

Nosocomial Fungal Infections: Epidemiology, Infection Control, and Prevention

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KEYWORDS

• Nosocomial • Fungal infection • *Candida* • *Aspergillus*

Fungal infections are an increasing cause of morbidity and mortality in hospitalized patients. This article reviews the current epidemiology of nosocomial fungal infections in adult patients, with an emphasis on invasive candidiasis and aspergillosis. Recently published recommendations and guidelines for the control and prevention of these nosocomial fungal infections are summarized.

IMPACT OF NOSOCOMIAL FUNGAL INFECTIONS

There has been an overall increase in fungal health care–associated infections (HAIs) in the last few decades, which is likely a consequence of the advances in medical and surgical therapies. The wider use of more aggressive modalities of treatments, such as hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), new chemotherapeutic agents, and immunomodulatory agents, has increased the population of immunocompromised patients at risk for invasive fungal infection.¹ The predisposing risk factors for opportunistic invasive fungal infections, particularly candidiasis and aspergillosis, in these immunocompromised hosts include neutropenia, qualitative neutrophil dysfunction, cell-mediated immune dysfunction, and disruption of mucosal integrity.² Moreover, the prevalence of invasive devices, especially intravascular central lines, has resulted in an increase in nosocomial catheter-related bloodstream infections (CRBSIs), candidemia, and disseminated candidiasis.^{3,4} Exposure to airborne fungal pathogens such as *Aspergillus* spp within the hospital environment, especially during construction, has caused outbreaks of nosocomial aspergillosis in severely immunocompromised patients such as patients who underwent HSCT.⁵

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Candida spp are the most common fungal pathogens causing serious HAIs, especially in patients admitted to intensive care units (ICUs).^{3,6-9} A recent study using the National Hospital Discharge Survey estimated the incidence rate of invasive candidiasis to have increased from 23 per 100,000 US population in 1996 to 29 per 100,000 in 2003.¹⁰ The corresponding incidence rate of invasive candidiasis per 10,000 hospital discharges increased from 20 in 1996 to 24 in 2003.¹⁰ Among invasive candidiasis, candidemia is estimated to account for 2 to 8 infections per 10,000 hospital discharges in recent studies from the United States and Europe.¹¹⁻¹⁴ The true incidence of health care-associated candidemia is likely to be higher because of the relatively poor diagnostic yield (approximately 50%) of positive blood culture results in patients with disseminated candidiasis with implicit candidemia. Matched cohort and case-control studies in various hospitalized patient populations, including those in the ICU and those who have undergone a transplant, report attributable mortality rates for candidemia ranging from 5% to 71%.¹⁵ A recent case-control study based on hospital discharge diagnosis estimated the mortality from candidemia to be age-related, 15% to 25% for adults and 10% to 15% for children.¹⁶ The excess health care cost, primarily related to an increased length of stay, is projected to be \$29,000 to as high as \$39,000 for each episode of candidemia.¹⁶⁻¹⁸ The estimated annual cost in the United States for the treatment of systemic fungal infections was \$2.8 billion in 1998, of which \$1.7 billion was for the treatment of candidiasis.¹⁹

Based on hospital discharge data, there were an estimated 10,190 aspergillosis-related hospitalizations and 1970 deaths during 1996 in the United States.²⁰ Unlike invasive candidiasis, the incidence rate of invasive aspergillosis per 100,000 US population declined from 3.4 in 1996 to 2.2 in 2003, with a decrease in the incidence rate from 3 to 2 per 10,000 hospital discharges.¹⁰ The reasons for this decline are unclear. However, in severely immunocompromised patients, such as HSCT recipients, invasive aspergillosis remains the most important cause of infection-related mortality.²¹ In a large prospective registry of 234 HSCT recipients with invasive fungal infection, aspergillosis accounted for 59% of all invasive fungal infections and was associated with a 6-week mortality rate of 22%.²¹ This mortality rate is lower than previously reported rates and may be related to the increasing use of nonmyeloablative HSCT, early diagnosis, and use of broad-spectrum antifungals such as voriconazole.²² The average length of stay for a hospitalization related to *Aspergillus* infection was 17 days at a cost of \$62,426, resulting in an overall estimated cost of \$633.1 million.²⁰

The overall burden of disease caused by nosocomial fungal infections is substantial. Limitations of the current diagnostic tests available to establish an early diagnosis of fungal infection and the emergence of fungal pathogens that are resistant to antifungal agents make the prevention of fungal HAIs increasingly important. Infection control strategies targeted to reduce nosocomial CRBSIs caused by *Candida* spp emphasize hand hygiene²³ and adherence to guidelines for prevention of intravascular catheter-related infections.^{24,25} Prevention of exposure to airborne *Aspergillus* spp and molds in the hospital environment can be minimized by implementing recommendations on environmental controls²⁶ and specific preventive measures targeting high-risk HSCT recipients.²⁷

