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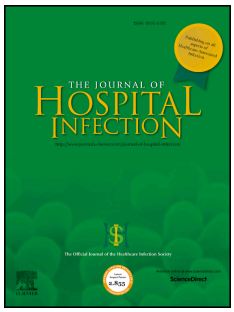

Prevention of healthcare-associated invasive aspergillosis during hospital construction/renovation works

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Summary

The association between healthcare associated invasive aspergillosis and hospital construction/building works is well recognized. This infection can cause significant morbidity and mortality and imposes a substantial burden on the healthcare system. The population of patients at-risk for this opportunistic infection has expanded and multi-triazole drug resistance has emerged globally. Therefore there is a need for a multi-faceted approach to prevent acquisition of invasive aspergillosis in acute care settings. This document is a summary of the Irish National Guidelines for the prevention of healthcare-associated aspergillosis which is based on published reports, international clinical guidelines, official engineering standards and technical guidelines. We discuss the key recommendations and strategies for the prevention of invasive aspergillosis from the planning/pre-construction, construction and post-construction phases. The importance of multi-disciplinary team involvement, education, and communication, is emphasized.

Keywords

Healthcare-associated invasive aspergillosis; hospital construction; air sampling; triazole resistance; specialized ventilation rooms

Introduction

Background

Healthcare associated invasive aspergillosis (HCA-IA) is now well described and a better understanding of the disease and preventive strategies has resulted in a reduction in incidence and mortality rates in high-risk populations where appropriate measures have been taken [1,2]. However, recent data have identified changes in the epidemiology of invasive aspergillosis (IA) with the recognition of more at-risk patients including those with severe influenza, chronic obstructive pulmonary disease (COPD), burns, cystic fibrosis, neonates, and also some patients not typically regarded as immunocompromised [3]. The association with certain types of construction activity is well recognised, and the need for preventive measures whilst such activities are taking place, has been accepted [4,5]. Similarly, immunocompromised patients are constantly exposed to airborne fungal spores

when outside the hospital setting and cases of IA have been linked to *Aspergillus* exposure in patients' homes [6–8]. Therefore, healthcare providers must ensure that all recognised risks are minimised.

This summary is based on the guidelines on the prevention of HCA-IA during hospital construction/renovation works published by the Irish *Aspergillus* Subcommittee of the Scientific Advisory Committee of the Health Protection Surveillance Centre [9], as well as on international clinical guidelines, official engineering standards and technical guidelines and published literature. Grading of the quality of the evidence was not performed since there are no published randomised controlled trials on the various recommended measures for the prevention of HCA-IA.

The burden of healthcare associated invasive aspergillosis during hospital construction or renovation

Aspergillus species are ubiquitous fungi that commonly can be recovered from soil, water, dust, organically enriched debris and decaying vegetation [10]. Many species of *Aspergillus* have been recognised in nature but only a few have been regularly associated with human disease. *Aspergillus fumigatus* belongs to the *Aspergillus* subgenus *Fumigati* section *Fumigati* and is the principal pathogenic *Aspergillus* species [11]. Invasive aspergillosis (IA) is primarily an infection of severely immunocompromised patients, notably patients with haematological malignancies undergoing intensive remission-induction chemotherapy, haematopoietic stem cell transplantation or solid organ transplant recipients [1,12–18]. Over the last decade it has been increasingly recognised that patients without known prior immunocompromise who are admitted to critical care, such as patients with severe COPD, influenza or other viral infections are at increased risk of IA [19–27].

Despite advances in our understanding of the interaction between *Aspergillus* species and the human immune response, improved diagnosis of IA, and more effective use of antifungal agents [28], this disease remains difficult to diagnose and treat early, therefore case fatality rates associated with IA remain high [16,29]. This makes prevention a priority in the management of at-risk patients. Recently, antifungal drug resistance in *A. fumigatus* affecting the triazole class, has been described and this threatens to limit future antifungal prophylactic and therapeutic options [30].

