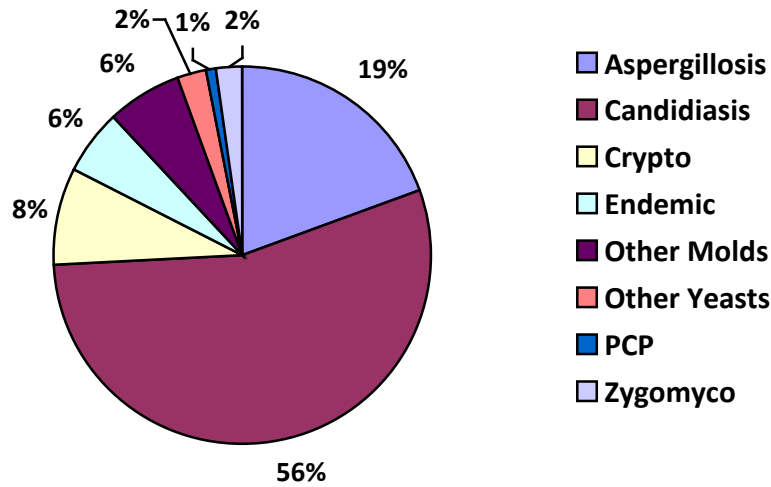


Figure 7B. Organisms Associated With Invasive Fungal Infections in Solid Organ Transplant Recipients. Crypto indicates cryptosporidium; PCP, pneumocystis pneumonia; Zygomycosis, zygomycosis.

Following stem cell transplant, invasive fungal infections were more likely to occur in the early posttransplant period, although the incidence varied with the infecting organism (Figure 8A). The observed distribution was slightly different for solid organ transplants (Figure 8B).

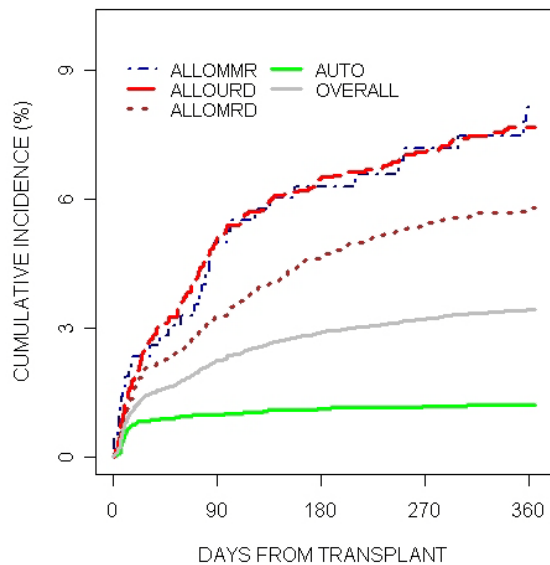


Figure 8A. Cumulative Incidence Curves for Any Invasive Fungal Infection Among Hematopoietic Stem Cell Transplant Recipients in the TRANSNET Surveillance Cohort, Stratified by Type of Stem Cell Transplant

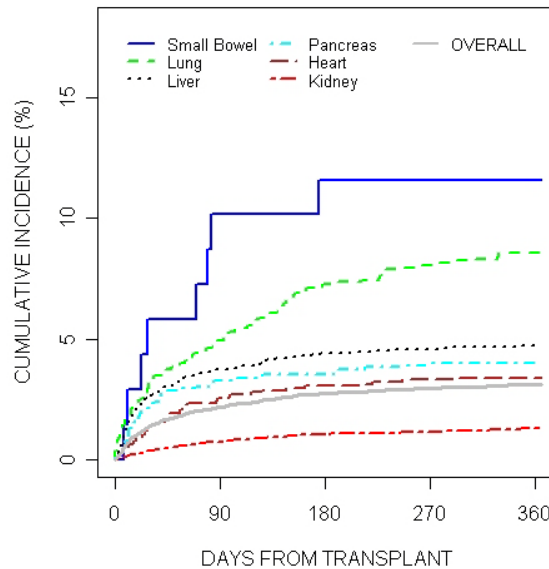


Figure 8B. Cumulative Incidence Curves for Any Invasive Fungal Infection Among Solid Organ Transplant Recipients in the TRANSNET Surveillance Cohort, Stratified by Type of Organ Transplant

The utility of the data from the TRANSNET study stems from its large, multicenter, and geographically diverse nature. The surveillance period of 5 years has allowed compilation of detailed diagnostic and microbiologic data, follow-up for incident cases, and some follow-up for the entire cohort. Unfortunately, assessment of specific risk factors is difficult because it is not a true cohort study. Also, there was limited validation of screening, case-finding, and follow-up. In addition, the study is limited by allowing only proven/probable cases and excluding possible cases.

In contrast to the TRANSNET survey, the Organ Transplant Infection Detection and Prevention study is a true cohort study. The purpose of this consortium of 6 centers sponsored by the CDC is to assess risk factors for infection in transplant recipients. Higher risk patients (eg, lung and allogeneic stem cell transplant recipients) were intentionally selected, with over 1200 patients enrolled for prospective evaluation over a 30-month follow-up period. However, relatively few invasive fungal infections have been observed in this cohort, including fewer than 30 cases of aspergillosis. The most common posttransplant infections were *Clostridium difficile* colitis and bacterial pneumonia. While this study is yielding valuable data (the first public presentation of data will be in 2010 at the Interscience Conference on Antimicrobial Agents and Chemotherapy meeting), it is time-consuming and generates unnecessary data, like other cohort studies.

Summary

Invasive fungal infections impose tremendous costs, both in morbidity and mortality and in financial expenditures. Diagnosis, treatment, and prophylaxis of these infections are an ongoing challenge for many patient populations, including those in the ICU, neonates, and transplant recipients. Application of new diagnostic assays for *Candida* (β -D-glucan) and *Aspergillus* (galactomannan) may lead to earlier and more accurate diagnoses, which in turn will allow for early intervention. Prospective epidemiologic surveys and algorithms will aid clinicians in their decisions regarding whom to treat, when treatment should begin, and what treatment is most likely to be effective. The recently released IDSA clinical practice guidelines for the treatment of *Candida* and for *Aspergillus* provide useful information for management of these invasive infections. The emergence of new, well-tolerated antifungal agents, such as the echinocandins, also provides an increased armamentarium against potentially invasive organisms.



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