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Emerging fungal infections in immunocompromised patients

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Abstract

Invasive fungal infections are infections of importance and are increasing in incidence in immunocompromised hosts such as patients who have had hematopoietic stem cell and solid organ transplants. Despite our expanded antifungal armamentarium, these infections cause considerable morbidity and mortality. Indeed, certain trends have emerged in these invasive fungal infections: a rise in the incidence of invasive mold infections, an increase in the non-albicans strains of *Candida spp*. causing invasive disease and, finally, the emergence of less susceptible fungal strains that are resistant to the broader-spectrum antifungal agents due to overutilization of these agents. Clinicians must recognize the patient groups that are potentially at risk for these invasive fungal infections, as well as the risk factors for such infections. By using more sensitive nonculture-based diagnostic techniques, appropriate therapy may be initiated earlier to enhance survival in these immunocompromised patient populations.

Introduction

The incidence of invasive fungal infections is rising [1-3], and although they are not yet as much of a threat as bacterial pathogens, their increase is significant enough for us to realize that a sinister shift in epidemiology has been occurring, especially in oncology patients and transplant recipients. In the United States from 1980 through 1997, the annual number of deaths in which an invasive mycosis was listed on the death certificate increased from 1,557 to 6,534—a 320% increase over 17 years [4]. Despite the expanded armamentarium of antifungal agents now available, invasive fungal infections continue to produce significant morbidity and mortality. This is because, with an increasing number of solid organ transplants being performed (over 23,000 organs were transplanted in the United States in 2008 alone—double the amount transplanted 10 years previously [5]), coupled with the use of newer and more potent chemotherapeutic agents and regimens, the pool of immunocompromised patients is increasing dramatically. These patient populations are extremely susceptible to invasive fungal infections because of their highly compromised immune status and the external pressures from antibiotic usage, which explains why the burden of invasive fungal infections is unfortunately rising commensurately with these medical advances. This article highlights recent invasive fungal infection epidemiologic pattern shifts and discusses the important factors to consider when approaching the unique patient populations affected by such infections.

The evolving epidemiology

Three epidemiological trends have emerged recently. First, in hematopoietic stem cell transplant (HSCT) recipients and in neutropenic patients with acute leukemia, an increased incidence of invasive mold infections—in particular, invasive aspergillosis—has occurred. This has necessitated changes in the first choice for antifungal therapy from less broad-spectrum agents covering *Candida spp*. predominantly to ones that are active against *Aspergillus* and other molds. Second, with the increasing incidence of non-albicans *Candida spp.*, the utility of fluconazole as first-line initial therapy for invasive candidiasis has waned due to reduced susceptibility of the yeasts to this drug. Unfortunately, resistance to even the newer echinocandin

class of antifungals is now also being observed. Finally, similar to the pattern of resistance arising because of antibiotic pressure, antimicrobial pressure exerted by the use of broad-spectrum antifungal agents such as voriconazole has precipitated the emergence of invasive mold infections caused by the *Zygomycetes* class of fungi. These trends are explored in more detail below.

The Transplant-Associated Infections Surveillance Network (TRANSNET), a consortium of 23 transplant centers in the United States, prospectively studied the epidemiology of invasive fungal infections in both solid-organ transplant and HSCT recipients over a 5-year period from 2001 to 2006 [6,7]. The most common invasive fungal infections in the solid-organ transplant recipients were candidiasis (53% of all invasive fungal infections found) followed by invasive aspergillosis (19%), cryptococcosis (8%), non-*Aspergillus* molds (8%), endemic fungi (5%), and zygomycosis (2%) [6]. In contrast, when looking at incidence rates in HSCT recipients only, invasive aspergillosis (43%) was more common than invasive candidiasis (28%) [7]. The rising prevalence of invasive aspergillosis and mold infections has also been observed in a single-center series of autopsy-proven patients with hematologic malignancies [8]. Comparing the prevalence from 1989 through to 2003, invasive aspergillosis and zygomycosis rose from 16% to 19% and from 1% to 3% respectively, while prevalence of invasive candidiasis fell from 13% to 8%. The shift toward more invasive mold infections is significant because the overall 1-year survival is lower in invasive aspergillosis compared to invasive candidiasis in both HSCT (25.4% versus 33.6%) [7] and solid-organ transplant patients (59% versus 66%) [6].

