

Infection Control Measures to Prevent Invasive Mould Diseases in Hematopoietic Stem Cell Transplant Recipients

Kimberly Partridge-Hinckley · Gale M. Liddell · Nikolaos G. Almyroudis · Brahm H. Segal

Received: 8 September 2009 / Accepted: 6 October 2009 / Published online: 27 October 2009
© Springer Science+Business Media B.V. 2009

Abstract Invasive mould diseases, particularly aspergillosis, are important causes of morbidity and mortality in allogeneic stem cell transplant recipients. Mould spores are ubiquitous in the environment. Guidelines established by the Centers for Disease Control (CDC) and other authoritative organizations focus on approaches to reduce exposure to mould spores. These recommendations include avoidance of areas and activities expected to result in high levels of mould spores (e.g., construction, gardening) and use of specially designed units (protected environments) where additional standards (e.g., HEPA-filtered rooms) are in place to minimize mould exposure. These recommendations are based on consensus criteria and limited clinical data largely derived from single-center retrospective studies. In addition, highly immunocompromised stem cell transplant recipients

are commonly managed as outpatients, where engineering standards of the inpatient protected environment are not feasible. In the absence of an outbreak with an identified environmental source (e.g., a contaminated air vent), it is not possible to reliably distinguish community-acquired from nosocomial aspergillosis. Adherence to infection control guidelines, acknowledging their limitations, combined with evidence-based targeted antifungal prophylaxis for the highest risk transplant recipients, is likely to be the most effective approach to prevent invasive mould diseases.

Keywords *Aspergillus* · Mould · Neutropenia · Transplant · Infection control · Prevention

K. Partridge-Hinckley (✉) · G. M. Liddell · N. G. Almyroudis · B. H. Segal
Division of Infection Control, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, USA
e-mail: kimberly.hinckley@roswellpark.org

B. H. Segal
e-mail: brahm.segal@roswellpark.org

N. G. Almyroudis · B. H. Segal
Department of Medicine, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, USA

B. H. Segal
Department of Immunology, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, USA

Epidemiology of Invasive Mould Diseases in Hematopoietic Stem Cell Transplant Recipients

In autologous hematopoietic stem cell transplant (HSCT) recipients, the risk of invasive mould diseases is principally related to neutropenia. Risk factors for invasive aspergillosis and other moulds after allogeneic HSCT are more complex and follow a general time line. The first period of risk corresponds to neutropenia following conditioning. The degree and duration of neutropenia predict the risk of invasive mould diseases. After neutrophil recovery, the risk of invasive mould disease corresponds to the

intensity of immunosuppressive therapy required to control graft-versus-host disease (GVHD). In severe GVHD, global immune impairment occurs that affects both innate phagocyte function and cellular and humoral immunity. Several studies have reported the predominance of invasive aspergillosis cases occurring in the post-engraftment rather than in the neutropenic period in allogeneic HSCT recipients with immunosuppressive therapy for GVHD and T-cell depletion being principal risk factors [1–4].

Reflecting the greater level and duration of immune impairment, opportunistic mould diseases are more common in allogeneic compared to autologous HSCT recipients. In a prospective surveillance study in the U.S., the aggregate cumulative incidence of aspergillosis at 12 months was 0.5% after autologous HSCT, 2.3% after allogeneic HSCT from an HLA-matched related donor, 3.2% after transplantation from an HLA-mismatched related donor, and 3.9% after transplantation from an unrelated donor [5]. Thus, donor–recipient HLA-antigen disparity, which predicts the risk and severity of GVHD, is one of the major determinants of risk of invasive aspergillosis.

Portals of Entry of Mould Infection

Inhalation is the principal portal of entry of moulds. Infection control approaches to prevent invasive mould disease in HSCT recipients focus on minimizing exposure to environmental mould spores. Moulds are ubiquitous in the environment, and it's impossible to eliminate mould exposure entirely. The two major principles are (1) avoidance of areas where mould spore levels are expected to be significantly elevated (e.g., construction sites, decaying vegetation) and (2) specially designed inpatient protected environments.