COMMON NOSOCOMIAL INFECTIONS CAUSED BY YEASTS

Candida spp

Certain *Candida* spp, especially *Candida albicans*, are part of the human microbial flora; hence, most candidal infections are endogenous in origin. Invasive candidiasis, namely, candidemia, disseminated hematogenous infections, or deep-seated

infections in normally sterile body sites, can occur in immunocompromised patients, such as those with neutropenia, and in critically ill patients. In patients with cancer and chemotherapy-induced neutropenia and mucositis, candidemia may originate from the gastrointestinal tract.²⁸ However, in critically ill patients, the source of candidemia is most likely the intravascular catheters colonized by *Candida* spp from the patient's endogenous microflora or *Candida* spp acquired from the health care environment.²⁹ *Candida* spp have been isolated from environmental cultures of the floor, countertops, and other inanimate surfaces in the hospital.^{30,31} Patient acquisition and colonization with *Candida* spp found in the hospital environment and food has been demonstrated.^{30–32} The propensity of *Candida* spp, especially *Candida parapsilosis*, to cause CRBSIs is likely related to this pathogen's ability to form biofilms on catheters.^{33,34} The true incidence of nosocomial candidemia is likely underestimated. This fact was highlighted in a recent molecular epidemiologic study of candidemia over a 16-year period in Iceland, which identified previously unrecognized smoldering nosocomial clusters in a third of a patient population with candidemia.³⁵

Overall, *Candida* spp were the fourth most common pathogen accounting for 11% of 28,502 HAIs reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention (CDC) between 2006 and 2007.³ *Candida* spp were the second most common pathogen causing 21% of catheter-associated urinary tract infections and the third most common pathogen accounting for 11% of CRBSIs.³ In a prospective nationwide surveillance study (surveillance and control of pathogens of epidemiological importance [SCOPE]) of 24,179 nosocomial bloodstream infections (BSIs) in 49 US hospitals (ICU and non-ICU patients) conducted between 1995 and 2002, the incidence rate of BSIs caused by *Candida* spp was 4.6 per 10,000 hospital admissions.⁴ *Candida* spp were the fourth most common pathogen isolated and accounted for 9% of BSIs. There was a significant increase in the proportion of *Candida* spp isolated in blood cultures, from 8% in 1995 to 12% in 2002. Although *Candida* spp accounted for 10% of BSIs among patients in ICUs, they also caused 8% of BSIs in patients in non-ICU settings. Other studies have also noted the increasing proportion of patients with candidemia in non-ICU settings, possibly because of the presence of long-term indwelling central venous lines.^{11,12,36} In population-based studies, the factors associated with candidemia have included extremes of age, African American population, underlying cancer or diabetes, and the presence of indwelling intravascular catheters.^{11,12,36} Additional risk factors for nosocomial candidemia in hospitalized patients include ICU stay; major surgery (especially abdominal surgery); renal failure; dialysis; use of broad-spectrum antibiotics, corticosteroids, or immunosuppressive agents; total parenteral nutrition; and colonization with *Candida* spp.^{29,37,38}

In the ARTEMIS DISK global antifungal surveillance project, of the 197,000 *Candida* spp isolated from patients with invasive candidiasis between 1997 and 2005, 90% of infections were caused by 5 species, *C albicans*, *Candida glabrata*, *C parapsilosis*, and *Candida tropicalis*.³⁹ Similarly, the *Candida* spp isolated from patients with nosocomial candidemia in the SCOPE study were *C albicans* (54%), *C glabrata* (19%), *C parapsilosis* (11%), and *C tropicalis* (11%).⁴ The overall crude mortality rate associated with candidemia was 47%, with the lowest rate of 30% for BSIs caused by *C parapsilosis* and the highest rate of 59% for *Candida krusei* fungemias.⁴ The relative frequencies of the nonalbicans *Candida* spp causing candidemia varies across the world and among types of health care centers. Overall, there has been a recent increase in the proportion of infections caused by nonalbicans *Candida* spp.^{3,10,40} In a recent study from the United States, nonalbicans *Candida* spp were reported to cause most of the candidemias.⁴¹ Most of the nonalbicans species, particularly *C glabrata*, seem to be reported from specialized cancer centers in the United States.^{40,42} In contrast, there

are low rates of *C glabrata* and high rates of *C parapsilosis* and *C tropicalis* reported from Latin America.¹⁰ The clinical significance of the isolation of nonalbicans *Candida* spp is the increased likelihood of resistance to fluconazole and other azoles. In particular, of the commonly isolated nonalbicans *Candida* spp, fluconazole resistance was noted in 16% of *C glabrata*, 78% of *C krusei*, and 11% of *Candida guilliermondii*.¹⁰

Although most cases of candidemia and invasive candidiasis are caused by endogenous patient microflora, exogenous transmission of *Candida* spp may occur particularly in neonatal ICUs. In a prospective study of candidemias in surgical and neonatal ICUs, 33% of surgical ICU and 29% of neonatal ICU medical personnel had *Candida* spp recovered from their hands.⁴³ *Candida* colonization of artificial nails of a health care worker (HCW) has also been implicated as a cause of postoperative candidal osteomyelitis.⁴⁴

Characteristics of specific *Candida* spp may influence the risk for exogenous transmission and nosocomial infections in certain patient populations.⁴⁵ In molecular epidemiologic studies, *C albicans* has been implicated in nosocomial transmission among patients in burn units.^{46,47} Person-to-person transmission has also been reported from geriatric short-stay units.⁴⁸

C glabrata seems to be more frequently isolated from older patients,⁴⁹ patients with cancer and prior exposure to fluconazole,^{42,50} and patients treated with piperacillin-tazobactam or vancomycin.⁵¹