The second trend observed is the increasing incidence of non-albicans *Candida spp.*. *Candida tropicalis*, *Candida parapsilosis*, and *Candida glabrata* have been isolated much more frequently as causes of invasive candidiasis worldwide, although *C. albicans* remains the most common [9]. In addition, the SENTRY Antimicrobial Surveillance Program, which is an international surveillance of blood stream infections, also described an increasing resistance to the azole class of antifungals among nosocomial isolates of *Candida spp*. [10]. Fluconazole resistance in *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* isolates was found in 7.7%, 5.8%, and 3.3%, respectively. For *C. tropicalis* in particular, 2.2% of the isolates were resistant to both fluconazole and voriconazole. Interestingly for *C. parapsilosis*, no echinocandin resistance was demonstrated. However, resistance to both azoles and echinocandins was prominent in *C. glabrata*, ranging from 3.2% resistance to micafungin to 7.7% with fluconazole. Resistance was even seen in the newer azoles, such as posaconazole (5.1%), and another, newer echinocandin, anidulafungin (3.8%). The most worrisome though, was the discovery of the propensity of *C. glabrata* to mutate to a multidrug-resistant phenotype *in vivo* in a single patient. The findings of resistance to fluconazole have been highlighted in the recommendations of the Infectious Diseases Society of America (IDSA), who recommend that infection with *C. parapsilosis* be treated with an azole (or with a lipid formulation of amphotericin B, alternatively) while infection with *C. glabrata* be treated with an echinocandin [11]. There is, however, some concern that the former recommendation may inadvertently result in increased azole resistance [10]. Indeed, it now appears crucial that microbiology laboratories perform antifungal susceptibility testing more readily for infections involving the non-albican *Candida spp*. to better guide the clinician in the optimal choice of antifungal agent.

The third trend relates to the emergence of zygomycosis and warrants further discussion. Following the landmark randomized, unblinded trial where voriconazole showed a superior 12-week survival rate compared with amphotericin B when used as primary therapy for invasive aspergillosis [12], voriconazole is now the drug of choice for the treatment of invasive aspergillosis as recommended by the IDSA [13]. It is of note though, that with the increasing use of voriconazole—as prophylaxis, empirical, preemptive, and targeted treatment for invasive aspergillosis in patients with hematologic malignancy—concerns have arisen about an increase in incidence of zygomycosis, an invasive mold infection resistant to voriconazole. In a series of 19 immunocompromised patients (including solid-organ transplant recipients, patients with hematologic malignancy or HIV-AIDS, and those using steroids) diagnosed with invasive zygomycosis, the increase in the number of cases was associated with the introduction of voriconazole and caspofungin and an increase in the number of HSCTs performed [14]. In a case-control study involving 14 leukemic and 13 HSCT patients, voriconazole prophylaxis was identified as an independent risk factor, increasing the risk for invasive zygomycosis by more than 10-fold [15]. Singh and colleagues performed a prospective, matched case-control study of 50 solid-organ transplant recipients and found that voriconazole and/or caspofungin use increased the risk of zygomycosis by 4.4 times [16].

The risk groups and risk factors for invasive fungal infection

Patients with acute leukemia, HSCT recipients, and solid-organ transplant recipients represent the three most common cohorts of patients at risk of invasive fungal infections. In approaching these immunocompromised patients, it is important to recognize that the probable etiologic pathogens may be predicted based on an

awareness of the underlying immunologic defect (e.g., neutrophil, T cell- or B cell-mediated) and the duration and severity of the defect(s). Extrinsic factors (radiation, drugs, or surgery, resulting in breaches in the mucocutaneous defensive surfaces of the body), intensity of immunosuppression (dose, duration, and temporal sequence of immunosuppressive regimen) and environmental exposures (community or nosocomial) may also play significant roles and influence which pathogen may produce an invasive fungal infection. The summary risk of infection depends on the overall net state of immunosuppression and the epidemiologic exposures encountered [17].

In patients with acute leukemia, the risk of invasive fungal infection is related to the status and type of leukemia (i.e., newly diagnosed *de novo* acute leukemia, post-remission status, relapsed leukemia, or acute leukemia refractory to treatment, as well as acute myelogenous leukemia versus acute lymphocytic or hairy cell leukemia), depth and duration of neutropenia, and the types of chemotherapeutic agents used to treat the leukemia. Neutrophils are rapidly destructive to fungal hyphae in particular, through toxic oxygen radicals. Protracted neutropenia coupled with breaches in skin (e.g., from a central intravascular line) and bowel (e.g., from mucotoxic chemotherapy) predispose patients to candidemia and invasive aspergillosis.