Moulds, in contrast to *Candida* species, are not normal endogenous flora, but there can be instances of persistent colonization. In patients with pre-existing structural lung disease, *Aspergillus* species can colonize cavities and bronchiectatic airways. Among single lung transplant recipients, colonization of the native lung with *Aspergillus* species can predispose to post-transplant invasive aspergillosis. Chronic sinusitis can predispose to persistent sinus fungal colonization.

In addition to inhalation, the skin and gastrointestinal tract are less common portals of entry of moulds. Cutaneous infection can follow traumatic inoculation.

For example, localized invasive fungal disease can occur around an intravenous catheter and is typically treated with local debridement and antifungal therapy. *Fusarium* species can colonize nails, leading to onychomycosis that can subsequently cause invasive disease and dissemination during neutropenia and immunosuppressive regimens [6, 7]. Primary gastrointestinal aspergillosis and other mould diseases can occur in the highly immunocompromised patient after ingestion of mould spores. Moulds are frequently found in naturopathic and herbal material [8, 9]; for this reason, HSCT recipients should be instructed to avoid these agents.

Prevention of Invasive Mould Diseases

Prevention of invasive mould infections is complex and multifaceted and requires a comprehensive infection prevention team. Authoritative guidelines on environmental control are largely based on expert consensus and retrospective studies. Although we focus on HSCT recipients, these guidelines can reasonably be applied to non-transplanted immunocompromised patients at high risk for invasive fungal disease (e.g., those undergoing therapy for acute leukemia). In addition, highly immunocompromised patients are commonly managed as outpatients, outside of the “protected environment” of specially designed transplant wards that meet CDC environmental guidelines. We will discuss infection control approaches that can reasonably be applied to these high-risk outpatients.

Potential Environmental Sources for Nosocomial Fungal Infection

Construction

Building construction projects, particularly those involving penetration of walls and demolition, increase ambient particulate debris and likely mould spores. Work involving water-damaged material further increases the risk of aerosolizing mould spores. Several studies at individual centers have linked construction projects with an increased frequency of invasive aspergillosis and other mould diseases [10–12].

An epidemiological investigation and detailed environmental assessment was undertaken at Johns Hopkins Hospital following an increased incidence of invasive aspergillosis in patients with leukemia and HSCT recipients [13]. The authors suggested that excess cases of aspergillosis were linked to *Aspergillus* spores entering the oncology unit from the physically adjacent hospital because the air pressure on the oncology unit was negative with respect to the adjacent hospital. In addition, particle dispersion from dry mopping was severalfold higher than wet mopping. Once the outbreak was identified, the combination of patient use of N-95 masks when leaving their HEPA-filtered rooms and wet mopping was associated with reduction in cases of aspergillosis.

Arnou et al. [14] demonstrated an increased incidence of aspergillosis in immunocompromised patients that coincided with hospital construction or renovation and with poor maintenance of air filters. Disturbing normally closed spaces, e.g. ceiling spaces can lead to contamination [15, 16]. Open windows, gaps in filters, and support frames that permit the entry of unfiltered air have been associated with cases of aspergillosis [11, 15, 17]. Air ducts contaminated with bird droppings, contaminated fire proofing, and damp wood have also been implicated [15, 18]. The dust produced with cleaning or vacuuming also represents a potentially high-risk environment. Patients should avoid such activities at home and a HEPA-filtered vacuum should be used in the inpatient setting [19].

Taken together outbreak studies support the following recommendations:

1. Controlling nosocomial aspergillosis requires a multi-disciplinary team involving facility and maintenance personnel who have a good understanding of building air flow, heating, ventilation and air conditioning (HVAC) systems, and air filter maintenance. It should also include infection prevention and control personnel to ensure that protective measures are followed and to conduct active surveillance for cases of invasive fungal disease (IFD). Housekeeping staff require education regarding proper cleaning and minimizing dust dispersal, and environmental safety personnel should be included as they are responsible for overall building safety measures.
2. There is a need for developing air sampling and pressure testing standards to determine the effectiveness of containment efforts during construction.
3. Some experts suggest measuring fungal spore concentration in periods of construction or during outbreaks [10, 13, 20–22]. However, this approach is limited by the lack of standardized methods for air sampling and quantitation of fungi (e.g., quantitative cultures versus spore counts by direct microscopic assessment) and lack of defined reference ranges for what constitutes unacceptably high levels of fungal spore concentrations in air samples.