C parapsilosis has emerged as an important cause of candidemia in the neonatal population^{52–55} and transplant recipients.⁵⁵ *C parapsilosis* is the most common *Candida* spp isolated from the hands of HCWs. In a prospective multicenter study of neonatal candidiasis, *C parapsilosis* was isolated from 19% of 2 989 cultures obtained from the hands of HCWs.⁵⁶ Colonization with *C parapsilosis* was also found on the hands of 7 of 21 neonatal ICU HCWs.⁵⁷ A recent review of molecular epidemiologic studies of outbreaks of *C parapsilosis* suggests horizontal transmission from HCWs to neonates.⁵⁸ The ability of *C parapsilosis* to produce biofilms^{34,59} may explain its propensity to cause outbreaks of nosocomial candidemias associated with central venous catheters (CVCs).^{60,61} In addition, outbreaks of *C parapsilosis* candidemia have been associated with the use of parenteral nutrition,⁶¹ which may be because of the selective growth advantage of *C parapsilosis* in glucose-rich hyperalimentation solutions.⁶² Hence, the frequent isolation of *C parapsilosis* should prompt measures to enhance hand hygiene and appropriate care of intravascular catheters.

C tropicalis is increasingly isolated from patients with hematologic malignancies in the setting of mucositis and neutropenia,⁶³ and colonization in these patients is predictive of subsequent infection.^{41,64}

C krusei was the fifth most common *Candida* spp isolated and accounted for 2.5% of 137,487 *Candida* isolates in a global antifungal surveillance program.⁶⁵ *C krusei*, intrinsically resistant to fluconazole, has often been reported in patients with hematologic malignancies and HSCT recipients with prior fluconazole and antifungal exposure and is associated with the highest mortality of all *Candida* spp.^{41,42,63,66,67} In nonneutropenic patients, risk factors for *C krusei* nosocomial candidemias include recent gastrointestinal surgery and exposure to fluconazole.⁶⁸

Emerging *Candida* spp that are relatively resistant to fluconazole, such as *C guilliermondii*⁶⁹ and *C rugosa*,^{70,71} have also been associated with nosocomial outbreaks, some involving intravascular catheters.

Other Yeasts

Malassezia spp are lipophilic yeasts that are frequent colonizers of the skin and are the cause of pityriasis. Few outbreaks of *Malassezia* fungemia have been reported in

low-birth-weight neonates and in immunocompromised adults.⁷²⁻⁷⁴ The prolonged use of intravascular catheters and parenteral lipid formulations were important predisposing conditions identified.^{72,74} Investigation of a group of 8 neonates with *Malassezia pachydermatis* fungemia reported colonization of the hands and pet dogs of HCWs, suggesting possible transmission from HCWs to patients.⁷³

Trichosporon spp are the cause of white piedra, a superficial infection of the hair shaft. Fungemia has been reported in immunocompromised patients, primarily those with hematologic malignancies, and HSCT and SOT recipients.⁷⁵⁻⁷⁷ Systemic disease has also been reported in nonneutropenic ICU and burn patients.⁷⁸⁻⁸⁰ One of the common risk factors in cases of nosocomial trichosporonosis is the presence of an indwelling intravascular catheter and exposure to prior antibiotics.^{75,76,80} The reported all-cause mortality rate is high and ranges from 42% to 83%, with the highest rates in patients with hematologic malignancies.^{75-77,80}

Most outbreaks of nosocomial invasive candidiasis and invasive infections with other yeasts have been associated with intravascular catheters. Hence, infection control strategies targeted to improve adherence to hand hygiene recommendations, including avoidance of long nails and artificial nails, and guidelines for care of intravascular catheters are important in the prevention of these infections.

NOSOCOMIAL INFECTIONS CAUSED BY MOLDS

Unlike invasive candidiasis, which can affect relatively noncompromised patients, invasive disease caused by *Aspergillus* spp and molds generally involves severely immunocompromised patients. Although several outbreaks of environmental airborne fungal infection within hospital settings have been reported, most cases of invasive aspergillosis are sporadic. At present, there is no uniform definition of what constitutes nosocomial aspergillosis.⁸¹ One of the primary reasons for the difficulty in defining hospital-acquired aspergillosis is that the incubation period of invasive aspergillosis is unknown. Moreover, the prolonged period of immunosuppression in high-risk patients such as HSCT recipients and frequent hospital admissions and discharges makes it difficult to determine if exposure to *Aspergillus* spores occurred during hospitalization or within the community. One definition that is frequently used considers nosocomial aspergillosis as invasive disease that occurs after 1 week of hospitalization or within 2 weeks of hospital discharge.⁸² Although most hospital outbreaks have been caused by *Aspergillus* spp, other airborne molds have also been implicated, including *Zygomycetes* spp,⁸³ *Fusarium* spp,⁸⁴ *Scedosporium* spp,^{85,86} and *Penicillium* spp.⁸⁷

Aspergillus spp

Aspergillus spp are ubiquitous molds found widely in the environment; they reproduce by means of asexual propagules termed conidia or spores. Exposure to airborne spores of *Aspergillus* occurs frequently in the environment, especially near decaying organic matter. Although these conidia (2.5–3.0 μm in diameter) are frequently inhaled, invasive pulmonary disease is rare in immunocompetent persons. Opportunistic invasive aspergillosis occurs primarily in severely immunocompromised patients. *Aspergillus fumigatus* is the species most often associated with disease, although other species, including *Aspergillus flavus*⁸⁸⁻⁹⁰ *Aspergillus niger*, *Aspergillus terreus*, *Aspergillus nidulans*, and *Aspergillus ustus*, have also been isolated from patients with invasive disease.