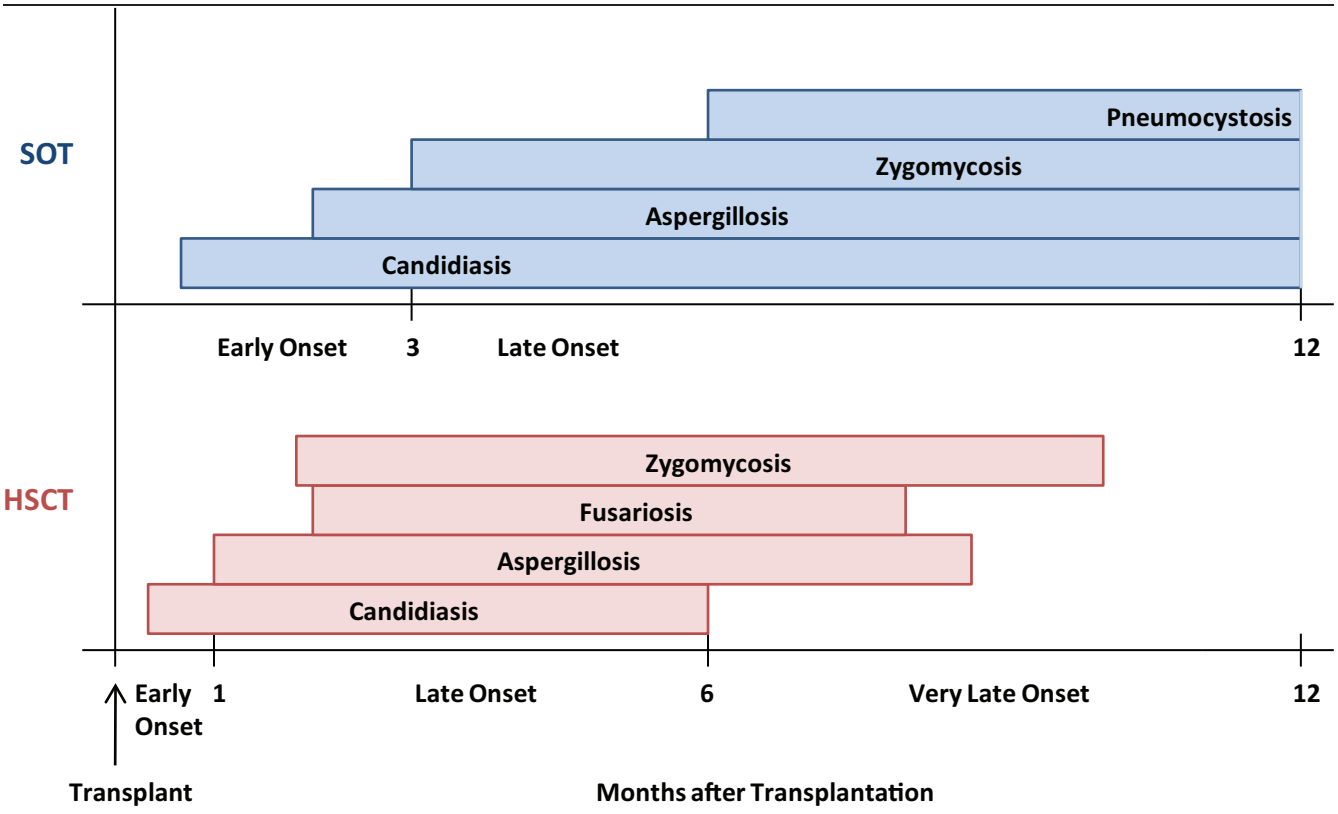
For the HSCT recipients, the influence of the host, the graft (with regard to the duration of neutropenia prior to engraftment), and complications of the procedures performed (e.g., use of central venous intravascular catheters) fluctuate throughout the post-transplant course, creating a dynamic timeline. Host factors (e.g., older age) and transplant variables (e.g., human leukocyte antigen mismatch) tend to influence invasive fungal infection risk early on. In particular, the use of immunosuppressives during the pre-engraftment phase to prevent graft-versus-host disease may result in severe neutrophil depletion and hence the propensity to develop invasive candidiasis and invasive aspergillosis. However, post-engraftment complications of the transplantation (e.g., chronic graft-versus-host disease and *Cytomegalovirus* disease, which produce profound mononuclear cell dysfunction) lead to alveolar macrophage phagocytic defects and the propensity to develop late-onset invasive aspergillosis [18] and other fungal infections such as zygomycosis. Some biologic factors like malnutrition, iron overload, diabetes mellitus, and cytopenias moderate the risk somewhat throughout the post-transplant course. One-year cumulative incidences for invasive fungal infection were highest for mismatched-related (8.1%) and matched-unrelated allogeneic (7.7%) HSCTs, followed by matched-related HSCT (5.8%) and autologous HSCT with the lowest incidence rate (1.2%) [7].