Plants, Soil, and Gardening

Exposure to plants and flowers has not been shown to conclusively cause fungal infections in HSCT recipients [23]. However, because *Aspergillus* species are commonly found in the soil outdoors and in ornamental plants (e.g. cacti), on the surface of dried flower arrangements and fresh flowers and within decaying vegetable matter, most experts recommend that plants and dried or fresh flowers not be permitted in hospital rooms of HSCT recipients or candidates undergoing conditioning regimes [15, 23–27]. In addition, activities such as gardening or mowing the lawn carry an increased risk of exposure to fungal spores. Direct inoculation of *Sporothrix shenkii* to the skin after even minor injury may occur. Cases of aspergillosis and other mould diseases have been linked to use of marijuana and other substance abuse materials [15, 20, 28].

Food

There are several studies demonstrating that moulds colonize plants and other food products. This is not surprising since moulds are saprophytes that obtain nutrients from different products that contain proteins, sugars, and minerals. In a Thai study, *Aspergillus flavus* was a dominant fungus in maize, peanuts, cashews, and copra [15, 29] *Aspergillus* species are also found in coffee beans, cereals, powdered milk, tea, chocolate, soy sauce, and tofu and have been linked to fungal infection in neutropenic patients [15, 25, 30]. *Aspergillus* species and other mould spores can be present in pepper, herbal teas, and freeze-dried soup [31, 32]. *Aspergillus*

species can also be used in the production of citric acid and as additives in processed food [15]. In a case report, *Mucor indicus* was isolated from the liver lesions of a HSCT recipient with hepatic zygomycosis and the naturopathic medications that he ingested [33]. Using an arbitrary-primed polymerase chain reaction (PCR) analysis, the isolates were shown to be genotypically identical.

Since moulds are so ubiquitous in the air we breathe and in the food we eat, it is an impossible goal to eliminate mould exposure entirely from HSCT recipients and other similarly immunocompromised persons. Several centers use “low microbial diets” to limit exposure to bacteria and fungi in high-risk patients. Criteria for “low microbial diet” differ among centers, and no standardized definition exists. A common sense approach involves avoiding fresh fruits and vegetables that cannot be effectively washed [34]. Recent CDC guidelines provide detailed recommendations regarding food safety among HSCT recipients [35].

Water

Standing water, water-damaged ceilings, floors, and walls, damp basements, and other moist indoor environments can be colonized with high levels of moulds and therefore pose a potential threat to highly immunocompromised patients [15, 24, 25, 36]. Nebulizers and ice machines can be contaminated as well [15, 36]. Warris et al. [37] reported that opportunistic fungal pathogens can be found in sinks and shower heads, with a significant increase in aerosolized spore counts in the air after showering. Nucci and Anaissie [38, 39] conducted a prospective study where *Fusarium* species were recovered from a hospital water system (water, water storage tanks, shower and sink drains, shower heads, and sink faucet aerators) and from hospital air and other environments and argued that hospital water systems could be an important source of nosocomial mould infections in immunocompromised patients. Raad et al. [40] reported that quantitative outdoor *Fusarium* spore levels were eightfold higher than the indoor levels. These studies illustrate that a large number of potential environmental niches within and outside of the hospital that can be important sources for high levels of mould exposure, and highlights the difficulty in linking an

outbreak of mould infection to a specific environmental source.

Seasonal Effects

Concentrations of ambient *Aspergillus fumigatus* spores are generally higher in the autumn and winter [15, 41, 42], but this is not a consistent finding. Potentially, the effect of seasons on ambient spore counts may be influenced by geography, humidity, and wind currents. In general, seasonal effects are not used to guide infection control policies regarding prevention of mould infections.

Fomites

Fomites are also a potential reservoir for mould species. For example, *Aspergillus niger* was linked to a cutaneous outbreak of aspergillosis in Manchester, England [15, 43]. It was recovered from fomites within a kitchen adjacent to the unit, within the patient rooms and food items. More specifically, it was isolated from two refrigerators, an ice machine, a microwave, tea caddy, a fire blanket, and ceiling air vent. Dust is a potential fomite for mould spores; to the extent possible, immunocompromised patients at risk for mould disease should avoid exposure to high levels of dust.