Aspergillosis is an important cause of morbidity and mortality, particularly in allogeneic HSCT recipients and neutropenic patients with hematologic malignancies.⁹¹⁻⁹⁶

Immunocompromised patients at a lower risk for invasive aspergillosis include SOT recipients,^{93,97,98} patients with AIDS,^{99–102} and those with chronic granulomatous disease.¹⁰³ There are increasing reports of invasive aspergillosis being described in critically ill patients in the ICU without the traditional risk factors, including patients with *chronic obstructive pulmonary disease*, liver cirrhosis, and those receiving corticosteroids.^{104–110}

***Aspergillus* outbreaks**

Although most cases of invasive aspergillosis are sporadic, the information on the environmental exposures and the association with infection has been derived from investigations of outbreaks of aspergillosis in hospital settings. A recent extensive review of nosocomial aspergillosis identified 53 reported outbreaks involving 458 patients.⁵ Of these, 33 outbreaks involving 299 patients (65%) occurred in HSCT recipients or patients with hematologic malignancies. Other patient populations involved in these outbreaks were SOT recipients (10%), predominately renal transplant recipients; other severely immunocompromised patients (13%); patients without severe immunodeficiency (8%); and patients on high-dose steroids (3%).⁵ Aspergillosis was associated with mortality greater than 50% in patients with hematologic malignancies, HSCT and SOT recipients, and patients with severe immunodeficiency. The most common site of infection was the lungs in 77% of cases, with about 5% involving surgical site or skin infections. *A fumigatus* and *A flavus* were the most commonly identified *Aspergillus* spp. Volumetric air sampling performed during the course of epidemiologic investigations in 24 of the outbreaks noted spore counts ranging from 0 to 100 spores per cubic meter. Outbreaks were primarily attributed to airborne infections related to construction or renovation activities in about 50% of cases and to compromised air quality in 17%.⁵ The various environmental vehicles implicated in the transmission of *Aspergillus* spp and other molds have also been detailed in the CDC guidelines for environmental infection control in health care facilities (HCFs). These vehicles include improperly functioning ventilation systems, poorly maintained air filters, contamination of false ceilings and insulation material, construction within and around the hospital, water leaks, food, and ornamental plants.²⁶

The most frequent nosocomial source of *Aspergillus* infection seems to be contaminated air, but *Aspergillus* has also been recovered from the hospital water supply and plumbing systems.^{111–113} The highest airborne *Aspergillus* spore counts were detected in patient's bathrooms, suggesting possible aerosolization of *Aspergillus* spores from the shower facilities.¹¹² The clinical implications of this finding remain to be defined.

Clusters of cutaneous aspergillosis have occurred in burn wounds as a result of the use of dressings contaminated with *Aspergillus* spores during hospital construction.¹¹⁴ Cutaneous aspergillosis has also occurred at intravenous (IV) insertion sites because of contaminated dressings used to secure arm boards that provided support for IV lines in children undergoing treatment of leukemia.¹¹⁵

Although the association between construction and invasive aspergillosis has often been reported, there is poor correlation of the *Aspergillus* spp recovered from the hospital environment and species isolated from patients with aspergillosis.^{112,116,117} One explanation for this discordance between hospital and patient strains of *Aspergillus* might relate to the lack of a clearly defined incubation period for aspergillosis and the relationship to exposure within the hospital environment and subsequent infection.⁸¹ Other factors include the methods of air sampling used,¹¹⁸ the broad diversity of *Aspergillus* spp in the environment,¹¹⁹ and the various methods used for typing of *Aspergillus* and other pathogenic molds.^{120,121}

Zygomycetes

Zygomycetes are ubiquitous molds and, like *Aspergillus* spp, are found in the soil and decaying organic matter in the environment. Although infection caused by Zygomycetes is uncommon, it is often a fatal disease. Population-based studies estimate an annual incidence of 0.43 to 1.7 cases per million persons.^{122,123} In a recent review of 929 patients with zygomycosis, the underlying conditions were diabetes (36%), malignancy (17%), SOT (7%), desferrioxamine therapy (6%), injection drug use (5%), and bone marrow transplantation (5%).¹²⁴ The overall mortality was 54%, with the mortality exceeding 80% in HSCT recipients, patients with renal failure, patients on desferrioxamine therapy, and patients with systemic lupus erythematosus. Mortality was 76% with pulmonary zygomycosis and 100% with disseminated and central nervous system diseases.¹²⁴ Infection often occurs via inhalation of fungal spores, resulting in sinopulmonary disease, but systemic infection can result from inoculation of the skin or gastrointestinal mucosa.¹²⁴ The treatment of localized infections is often surgical, and antifungal therapeutic options are limited to amphotericin B or posaconazole.¹²⁵