In solid-organ transplant recipients, based on the types of organ transplanted, 1-year cumulative incidences for invasive fungal infection were highest for small bowel (11.6%) and lowest for kidney transplant recipients (1.3%) with a trend toward a slight increase in cumulative incidence from 2002 to 2005 [6]. Rejection and exogenous immunosuppressive agents, especially high-dose steroids and antilymphocyte globulin use, escalate the risk for acquiring invasive fungal infections. Medical and surgical factors both play crucial roles [19]. For example, prolonged ischemia time has been associated with the development of invasive aspergillosis in lung transplant recipients [20]. For liver transplant recipients, fulminant hepatic failure, retransplantation, and renal failure requiring dialysis are risk factors for invasive fungal infection [21]. Diabetes mellitus and need for prolonged hemodialysis before transplant are unique risks for renal transplant recipients [22]. In pancreas transplant recipients, older donor age, enteric (versus bladder) drainage, pancreas transplant after kidney transplant (versus pancreas only), post-transplant pancreatitis, retransplantation, and preoperative peritoneal dialysis have been identified as risk factors for invasive fungal infection (candidiasis) [23].

Timing of invasive fungal infections

The time to development of invasive fungal infection after transplantation depends on the transplant type, the use and duration of use of antifungal prophylaxis, and the fungal pathogen. In the HSCT population, the timeline is split into three time periods from the time of transplantation: early onset (≤1 month [pre-engraftment phase]), late onset (1–6 months [post-engraftment phase]) and very late onset (>6 months) (Figure 1). In the TRANSNET report, the median time after transplantation to onset of invasive fungal infection was 61, 99, 123, and 135 days for candidiasis, aspergillosis, fusariosis, and zygomycosis cases, respectively [7]. Another multicenter report of invasive fungal infections occurring between 2004 and 2007 from the Prospective Antifungal Therapy (PATH) Alliance registry found that invasive candidiasis tended to occur earlier after autologous HSCT (median 28 days) compared with allogeneic HSCT (median 108 days) [24]. The earlier onset of invasive candidiasis is usually related to neutropenia and mucositis whereas the later onset is more often seen in allogeneic HSCT recipients due to the development of graft-versus-host disease and the need for chronic central venous catheter usage. Invasive aspergillosis occurs more frequently but is encountered later in allogeneic HSCT recipients compared with autologous HSCT, and this late occurrence

Figure 1. Timing of invasive fungal infections after organ transplantation



Solid-organ transplantation (SOT) figures are based on the US Transplant-Associated Infection Surveillance Network (TRANSNET) data from 2001 to 2006 [6]. Hematopoietic stem cell transplantation (HSCT) figures are based on US TRANSNET data from 2001 to 2006 [7].

confers a higher mortality [7]. A study that examined the records of 5,589 patients who underwent HSCT from 1985 through 1999 found that the majority of scedosporiosis cases tended to occur within the first 40 days after transplant and, unfortunately, all those with scedosporiosis died within 1 month of infection [25].

In the solid-organ transplant population, the timeline has traditionally been divided into three time periods not dissimilar to the HSCT population [17]. However, recent data has demonstrated that invasive fungal infections are occurring later [6]. The median time to onset is 103 days for invasive candidiasis, 184 days for invasive aspergillosis, 312 days for zygomycosis, 343 days for endemic fungal infections, 467 days for non-*Aspergillus* molds, and 575 days for cryptococcosis. The majority of infections occur more than 90 days after transplantation. The occurrence of early infections (≤90 days) is dominated by invasive candidiasis and invasive aspergillosis. Significant numbers occur beyond 3 years after transplantation.