Hands

Cross-infection from health care provider hands and patients' relatives and friends is a well-recognized mode of transmission of bacteria and has been linked to outbreaks by antibiotic-resistant bacteria. *Candida* species are endogenous flora, and candidemia typically results from unique candidal strains that colonize the patient rather than transmission from another person. However, there have been cases of hospital outbreaks of candidiasis for example, in neonatal intensive care units attributed to colonization of staff or equipment [44, 45]. Other studies suggest the potential for nosocomial acquisition of *Candida* species among adults, including HSCT recipients [46, 47]. It is unclear whether hand carriage can be a mode for transmission of *Aspergillus* or other mould species [15]; based on common sense, hand washing should be required among staff and visitors of HSCT

recipients to minimize the chance of transmission of bacteria, viruses, and fungi.

Protective Environments

The benefit of protective environments (PE) to reduce mould infections among HSCT recipients is supported by limited data, frequently derived from studies of outbreaks. In a retrospective cohort study by Hahn et al. [48], use of HEPA filtration was effective in controlling an outbreak of aspergillosis. The outbreak was linked to contaminated insulation. During the outbreak, 10 out of 55 patients on a hematologic oncology unit were diagnosed with nosocomial invasive diseases with *Aspergillus flavus* within a 6-month period. After the institution of HEPA filters, the incidence decreased to 2 cases within a 2 year subsequent period. Anderson et al. [49] reported an outbreak of nosocomial aspergillosis on a pediatric oncology ward. Six out of 148 patients on this unit developed aspergillosis over the course of a year. The outbreak was potentially linked to a disposal unit on the ward where clinical waste was dropped into a conduit that led to the basement. The rubber gasket on the door to the conduit was ill fitting. *Aspergillus* species were cultured from the door frame and from the ward vacuum cleaner, which may have been a vehicle for spread of spores to the patients. Subsequent to these findings, the door to the disposal conduit was permanently sealed closed, and the vacuum cleaner was replaced with a high efficiency machine. There were no further identified cases of aspergillosis in an 18-month period since these actions were taken [49].

In 2007, the CDC issued updated recommendations regarding environmental controls for allogeneic HSCT recipients [50]. Their strongest recommendation is for daily pressure monitoring of rooms (1A) but the recommendation for a positive pressure relationship for the patient room to the corridor is not as strong (1B). Per the CDC, 1A is strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiological studies; whereas, 1B is supported by some experimental, clinical, or epidemiological studies, and a strong theoretical rationale. There can be variability in pressure differentials in patient rooms in PEs [51]. To maintain consistent pressure levels,

creating an airtight seal and continuous pressure monitoring have been recommended by some experts [51]. These approaches are reasonable; however, we disagree with rating the recommendation for daily pressure monitoring as a category 1A, which denotes a much higher level of evidence than actually exists. There is greater data that supports environmental controls in the presence of demolition and construction.

Other 1B recommendations include 99.97% HEPA filtration for particles >0.3 microns; directional air flow; 12 air changes per hour; well sealed rooms, avoidance of carpeting and minimizing patient time outside of a PE. Recommendations supported by lower levels of evidence are centered on wet dusting, prohibiting dried and fresh flowers and potted plants; and the use of N95 masks by HSCT patients during periods of construction when leaving PE.

Hospitals without protective environments should do what is feasible when caring for immunocompromised HSCT recipients. Maintenance of positive pressure in patient rooms by adjusting the HVAC system and use of portable HEPA filters should be considered.