Nosocomial infections caused by Zygomycetes have been recently reviewed.⁸³ Clusters of cutaneous infections have occurred in orthopedic and cardiothoracic patients, children with leukemia, and burn patients. These infections were associated with Elastoplast adhesive dressings possibly contaminated with *Rhizopus* and *Absidia* spp.^{83,126} Outbreaks in patients with hematologic malignancies have resulted from airborne transmission associated with contamination of hospital ventilation systems.^{127–129} Unusual routes of transmission have been traced to the use of contaminated wooden tongue depressors^{130,131} and nonsterile karaya (plant-derived adhesive) for securing ostomy bags.¹³² A recent outbreak of gastrointestinal zygomycosis caused by *Rhizopus* in 12 patients with hematologic malignancies was traced to contaminated cornstarch used as an excipient in the manufacture of allopurinol and ready-to-eat foods.¹³³

Fusarium spp

Fusarium is a soil saprophyte and causes keratitis and onychomycosis in humans. Outbreaks of keratitis caused by possible contamination of contact lens solutions have been described.^{134,135} Invasive disease has generally been reported in patients with prolonged neutropenia, especially in HSCT recipients,^{84,136} and to a lesser extent in SOT recipients.¹³⁷ The incidence of fusariosis has been estimated to be 4 to 5 cases per 1000 HLA antigen-matched allogeneic HSCT recipients to as high as 20 cases per 1000 HLA antigen-mismatched recipients. Fusariosis in HSCT recipients has a bimodal distribution, with a peak before engraftment and later during the period of graft-versus-host disease (GVHD), and is associated with an actuarial survival of 13%.¹³⁶ Most infections are believed to be caused by airborne transmission; however, contamination of the water system in the hospital has been reported to result in dispersal of airborne conidia.⁸⁴ DNA sequencing has demonstrated evidence of widespread distribution of clones that were similar to isolates recovered from nosocomial infections in patients.¹³⁸

Other Molds

Several other pathogenic molds have been associated with HAIs. Outbreaks caused by *Scedosporium* spp have been reported in patients with leukemia undergoing chemotherapy.^{85,86,139} *Paecilomyces* spp have a propensity to cause intraocular implant infections and have been associated with possible contamination of the air

in the operating room.¹⁴⁰ Cutaneous inoculation of *Paecilomyces* spp from contaminated skin lotion has resulted in cutaneous and invasive infections in HSCT recipients.¹⁴¹ *Phialemonium* spp have been linked to outbreaks of intravascular infections in patients undergoing hemodialysis resulting from contamination of water distribution systems.^{142–144} Outbreak of infections caused by *Phialemonium* has also been linked to contaminated prefilled syringes of vasoactive agents used for injection of penile implants.¹⁴⁵ *Curvularia* spp have been isolated from saline-filled breast implants, resulting from contamination of saline stored beneath a water-damaged ceiling.¹⁴⁶

Pneumocystis jiroveci

Opportunistic pneumonia caused by *Pneumocystis jiroveci*, now classified as a fungus, is believed to be because of the reactivation of latent infection during periods of severe T-cell-mediated immunosuppression, as in transplant recipients and patients with AIDS. However, recent reports suggest possible person-to-person airborne transmission of infection.^{147–153} Polymerase chain reaction (PCR) testing identified *P jiroveci* DNA in close contacts of patients with HIV infection and *Pneumocystis* pneumonia, including HCWs.^{147,148} Molecular evidence has also identified person-to-person transmission of *P jiroveci* to be the likely cause of outbreaks of *Pneumocystis* pneumonia, particularly among renal transplant recipients.^{149–156} Most of the renal transplant recipients were not receiving anti-*Pneumocystis* pneumonia prophylaxis. However, population-based studies have not detected an increased risk of *P jiroveci* infections in the contacts of HIV-seropositive persons.^{157,158} Current guidelines do not recommend specific isolation measures for the care of hospitalized patients with *Pneumocystis* pneumonia.^{27,159}

STRATEGIES FOR PREVENTION OF NOSOCOMIAL CANDIDIASIS

Prevention of Intravascular Catheter-related Candidemia

Guidelines for the prevention of intravascular CRBSIs have been published.^{24,25} Evidenced-based recommendations emphasize (1) education and training of HCWs who insert and maintain catheters, (2) use of maximal sterile-barrier precautions during CVC insertion, (3) use of 2% chlorhexidine for skin antiseptics, (4) avoiding routine replacement of CVCs, and (5) use of antibiotic/antiseptic-impregnated CVCs if there are high rates of infection despite implementation of recommendations.²⁴ The measures strongly recommended for implementation as described in the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America guidelines for the prevention of CRBSIs are discussed in detail by Drs David J. Weber and William A. Rutala elsewhere in this issue.