Diagnostics

In a case series involving patients with hematologic malignancies, although there was a high prevalence of invasive fungal infection (31%) at autopsy, with 77% of the patients' deaths related to infection, only one-third of them were diagnosed by the accepted criteria before the patients died [8]. This highlighted the inadequacies of current diagnostic methods for invasive fungal infections.

Although traditional microbiological culture-based testing for fungi produces low yields and creates time delays, it is inexpensive and provides valuable material on which to perform drug-sensitivity testing, which has become increasingly relevant due to the changing patterns of resistance. Another factor to consider is that histological evaluation of tissue specimens for fungi may be too invasive for most patients and may not be specific enough for some fungal species.

New methods to detect invasive fungal infections early and with high sensitivity and specificity are needed.

Galactomannan, a component of the cell wall of *Aspergillus spp.*, is released during early stages of growth thereby allowing the tests for its presence to be fairly sensitive (71%) and specific (89%) [26]. It can be detected in serum and also bronchoalveolar lavage fluid thus providing a surrogate marker for the diagnosis of invasive aspergillosis. The recent development of *Aspergillus* polymerase chain reaction for the rapid diagnosis of infections holds promise for increasing the sensitivity and specificity further, but standardization issues of the assays remain unresolved [27].

Testing of beta-glucan (a major cell wall constituent characteristic of most fungi), although approved in some jurisdictions for detecting invasive candidiasis and other fungal infections (except zygomycosis), has not received widespread acceptance due to difficulties in performance techniques and lack of specificity [28]. Nevertheless, with the increasing reliance on serum or bronchoalveolar lavage galactomannan testing and serum beta-glucan assays, centers are now performing fewer biopsies and obtaining fewer histopathology specimens [8], commonly employed to confirm a proven case of invasive fungal infection according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [29].

Computed tomography (CT) scans of the chest are widely used as diagnostic tools when dealing with pulmonary or hepatic invasive fungal infections in immunocompromised patients. Fungal infections such as invasive aspergillosis present with nodules surrounded by haziness (halo sign) and may be associated with cavitatory lesions. Identifying these lesions early via CT scans has helped to cut the time it takes to diagnose invasive mold infections and allow earlier initiation of appropriate antifungal therapy. Similarly, defects in the liver architecture noted on CT scanning of the abdomen provide an early sign of an invasive fungal infection involving the liver. The current EORTC/MSG criteria for diagnosis of invasive fungal infections involve a combination of host factors, histopathology, imaging, and microbiological cultures or markers to clinch diagnosis [29]. These criteria enabled some standardization of the diagnosis of invasive fungal infections.

Table 1. Pharmacologic therapy against common invasive fungal pathogens in immunocompromised patients

		Therapy		
Pathogen	**Condition**	**Primary**	**Alternative**	**Comments**
Candida spp. [11]	Non-neutropenic adult with candidemia	Fluconazole; echinocandin	L-AmB; AmB-d; voriconazole	Use echinocandin for moderately severe to severe illness and for patients with recent azole exposure (within past 30 days); transition to fluconazole after initial echinocandin is appropriate in many cases; remove all intravascular catheters, if possible; treat 14 days after first negative blood culture result and resolution of signs and symptoms associated with candidemia; ophthalmological examination recommended for all patients
	Neutropenic patient with candidemia	Echinocandin; L-AmB	Fluconazole; voriconazole	Echinocandin or L-AmB is preferred for most patients; fluconazole for patients without recent azole exposure and who are not critically ill (neutropenia for ≤7 days); voriconazole is recommended when additional coverage for molds is desired; intravascular catheter removal is advised
Aspergillus spp. [13]	Invasive aspergillosis of the lungs, sinus, tracheobronchial tree, heart, bone, or CNS	Voriconazole	L-AmB; ABLC; caspofungin; micafungin; posaconazole; itraconazole	Primary combination therapy is not routinely recommended based on lack of clinical data; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients; surgery may be needed
Fusarium spp. [30,31]	Invasive fusariosis of the lungs or sinus, or disseminated invasive fusariosis	Voriconazole; L-AmB	Posaconazole	The recovery of neutrophil count is the most important determinant of prognosis; potential adjuvant therapy with G-CSF, GM-CSF, or donor-lymphocyte infusion; voriconazole is less active against non-*solani Fusarium spp.*
Scedosporium spp. [30,32,33]	Invasive scedosporiosis of the lung, sinus, CNS, or bone, or disseminated invasive scedosporiosis	Voriconazole	Posaconazole	*Scedosporium prolificans* is intrinsically resistant to all anti-fungal agents
Zygomycosis [34,35]	Invasive zygomycosis	L-AmB	AmB-d; posaconazole	The MICs of posaconazole vary considerably across pathogenic *Zygomycetes spp.*; surgery is often needed