Precautions in the Outpatient Setting

Recommendations discussed previously are tailored to inpatients who are generally admitted to designated transplant wards with PEs. However, allogeneic HSCT recipients requiring intensive immunosuppressive regimens are frequently managed as outpatients where this level of environmental protection is not feasible. There are a number of consensus-driven, common sense recommendations by the CDC to reduce exposure to mould spores in the outpatient setting. These include avoiding sources of mould such as construction sites; areas with standing water and damp basements. Patients should don masks if construction is unavoidable. They should avoid activities such as gardening; mowing; handling fresh flowers; and vacuuming. Family members should vacuum using HEPA equipped machines and use a wet method for dusting. Patients should leave the room during these activities. Patients should use a common sense approach dealing with food check expiration dates; inspect for mould growth; leftover foods placed in the refrigerator should be discarded

after 72 h. Well water should be filtered or tested by health officials, and fruits and vegetables should be thoroughly washed. Meticulous hand hygiene is always advised.

Community Versus Healthcare-acquired Invasive Fungal Diseases and Evaluating Outbreaks

A distinction between community versus hospital-acquired fungal disease becomes important when considering a specific source of environmental contamination (e.g. contaminated vent or water). Because the incubation period preceding clinically apparent invasive aspergillosis and other moulds is unknown, it is impossible to determine whether a fungal disease is community versus hospital-acquired based on when fungal disease became evident in relation to the time of hospitalization [10, 15, 52]. An arbitrary cut-off of 7 days has been used by some experts as an incubation period for fungal infections [53].

Distinguishing community-acquired versus hospital-acquired fungal infection is particularly important when there is a concern about an outbreak of invasive fungal disease. We will define an outbreak as a measurable increase in the incidence of a fungal disease resulting from spread of the pathogen from either an infected person or an environmental source. Investigation of an outbreak should be considered when the incidence of a given fungal disease is significantly above a historical baseline. In the case of invasive mould diseases, an environmental source of infection (e.g., a contaminated vent) should also be considered when fungal disease occurs in patients with lower levels of immunocompromise. An increased frequency of cases of less common invasive mould diseases (e.g., *Fusarium* species or dark-walled moulds) among hospitalized patients should also raise concern about a contaminated source.

The most persuasive evidence of nosocomial mould infection is demonstration of clonality among strains isolated from different patients during an outbreak. In this setting, identifying an environmental niche with levels of this strain severalfold above ambient levels would provide useful data regarding the source of fungal disease and guide efforts for abatement.

Underestimating and Overestimating Fungal Disease

Diagnosis of invasive fungal diseases used to rely exclusively on hard endpoints: either isolation of the fungus from a normally sterile site or documentation of fungal disease histologically. Because invasive procedures are often difficult to perform in immunocompromised patients with significant comorbidities, the diagnosis of fungal disease was frequently delayed or only made at autopsy [54]. Indeed, the lack of good diagnostic tools for invasive fungal disease was the basis for empirical antifungal therapy initiated in patients with neutropenia and persistent fever of unknown etiology [55].

We now have laboratory markers that facilitate the early diagnosis of invasive fungal diseases that may have previously been undiagnosed. Examples include detection of fungal cell wall constituents (e.g., galactomannan and beta-glucan assays) and PCR. Based on these diagnostic adjuncts, the EORTC/MSG defined three levels of diagnostic probability regarding invasive fungal diseases: “proven”, “probable”, and “possible” [56]. These criteria were designed for clinical research, but can also be applied to infection control surveillance.

These diagnostic adjuncts enable us to diagnose invasive fungal diseases that may have otherwise gone undiagnosed. However, they can also produce false-positive results that will overestimate the incidence of fungal disease. A meta-analysis of 27 reports of serum galactomannan (a diagnostic marker for invasive aspergillosis) demonstrated an overall sensitivity of 71% and specificity of 89% when studied against proven cases of invasive aspergillosis when used for surveillance [57]. As the number of diagnostic adjuncts increases, there will, by definition, be a greater chance of at least one of the tests producing a false-positive result. The requirement that only one of these tests be positive on a single occasion (as opposed to requiring positive results on 2 consecutive occasions) further increases the likelihood of a false-positive result. Indeed, there may be considerable variability among centers in the reported incidence of invasive fungal diseases based on which (if any) diagnostic adjuncts are used and whether they are used as surveillance tools in high-risk patients or only when there is clinical suspicion of fungal

disease. Seen in this light, other variables related to clinical practice, such as the frequency of obtaining blood cultures (to detect bacterial and *Candida* bloodstream infections) and chest CT scan imaging in high-risk patients with persistent neutropenic fever will also influence detection of fungal disease. This variability in diagnostic approaches poses challenges in comparing incidences of invasive fungal diseases among different centers.