The effectiveness of these strategies, using the 5 processes, namely, appropriate hand hygiene, chlorhexidine antiseptics, full-barrier precautions, the preferred use of the subclavian site, and removal of unnecessary CVCs for the prevention of CRBSIs, was examined in 103 ICUs in Michigan.¹⁶⁰ The median rate of CRBSIs during the 18 months after implementation declined 66% from 2.7 to 0 per 1000 catheter-days.¹⁶⁰ A similar reduction in CRBSIs has been reported in surgical ICUs after implementation of these guidelines.¹⁶¹

STRATEGIES FOR PREVENTION OF NOSOCOMIAL ASPERGILLOSIS AND MOLD INFECTIONS

Aspergillosis is primarily acquired by inhalation of fungal spores and subsequent invasive disease in immunocompromised patients with prolonged neutropenia or those on high-dose corticosteroid therapy. Hence, the primary infection control strategy is to

minimize exposure to airborne environmental fungal spores within HCFs during the high-risk period. Exposure to fungal spores of *Aspergillus* spp and other pathogenic molds after hospital discharge may occur in high-risk patients, such as the allogeneic HSCT recipient with chronic GVHD who is administered steroids. Patient education to minimize exposures to fungal spores and chemoprophylaxis with antifungal agents may be necessary. Guidelines for the use of antifungal agents for prophylaxis against invasive aspergillosis have been recently published.^{27,162}

The CDC and the Healthcare Infection Control Practices Advisory Committee have published recommendations regarding environmental infection control measures in HCFs.²⁶ These recommendations include infection control strategies and engineering controls directed primarily for the prevention of exposure of immunocompromised patients to environmental airborne fungal spores of *Aspergillus* and other molds. Additional recommendations to prevent HCF-associated pulmonary aspergillosis have also been published.¹⁵⁹

Because opportunistic *Aspergillus* and airborne mold infections occur primarily in severely immunocompromised patients such as HSCT recipients, one of the main components of these prevention strategies is the provision of a protected environment (PE) for these patients within the HCF.

Protected Environment

A PE is a specialized patient care environment in acute care hospitals for the care of allogeneic HSCT recipients.^{26,27} The benefit of a PE for other immunocompromised patients, such as autologous HSCT or SOT recipients, remains undefined.¹⁵⁹ A PE is designed to minimize HSCT patient exposure to airborne environmental *Aspergillus* spores. The essential features of a PE are shown in **Box 1**. Additional infection control measures for patients housed in a PE include (1) daily monitoring and maintenance of a positive pressure in PE areas, (2) minimizing exposures to activities that can cause aerosolization of fungal spores (eg, vacuuming), (3) minimizing the length of time that the patients are outside the PE for procedures, and (4) provision of high-efficiency respiratory protection (eg, N95 respirators; 3M, St Paul, MN, USA) when outside the PE if there is ongoing construction activity in the HCF.¹⁵⁹ The effectiveness of respirators in the absence of construction or the use of surgical masks to prevent fungal infection has not been evaluated.

Box 1

Protective environment

Requirements of protective environment rooms

- Central or point-of-use high-efficiency particulate air (HEPA) filters with 99.97% efficiency for removing particles 0.3 μm or larger
- Directed airflow, air intake occurs at 1 side and air exhaust occurs at the opposite side of the room
- Positive air pressure differential between room and corridor (≥ 2.5 Pa)
- Maintenance of 12 or more air changes per hour
- Well sealed patient rooms

Data from Sehulster L, Chinn RY. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 2003;52(RR-10):1-42.

The other infection control strategies and engineering controls recommendations that reduce exposure to environmental airborne *Aspergillus* and other fungal spores emphasize the provision of safe air during routine care and importantly during hospital construction.^{26,159} These strategies are outlined in **Box 2**.

Infection Control Risk Assessment

ICRA is a multistep process that determines the potential effect of construction within an HCF on the environment and exposure of at-risk patients to infectious agents, particularly fungal spores.^{163,164} The members of the ICRA include the infection control team, construction engineers, and hospital administration. The steps in the ICRA process before start of any construction activity are the following:

1. Categorize the type of construction activity (types A–D) based on the degree of dust generated. Type A activities are those that produce no dust (eg, electrical trim work or minor plumbing), and type D activities are major demolition or construction.
2. Identify the patients who will be affected by the construction activity and determine the level of infection risk: low risk (eg, office areas), medium risk (eg, physical therapy), high risk (eg, emergency department), and highest risk (eg, immunocompromised patient areas).
3. Match the patient risk group with the type of construction activity and determine the class of infection control precautions necessary. The classes of infection control precautions range from class 1 (minimal precautions) to class 4 (major precautions, including barriers and safe air handling).

Implementation of recommended infection control strategies during hospital construction has been successful in the prevention of fungal contamination of air in patient care areas in prospective environmental surveillance studies using cultures and PCR assays for detection of airborne fungi.^{165–167} Newer mobile nonfiltration-based air treatment systems that use exposure to electric fields and electrostatic nanofiltration to destroy airborne organisms have also been effective in preventing fungal contamination during construction.^{168,169}

Additional recommendations for the prevention and control of nosocomial aspergillosis are included in **Box 3**.

STRATEGIES FOR PREVENTION OF FUNGAL INFECTION IN HSCT RECIPIENTS

The term severely immunocompromised patient often refers to the allogeneic HSCT recipient. To implement strategies to prevent fungal infections in this population, it is important to define the high-risk periods after HSCT. In the allogeneic HSCT recipient, the risk of infections is related to the time from transplant.²⁷ The post-HSCT period is generally divided into 3 phases:

- Phase I: the preengraftment period (<15–45 days post-HSCT). Risk of infection is related to prolonged neutropenia and disruption of the mucocutaneous barriers because of cytotoxic chemotherapy. Infections during this period are generally caused by bacteria, *herpes simplex virus*, *Candida*, and *Aspergillus* spp.
- Phase II: the postengraftment phase (30–100 days post-HSCT). Risk of infection is related to impaired cell-mediated immunity based on the severity of GVHD and the intensity of immunosuppressive therapy used for treatment. Infections during this period are caused by cytomegalovirus (CMV), *Aspergillus* spp, and *P jiroveci*.