AmB-d, amphotericin B deoxycholate; ABLC, amphotericin B lipid complex; CNS, central nervous system; G-CSF, granulocyte colony-stimulating growth factor; GM-CSF, granulocyte-macrophage colony-stimulating growth factor; L-AmB, liposomal amphotericin B; MIC, minimum inhibitory concentration.

Management

The management of invasive fungal infections begins with a high index of suspicion and prompt diagnosis. Clearly the early initiation of antifungal therapy is a major contributor to enhanced survival. Reducing immunosuppression whenever possible with prompt initiation of appropriate antifungal therapy (monotherapy or combination) (Table 1) remains the mainstay for the treatment of invasive fungal infections. However, rapid reduction of immunosuppressive therapy in conjunction with initiation of antifungal therapy in solid-organ transplant recipients may lead to the development of immune reconstitution inflammatory syndrome, the clinical manifestations of which mimic worsening disease [36]. Reversal of neutropenia with granulocyte colony-stimulating factor or granulocyte infusions may be used to hasten recovery from neutropenia.

Surgery may be required depending on the type of invasive fungal infection. Recommendations for surgery may be considered in patients with invasive aspergillosis who have a solitary lung lesion before chemotherapy or HSCT, those with hemoptysis from a lung lesion, those with disease that invades the chest wall, or situations where the infection involves the pericardium or great vessels [13]. For zygomycosis, surgery is often required in addition to antifungal therapy.

Conclusion

The epidemiologic changes in the occurrence of invasive fungal infections in a rapidly expanding population of immunocompromised patients present a real challenge to physicians managing them. The persistently high morbidity and mortality associated with these infections continues despite the increasing spectrum of antifungal pharmacotherapy. Perhaps the best approach to counter the ubiquitous fungi that cause invasive fungal infections may be to develop less damaging methods of immune suppression. If we can shorten the duration of neutropenia and improve our immune suppression regimens to better achieve immune tolerance of the allograft, we might gain an upper hand in our fight against these sophisticated eukaryotes.

Abbreviations

CT, computed tomography; EORTC/MSG, European Organization for Research and Treatment of Cancer/Mycoses Study Group; HSCT, hematopoietic stem cell transplant; IDSA, Infectious Diseases Society of America; TRANSNET, Transplant-Associated Infections Surveillance Network.

Competing interests

Chian-Yong Low declares that he has no competing interests. Coleman Rotstein declares that he has received grant/research support from Astellas Pharma, Basilea, and Pfizer Inc., has been a consultant for Astellas Pharma, Merck, and Pfizer Inc., and received speaking honoraria from Astellas Pharma, Merck, and Pfizer Inc.

References

1. Martin GS, Mannino DM, Eaton S, Moss M: **The epidemiology of sepsis in the United States from 1979 through 2000.** *N Engl J Med* 2003, **348:**1546-54.

2. Zilberberg MD, Shorr AF, Kollef MH: **Secular trends in candidemia-related hospitalization in the United States, 2000–2005.** *Infect Control Hosp Epidemiol* 2008, **29:**978-80.

3. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB: **Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study.** *Clin Infect Dis* 2004, **39:**309-17.

4. McNeil MM, Nash SL, Hajjeh RA, Phelan MA, Conn LA, Plikaytis BD, Warnock DW: **Trends in mortality due to invasive mycotic diseases in the United States, 1980–1997.** *Clin Infect Dis* 2001, **33:**641-7.