Gaps in Knowledge and Future Perspectives

Infection control guidelines aimed at reducing invasive mould diseases in immunocompromised patients appropriately focus on limiting inhalational exposure. The clinical database supporting these recommendations principally relies on the experience of individual cancer centers, frequently during outbreaks. Such studies have important limitations, including the potential for publication bias when a given intervention is temporally associated with a positive result at an individual center. We do not have randomized controlled studies to support these recommendations nor are such studies likely to be pursued due to logistical and ethical concerns. Therefore, it is difficult to definitively measure the benefit of a given environmental infection control recommendation (e.g. HEPA-filtered rooms). Adherence to infection control guidelines, acknowledging their limitations, combined with evidence-based targeted antifungal prophylaxis for the highest risk transplant recipients [58], is likely to be the most effective approach to prevent invasive mould diseases.

Molecular-based methods for diagnosis of invasive fungal diseases may lead to progress related to environmental infection control. PCR-based diagnosis of invasive fungal diseases, although promising, is currently investigational. Potential advantages include rapidity, low cost, the ability to establish a diagnosis at the species level and to detect genes that confer antifungal resistance [59]. These molecular methods may also aid in evaluating clonality during suspected outbreaks of fungal diseases. Limitations include lack of standardized methods, difficulty in reliably distinguishing fungal colonization from disease, and the potential for contamination with fungal DNA.

Note added in proof Since the initial submission of this manuscript, updated CDC guidelines on preventing infectious complications in HSCT recipients have been published [35].

References

1. Segal BH. Aspergillosis. *N Engl J Med*. 2009;360:1870–84.
2. van Burik JA, Carter SL, Freifeld AG, et al. Higher risk of cytomegalovirus and aspergillus infections in recipients of T cell-depleted unrelated bone marrow: analysis of infectious complications in patients treated with T cell depletion versus immunosuppressive therapy to prevent graft-versus-host disease. *Biol Blood Marrow Transplant*. 2007;13:1487–98.
3. 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.
4. Jantunen E, Ruutu P, Niskanen L, et al. Incidence and risk factors for invasive fungal infections in allogeneic BMT recipients. *Bone Marrow Transplant*. 1997;19:801–8.
5. Morgan J, Wannemuehler KA, Marr KA, et al. Incidence of invasive aspergillosis following hematopoietic stem cell and solid organ transplantation: interim results of a prospective multicenter surveillance program. *Med Mycol*. 2005;43(Suppl 1):S49–58.
6. Boutati EI, Anaissie EJ. Fusarium, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. *Blood*. 1997;90:999–1008.
7. Nucci M, Marr KA, Queiroz-Telles F, et al. Fusarium infection in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2004;38:1237–42. Epub 2004 Apr 15.
8. Halt M. Moulds and mycotoxins in herb tea and medicinal plants. *Eur J Epidemiol*. 1998;14:269–74.
9. Efuntoy MO. Fungi associated with herbal drug plants during storage. *Mycopathologia*. 1996;136:115–8.
10. Chang CC, Athan E, Morrissey CO, Slavin MA. Preventing invasive fungal infection during hospital building works. *Intern Med J*. 2008;38:538–41.
11. Weems JJ Jr, Davis BJ, Tablan OC, Kaufman L, Martone WJ. Construction activity: an independent risk factor for invasive aspergillosis and zygomycosis in patients with hematologic malignancy. *Infect Control*. 1987;8:71–5.
12. Weber SF, Peacock JE Jr, Do KA, Cruz JM, Powell BL, Capizzi RL. Interaction of granulocytopenia and construction activity as risk factors for nosocomial invasive filamentous fungal disease in patients with hematologic disorders. *Infect Control Hosp Epidemiol*. 1990;11:235–42.
13. Thio CL, Smith D, Merz WG, et al. Refinements of environmental assessment during an outbreak investigation of invasive aspergillosis in a leukemia and bone marrow transplant unit. *Infect Control Hosp Epidemiol*. 2000;21:18–23.
14. Arnow PM, Sadigh M, Costas C, Weil D, Chudy R. Endemic and epidemic aspergillosis associated with