Box 2**Environmental infection control measures in healthcare facilities to minimize exposure to fungal spores**

<u>Recommendations</u>	<u>Rating Category^a</u>
<i>Air handling systems</i>	
<ul style="list-style-type: none"> • Use the American Institute of Architects (AIA) guidelines or state regulations for design and construction of ventilations systems¹⁶⁴ • Conduct ICRA and provide adequate number of PE rooms for the HSCT population • Monitor ventilation systems for removal of particulates and excess moisture 	<p>IC</p> <p>IA, IC</p> <p>IB, IC</p>
Proper location and maintenance of air intake and exhaust outlets, for example, removal of bird roosts from near air intake outlets to prevent entry of fungal spores	
Appropriate installation, maintenance, and disposal of HVAC filters	
Monitor PE areas for ACH, filtration, and pressure differentials	
<ul style="list-style-type: none"> • Develop a contingency plan for backup capacity in case of a power failure • Coordinate HVAC system shutdowns with infection control staff to allow for safe air handling to PE areas and to relocate immunocompromised patients if necessary 	<p>IC</p> <p>IC</p>
<i>Infection control measures during construction projects</i>	
<ul style="list-style-type: none"> • Set up a multidisciplinary team that includes infection control staff to coordinate proactive preventive measures to reduce exposure to fungal spores and monitor adherence • Provide education to HCWs and the construction crew in immunocompromised patient care areas regarding airborne infections • Perform an ICRA to assess potential exposure of high-risk patients to high ambient air fungal spore count • Develop and implement measures to keep airborne spores from construction areas away from patient care units 	<p>IB,IC</p> <p>IB</p> <p>IB, IC</p> <p>IB, IC</p>
Dust control measures (eg, dust barriers, safe air handling, negative pressure in construction work zones)	
Water damage response plan to prevent fungal growth	
<ul style="list-style-type: none"> • Maintain surveillance for cases of HCF-associated aspergillosis and mold infections in immunocompromised patients • Undertake an epidemiologic investigation if a case of nosocomial <i>Aspergillus</i> or other mold infection is detected 	<p>IB</p> <p>IB</p>
Surveillance for additional cases	
Determine appropriate air handling in the PE and in construction areas	
Conduct environmental assessment to identify the source	
Take corrective action to improve deficiencies identified and to eliminate the source of fungal spores	

Environmental services recommendations to minimize exposure to fungal spores

- Avoid carpeting and upholstered furniture and furnishings in areas housing immunocompromised patients IB
 - Avoid cleaning methods that disperse dust IB
- Wet dust horizontal surfaces using EPA-registered hospital disinfectant
- Equip vacuums with HEPA filters
- Close the doors of rooms of immunocompromised patients when cleaning
- Dry carpeting immediately if wet to prevent growth of fungi, replace if wet after 72 hours
- Avoid fresh flowers and potted plants in areas housing immunocompromised patients II

Abbreviations: ACH, air changes per hour; EPA, environmental protection agency; HSCT, hematopoietic stem cell transplantation HVAC, heating ventilation air conditioning; ICRA, infection control risk assessment; PE, protected environment.

^a Ratings category: IA, strongly recommended for all hospitals and supported by well-designed experimental or epidemiologic evidence; IB, strongly recommended for all hospitals and viewed as effective by experts because of strong rationale and suggestive evidence; IC, required by state or federal regulation or representing an established association standard; II, suggested for implementation in many hospitals, supported by suggestive clinical or epidemiologic studies with a strong theoretical rationale or definitive studies applicable to some but not all hospitals.

Data from Sehulster L, Chinn RY. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 2003;52(RR-10):1-42; and Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep 2004;53(RR-3):1-36.

- Phase III: the late phase (>100 days post-HSCT). Risk of infection is dictated by chronic GVHD and its treatment. Pathogens are primarily CMV, varicella-zoster virus, encapsulated bacteria, and *Aspergillus* spp.

As a general measure, avoidance of certain foods has been recommended to reduce exposure to fungi, primarily during the high-risk period of neutropenia (such as during receipt of conditioning therapy).²⁷ These foods include unpasteurized dairy products, cheeses made from mold cultures, uncooked eggs, meat, fish, tofu, unwashed vegetables, and fruits.²⁷

Invasive aspergillosis displays a bimodal distribution, with increasing number of cases of late-onset disease (>40 days post-HSCT) that is associated with immunosuppression for chronic GVHD.^{22,170,171} A similar pattern of late-onset disease has also been noted with invasive infection with Zygomycetes and *Fusarium* spp in HSCT recipients.^{136,172} Educating the patient in minimizing exposure to *Aspergillus* spp and pathogenic molds outside the hospital is important. However, because the risk of exposure within the hospital and community settings cannot be eliminated, novel strategies such as the use of antifungal prophylaxis may be necessary.