5. **U.S. Department of Health and Human Services–Organ Procurement and Transplantation Network (OPTN).** [http://optntransplant.hrsa.gov/]

6. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, Brumble LM, Herwaldt L, Ito J, Kontoyiannis DP, Lyon GM, Marr KA, Morrison VA, Park BJ, Patterson TF, Perl TM, Oster RA, Schuster MG, Walker R, Walsh TJ, Wannemuehler KA, Chiller TM: **Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET).** *Clin Infect Dis* 2010, **50:**1101-11.

   F1000 Factor 11
   Evaluated by Neil Ampel 18 Mar 2010, Coleman Rotstein 24 Jun 2011

7. Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, Ito J, Andes DR, Baddley JW, Brown JM, Brumble LM, Freifeld AG, Hadley S, Herwaldt LA, Kauffman CA, Knapp K, Lyon GM, Morrison VA, Papanicolaou G, Patterson TF, Perl TM, Schuster MG, Walker R, Wannemuehler KA, Wingard JR, Chiller TM, Pappas PG: **Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database.** *Clin Infect Dis* 2010, **50:**1091-100.

8. Chamilos G, Luna M, Lewis RE, Bodey GP, Chemaly R, Tarrand JJ, Safdar A, Raad II, Kontoyiannis DP: **Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003).** *Haematologica* 2006, **91:**986-9.

   F1000 Factor 6
   Evaluated by Coleman Rotstein 24 Jun 2011

9. Pfaller MA, Diekema DJ: **Epidemiology of invasive candidiasis: a persistent public health problem.** *Clin Microbiol Rev* 2007, **20:**133-63.

   F1000 Factor 6
   Evaluated by Coleman Rotstein 24 Jun 2011

10. Pfaller MA, Moet GJ, Messer SA, Jones RN, Castanheira M: **Candida bloodstream infections: comparison of species distributions and antifungal resistance patterns in community-onset and nosocomial isolates in the SENTRY Antimicrobial Surveillance Program, 2008–2009.** *Antimicrob Agents Chemother* 2011, **55:**561-6.

    F1000 Factor 6
    Evaluated by Coleman Rotstein 24 Jun 2011

11. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L,

Reboli AC, Rex JH, Walsh TJ, Sobel JD; Infectious Diseases Society of America: **Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America.** *Clin Infect Dis* 2009, **48:**503-35.

Changes Clinical Practice
F1000 Factor 6
Evaluated by Larry Bush 07 Apr 2010

12. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, de Pauw B; Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group: **Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis.** *N Engl J Med* 2002, **347:**408-15.

F1000 Factor 8
Evaluated by Coleman Rotstein 24 Jun 2011

13. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Segal BH, Steinbach WJ, Stevens DA, van Burik JA, Wingard JR, Patterson TF; Infectious Diseases Society of America: **Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America.** *Clin Infect Dis* 2008, **46:**327-60.

Changes Clinical Practice
F1000 Factor 6
Evaluated by Coleman Rotstein 05 May 2011

14. Ambrosioni J, Bouchuiguir-Wafa K, Garbino J: **Emerging invasive zygomycosis in a tertiary care center: epidemiology and associated risk factors.** *Int J Infect Dis* 2010, **14**(Suppl 3):e100-3.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

15. Kontoyiannis DP, Lionakis MS, Lewis RE, Chamilos G, Healy M, Perego C, Safdar A, Kantarjian H, Champlin R, Walsh TJ, Raad II: **Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases.** *J Infect Dis* 2005, **191:**1350-60.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

16. Singh N, Aguado JM, Bonatti H, Forrest G, Gupta KL, Safdar N, John GT, Pursell KJ, Muñoz P, Patel R, Fortun J, Martin-Davila P, Philippe B, Philit F, Tabah A, Terzi N, Chatelet V, Kusne S, Clark N, Blumberg E, Julia MB, Humar A, Houston S, Lass-Flörl C, Johnson L, Dubberke ER, Barron MA, Lortholary O: **Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome.** *J Infect Dis* 2009, **200:**1002-11.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

17. Fishman JA, Rubin RH: **Infection in organ-transplant recipients.** *N Engl J Med* 1998, **338:**1741-51.

18. Marr KA, Carter RA, Boeckh M, Martin P, Corey L: **Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors.** *Blood* 2002, **100:**4358-66.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

19. Gabardi S, Kubiak DW, Chandraker AK, Tullius SG: **Invasive fungal infections and antifungal therapies in solid organ transplant recipients.** *Transpl Int* 2007, **20:**993-1015.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

20. Iversen M, Burton CM, Vand S, Skovfoged L, Carlsen J, Milman N, Andersen CB, Rasmussen M, Tvede M: **Aspergillus infection in lung transplant patients: incidence and prognosis.** *Eur J Clin Microbiol Infect Dis* 2007, **26:**879-86.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

21. Eschenauer GA, Lam SW, Carver PL: **Antifungal Prophylaxis in Liver Transplant Recipients.** *Liver Transpl* 2009, **15:**842-58.