- in-hospital replication of *Aspergillus* organisms. *J Infect Dis.* 1991;164:998–1002.
15. Manuel RJ, Kibbler CC. The epidemiology and prevention of invasive aspergillosis. *J Hosp Infect.* 1998;39:95–109.
 16. Rhame FS. Prevention of nosocomial aspergillosis. *J Hosp Infect.* 1991;18(Suppl A):466–72.
 17. Sarubbi FA Jr, Kopf HB, Wilson MB, McGinnis MR, Rutala WA. Increased recovery of *Aspergillus flavus* from respiratory specimens during hospital construction. *Am Rev Respir Dis.* 1982;125:33–8.
 18. Aisner J, Schimpff SC, Bennett JE, Young VM, Wiernik PH. Aspergillus infections in cancer patients. Association with fireproofing materials in a new hospital. *JAMA.* 1976;235:411–2.
 19. Carter CD, Barr BA. Infection control issues in construction and renovation. *Infect Control Hosp Epidemiol.* 1997;18:587–96.
 20. Munoz P, Burillo A, Bouza E. Environmental surveillance and other control measures in the prevention of nosocomial fungal infections. *Clin Microbiol Infect.* 2001;7(Suppl 2):38–45.
 21. Dewhurst AG, Cooper MJ, Khan SM, Pallett AP, Dathan JR. Invasive aspergillosis in immunosuppressed patients: potential hazard of hospital building work. *BMJ.* 1990;301:802–4.
 22. Leenders AC, van Belkum A, Behrendt M, Luijendijk A, Verbrugh HA. Density and molecular epidemiology of *Aspergillus* in air and relationship to outbreaks of *Aspergillus* infection. *J Clin Microbiol.* 1999;37:1752–7.
 23. Dykewicz CA. Hospital infection control in hematopoietic stem cell transplant recipients. *Emerg Infect Dis.* 2001;7:263–7.
 24. Denning DW. Epidemiology and pathogenesis of systemic fungal infections in the immunocompromised host. *J Antimicrob Chemother.* 1991;28(Suppl B):1–16.
 25. Walsh TJ, Dixon DM. Nosocomial aspergillosis: environmental microbiology, hospital epidemiology, diagnosis and treatment. *Eur J Epidemiol.* 1989;5:131–42.
 26. 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;52:1–42.
 27. Rhame FS, Streifel AJ, Kersey JH Jr, McGlave PB. Extrinsic risk factors for pneumonia in the patient at high risk of infection. *Am J Med.* 1984;76:42–52.
 28. Marks WH, Florence L, Lieberman J, et al. Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. *Transplantation.* 1996;61:1771–4.
 29. Pitt JI, Hocking AD, Bhudhasamai K, Miscamble BF, Wheeler KA, Tanboon-Ek P. The normal mycoflora of commodities from Thailand. 1. Nuts and oilseeds. *Int J Food Microbiol.* 1993;20:211–26.
 30. Studer-Rohr I, Dietrich DR, Schlatter J, Schlatter C. The occurrence of ochratoxin A in coffee. *Food Chem Toxicol.* 1995;33:341–55.
 31. Bouakline A, Lacroix C, Roux N, Gangneux JP, Derouin F. Fungal contamination of food in hematology units. *J Clin Microbiol.* 2000;38:4272–3.
 32. De Bock R, Gyssens I, Peetermans M, Nolard N. Aspergillus in pepper. *Lancet.* 1989;2:331–2.
 33. Oliver MR, Van Voorhis WC, Boeckh M, Mattson D, Bowden RA. Hepatic mucormycosis in a bone marrow transplant recipient who ingested naturopathic medicine. *Clin Infect Dis.* 1996;22:521–4.
 34. Kusne S, Krystofiak S. Infection control issues after bone marrow transplantation. *Curr Opin Infect Dis.* 2001;14:427–31.
 35. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15:1143–238.
 36. Kibbler CC. Epidemiology of fungal disease. In: Kibbler CC, Mackenzie DWR, Odds FC, editors. Principles and practice of clinical mycology. New York: John Wiley; 1996. p. 13–21.
 37. Warris A, Gaustad P, Meis JF, Voss A, Verweij PE, Abrahamson TG. Recovery of filamentous fungi from water in a paediatric bone marrow transplantation unit. *J Hosp Infect.* 2001;47:143–8.
 38. Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. *Clin Microbiol Rev.* 2007;20:695–704.
 39. Anaissie EJ, Kuchar RT, Rex JH, et al. Fusariosis associated with pathogenic fusarium species colonization of a hospital water system: a new paradigm for the epidemiology of opportunistic mold infections. *Clin Infect Dis.* 2001;33:1871–8.
 40. Raad I, Tarrand J, Hanna H, et al. Epidemiology, molecular mycology, and environmental sources of Fusarium infection in patients with cancer. *Infect Control Hosp Epidemiol.* 2002;23:532–7.
 41. Mullins J, Hutcheson PS, Slavin RG. Aspergillus fumigatus spore concentration in outside air: Cardiff and St Louis compared. *Clin Allergy.* 1984;14:351–4.
 42. Noble WC, Clayton YM. Fungi in the air of hospital wards. *J Gen Microbiol.* 1963;32:397–402.
 43. Loudon KW, Coke AP, Burnie JP, Shaw AJ, Oppenheim BA, Morris CQ. Kitchens as a source of *Aspergillus niger* infection. *J Hosp Infect.* 1996;32:191–8.
 44. Saxen H, Virtanen M, Carlson P, et al. Neonatal *Candida parapsilosis* outbreak with a high case fatality rate. *Pediatr Infect Dis J.* 1995;14:776–81.
 45. Sherertz RJ, Gledhill KS, Hampton KD, et al. Outbreak of *Candida* bloodstream infections associated with retrograde medication administration in a neonatal intensive care unit. *J Pediatr.* 1992;120:455–61.
 46. Vazquez JA, Dembry LM, Sanchez V, et al. Nosocomial *Candida glabrata* colonization: an epidemiologic study. *J Clin Microbiol.* 1998;36:421–6.
 47. Sanchez V, Vazquez JA, Barth-Jones D, Dembry L, Sobel JD, Zervos MJ. Nosocomial acquisition of *Candida parapsilosis*: an epidemiologic study. *Am J Med.* 1993;94:577–82.
 48. Hahn T, Cummings KM, Michalek AM, Lipman BJ, Segal BH, McCarthy PL Jr. Efficacy of high-efficiency particulate air filtration in preventing aspergillosis in immunocompromised patients with hematologic malignancies. *Infect Control Hosp Epidemiol.* 2002;23:525–31.