Chemoprophylaxis for Fungal Infection in HSCT Patients

Prevention of invasive candidiasis

Antifungal chemoprophylaxis during the preengraftment period of neutropenia and mucositis can prevent the dissemination of endogenous *Candida* spp from the

Box 3

Recommendations for prevention and control of health care–associated pulmonary aspergillosis

Recommendations	Rating Category ^a
<i>Staff education</i>	
• Educate HCWs about infection control procedures to reduce HCA-PA	II
<i>Surveillance</i>	
• Conduct surveillance for HCA-PA in patients in severely immunocompromised patients ^b	IA
• Monitor for HCA-PA by surveillance and periodic review of microbiologic and histopathologic data	II
• Do not perform routine surveillance cultures of patients or devices	IB
• Monitor ventilation status of PE and maintain appropriate standards	IB
<i>Specialized care units for high-risk patients</i>	
• Provide a PE for care of allogeneic HSCT recipients	IB
• Do not routinely use LAF in the PE	IB
• No recommendation for a PE for autologous HSCT and SOT recipients	UR
• Minimize the time high-risk patients are outside the PE for procedures	II
High-risk patients to wear N95 respirators outside the PE during ongoing construction	
No recommendation for type of mask outside the PE when no construction	
<i>When case of aspergillosis occurs</i>	
• Assess if health care related or community acquired	II
Determine if there is an increase in the number of cases of HCA-PA and length of hospital stay	IB
Determine if there is ventilation deficiency in the PE	IB
• If not health care related, continue routine maintenance as mentioned earlier	IB
• If health care related, conduct epidemiologic investigation to identify and eliminate source	IB
• Use EPA-registered antifungal biocide for decontamination of structural materials	IB

Abbreviations: EPA, environmental protection agency; HCA-PA, health care–associated pulmonary aspergillosis; HCW, healthcare worker; HSCT, hematopoietic stem cell transplantation; LAF, laminar airflow; PE, protective environment; SOT, solid organ transplantation.

^a Ratings category: IA, strongly recommended for all hospitals and supported by well-designed experimental or epidemiologic evidence; IB, strongly recommended for all hospitals and viewed as effective by experts because of strong rationale and suggestive evidence; II, suggested for implementation in many hospitals, supported by suggestive clinical or epidemiologic studies with a strong theoretical rationale or definitive studies applicable to some but not all hospitals; UR, unresolved, practices for which insufficient evidence or consensus regarding efficacy exists.

^b Severely immunocompromised patients, those with absolute neutrophil counts $<500/\text{mm}^3 \times 2$ weeks or $<100/\text{mm}^3 \times 1$ week, eg, HSCT and SOT recipients and patients on prolonged high-dose steroids.

Data from Sehulster L, Chinn RY. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 2003;52(RR-10):1–42; and Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care–associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep 2004;53(RR-3):1–36.

gastrointestinal tract of patients. Fluconazole started with the conditioning regimen and continued till resolution of neutropenia is effective in the prevention of invasive candidiasis and is recommended.^{27,173,174} Other agents shown to be effective in the prophylaxis of candidiasis in HSCT recipients are micafungin,¹⁷⁵ posaconazole,¹⁷⁶ and itraconazole.¹⁷⁷ Chemoprophylaxis of invasive candidiasis in nonneutropenic patients may be effective in carefully selected ICU patients,^{178,179} including liver¹⁸⁰ and pancreas¹⁸¹ transplant recipients and patients with a gastrointestinal leak.¹⁸² Clinical variables that are predictive of identifying ICU patients at high risk for invasive candidiasis, and thus potential candidates for prophylaxis, include patients receiving systemic antibiotic steroids, immunosuppressive agents, or *total parenteral nutrition*; patients undergoing dialysis; patients with a CVC; patients with pancreatitis; and patients who have had recent major surgery.³⁸

Prevention of Aspergillosis

Given the prolonged duration of the risk for aspergillosis in HSCT recipients with chronic GVHD, recent guidelines recommend the use of an antimold prophylaxis.^{27,162} Antifungal agents that have demonstrated efficacy in the prevention of mold infections in HSCT recipients include posaconazole,¹⁷⁶ itraconazole,^{177,183} and aerosolized liposomal amphotericin B.¹⁸⁴ The duration of prophylaxis is not clearly defined but is generally dictated by the severity of GVHD and the intensity of immunosuppression used to treat GVHD.¹⁶² The use of antiaspergillus prophylaxis has also been recommended for patients with acute myelogenous leukemia and myelodysplastic syndromes during periods of prolonged neutropenia.

Prevention of *Pneumocystis pneumonia*

Pneumocystis pneumonia prophylaxis is recommended for HSCT and SOT recipients during high-risk periods of immunosuppression, especially the first 100 days after transplantation. The preferred regimen is trimethoprim-sulfamethoxazole, with alternative agents being aerosolized pentamidine, oral dapsone, and oral atovaquone.²⁷

SUMMARY

Nosocomial fungal infections, especially candidemias and invasive aspergillosis, can result in significant morbidity and mortality in the critically ill and severely immunocompromised patients. Implementation of recommended infection control strategies can prevent catheter-related candidemia and minimize exposure of severely immunocompromised patients to airborne *Aspergillus* spores within the hospital environment. In select patient populations at high risk for invasive fungal infections, antifungal prophylaxis should be considered.

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