22. Singh N: **Fungal infections in the recipients of solid organ transplantation.** *Infect Dis Clin North Am* 2003, **17:**113-34.

23. Benedetti E, Gruessner AC, Troppmann C, Papalois BE, Sutherland DE, Dunn DL, Gruessner RW: **Intra-abdominal fungal infections after pancreatic transplantation: incidence, treatment, and outcome.** *J Am Coll Surg* 1996, **183:**307-16.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

24. Neofytos D, Hom D, Anaissie E, Steinbach W, Olyaei A, Fishman J, Pfaller M, Chang C, Webster K, Marr K: **Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry.** *Clin Infect Dis* 2009, **48:**265-73.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

25. Marr KA, Carter RA, Crippa F, Wald A, Corey L: **Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients.** *Clin Infect Dis* 2002, **34:**909-17.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

26. Pfeiffer CD, Fine JP, Safdar N: **Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis.** *Clin Infect Dis* 2006, **42:**1417-27.

F1000 Factor 6
Evaluated by Coleman Rotstein 24 Jun 2011

27. Klingspor L, Loeffler J: **Aspergillus PCR formidable challenges and progress.** *Med Mycol* 2009, **47**(Suppl 1):S241-7.

28. Obayashi T, Negishi K, Suzuki T, Funata N: **Reappraisal of the serum (1→3)-β-D-glucan assay for the diagnosis of invasive fungal infections – a study based on autopsy cases from 6 years.** *Clin Infect Dis* 2008, **46:**1864-70.

29. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Muñoz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, *et al.*: **Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group.** *Clin Infect Dis* 2008, **46:**1813-21.

30. Perfect JR, Marr KA, Walsh TJ, Greenberg RN, DuPont B, de la Torre-Cisneros J, Just-Nübling G, Schlamm HT, Lutsar I, Espinel-Ingroff A, Johnson E: **Voriconazole treatment for less-common, emerging, or refractory fungal infections.** *Clin Infect Dis* 2003, **36:**1122-31.

31. Kontoyiannis DP, Bodey GP, Hanna H, Hachem R, Boktour M, Girgaway E, Mardani M, Raad II: **Outcome determinants of fusariosis in a tertiary care cancer center: the impact of neutrophil recovery.** *Leuk Lymphoma* 2004, **45:**139-41.

32. Troke P, Aguirrebengoa K, Arteaga C, Ellis D, Heath CD, Lutsar I, Rovira M, Nguyen Q, Slavin M, Chen SC; Global Scedosporium Study Group: **Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients.** *Antimicrob Agents Chemother* 2008, **52:**1743-50.

33. Caira M, Girmenia C, Valentini CG, Sanguinetti M, Bonini A, Rossi G, Fianchi L, Leone G, Pagano L: **Scedosporiosis in patients with**

acute leukemia: a retrospective multicenter report. *Haematologica* 2008, **93:**104-10.

34. Spellberg B, Walsh TJ, Kontonyiannis DP, Edwards J Jr, Ibrahim AS: **Recent advances in the management of mucormycosis: from bench to bedside.** *Clin Infect Dis* 2009, **48:**1743-51.

35. van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP: **Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases.** *Clin Infect Dis* 2006, **42:**e61-5.

36. Singh N, Lortholary O, Alexander BD, Gupta KL, John GT, Pursell K, Munoz P, Klintmalm GB, Stosor V, del Busto R, Limaye AP, Somani J, Lyon M, Houston S, House AA, Pruett TL, Orloff S, Humar A, Dowdy L, Garcia-Diaz J, Kalil AC, Fisher RA, Husain S; Cryptococcal Collaborative Transplant Study Group: **An immune reconstitution syndrome-like illness associated with Cryptococcus neoformans infection in organ transplant recipients.** *Clin Infect Dis* 2005, **40:**1756-61.