49. Anderson K, Morris G, Kennedy H, et al. Aspergillosis in immunocompromised paediatric patients: associations with building hygiene, design, and indoor air. *Thorax*. 1996; 51:256–61.
50. Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *Am J Infect Control*. 2007;35:S65–164.
51. Rice N, Streifel A, Vesley D. An evaluation of hospital special-ventilation-room pressures. *Infect Control Hosp Epidemiol*. 2001;22:19–23.
52. Hajjeh RA, Warnock DW. Counterpoint: invasive aspergillosis and the environment—rethinking our approach to prevention. *Clin Infect Dis*. 2001;33:1549–52.
53. Kusne S, Krystofiak S. Infection control issues after solid organ transplantation. In: Bowden RA, Ljungman P, Paya CV, editors. *Transplant infections*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003. p. 589–607.
54. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med*. 1982;72:101–11.
55. Segal BH, Almyroudis NG, Battiwalla M, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. *Clin Infect Dis*. 2007;44: 402–9.
56. De Pauw B, Walsh TJ, Donnelly JP, 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.
57. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. *Clin Infect Dis*. 2006;42:1417–727.
58. Segal BH, Freifeld AG, Baden LR, et al. Prevention and treatment of cancer-related infections. *J Natl Compr Canc Netw*. 2008;6:122–74.
59. Einsele H, Loeffler J. Contribution of new diagnostic approaches to antifungal treatment plans in high-risk haematology patients. *Clin Microbiol Infect*. 2008;14(Suppl 4): 37–45.