In the healthcare setting a number of environmental risks for IA are recognised although some are better defined than others. One of the major environmental risks continues to be patient exposure to construction work and generation of *Aspergillus* and other mould spores. *Aspergillus* spores are well adapted to airborne dissemination [31,32]. They are passively liberated during construction/renovation activities and can be transported great distances as airborne particles by normal atmospheric conditions such as convection currents and wind. The respiratory tract is the most common portal of entry and the small diameter of the spores (c. 2.5–3.5 µm) permits them to reach the pulmonary alveolar spaces, where they may germinate to form hyphae [33]. Pulmonary aspergillosis may then develop following inhalation of airborne fungal spores, and high spore counts within patient-care areas represent an extrinsic risk factor for invasive disease [34]. Hospital-acquired outbreaks of IA have become a well-recognised complication of construction, demolition or renovation work in or near hospital wards in which immunocompromised patients are housed [4,35,36]. In a review of outbreaks reported between 1966 and 2005, there were 53 affecting 458 patients [16]. In all but one outbreak, transmission was airborne and the respiratory tract was primarily affected. The most common (49%) probable or possible source was construction work or renovation activities within or around the hospitals while the source remained unknown in 12 outbreaks. The minimum airborne concentration of *Aspergillus* spores necessary to cause disease remains unknown, however the authors concluded that airborne mould spores at any concentration may represent a threat for severely immunocompromised patients. A patient's risk of developing IA and its outcome vary according to the level of the individual's exposure to sources of fungal spores and their net state of immunocompromise [37].

Allogeneic haematopoietic stem cell transplant (HSCT) recipients and patients with acute myeloid leukaemia (AML) are the population consistently at most risk mainly because of severe prolonged neutropenia. However, not all cases of *Aspergillus* infection that present clinically as IA in the hospital have been nosocomially acquired as patients may already be colonised with *Aspergillus* spp. prior to their admission and starting immunosuppressive therapy [38]. Over the past decade, a decreased incidence of IA has been seen in this group, due to improved preventive measures of isolation and antifungal prophylaxis [2]. Other conditions have frequently been reported as risk factors for construction-related nosocomial fungal infections: graft–versus-host disease requiring immunosuppressive treatment, prolonged neutropenia following cytotoxic chemotherapy, prolonged use of antibiotics, steroid therapy, and tumour necrosis factor α antagonists [38]. As the complexity of therapeutics increases and the survival rates from oncologic and haematologic conditions improves, it is likely that more patients will be at-risk of IA [3,19,20]. Published incidence

rates for IA in at-risk groups is shown in Table I. At-risk patients may be categorised according to their degree of immunocompromise as enumerated in Table II. This list is however not exhaustive and all patients should be individually risk assessed.

The key measures for prevention of HCA-IA during construction and/or renovation are divided into three phases: planning and pre-construction phase, construction phase, and post-construction phase [4,6,9,35,39–44]**.**

I.Planning and Pre-Construction Phase

Invasive Aspergillosis Risk Assessment

Prior to commencing any construction/renovation activity, a formal Invasive Aspergillosis Risk Assessment (IARA) must be performed [4–6,42,45]. The IARA involves a multidisciplinary team (MDT), the membership of which will be determined by the size and scope of the works and should as a minimum include representation from the following: Management of the healthcare facility, Project Team, Technical services, Infection Prevention and Control Team (IPCT), Healthcare personnel from relevant clinical area(s) and Health Business Services (HBS) Estates. There are four steps in the risk assessment process:

Step 1. Consider patient risk factors and assign to the correct at-risk group, Group 1-4 (Table II). If more than one risk group is identified within a specific cohort, select the higher risk group.

Step 2. Detail the construction activity and assign a type: A1, A2, B, C or D (Supplementary Table I). A combination of factors is taken into account and includes if the construction activity is major or minor, external or internal, containable or non-containable.

Step 3. Determine the construction site preventive measures and assign a class, 0-III (Supplementary Table II). Depending on the class selected, measures include dust control, debris removal and cleaning, patient risk reduction, ventilation systems and traffic control.

Step 4. Verify risk assessment by utilising a matrix as shown in Table III where the type of construction/renovation work is plotted against the patient risk group.

A document outlining the agreed measures required to reduce risk of IA for that specific project should be circulated to relevant stakeholders prior to the commencement of a project and will form the basis for the methods statement produced by the contractor. Implementation of the recommended preventive measures should be assigned to the appropriate groups which extend from ward level to the project manager and hospital management. Compliance with the recommended measures should be monitored by the relevant departments e.g. technical services, IPCT and cleaning staff with prior agreement on the monitoring procedures, reporting arrangements utilising a checklist (Supplementary Table III). Any breaches to the agreed measures should be notified immediately and in such instances, if significant risks to patients have been identified, it may be deemed necessary to convene an emergency meeting of the MDT to consider the required action. This could include cessation of the building works until necessary corrective actions have been implemented. The process and procedures for all such cessation of works must be agreed in advance between the stakeholders and specified clearly in the contract tender documents. The instruction to cease must be implemented strictly in accordance with provisions of the contract conditions.

Microbiological Air sampling – determining a baseline

Environmental air sampling for *Aspergillus* although not performed routinely, is recommended where major construction/refurbishment works are to be undertaken, so that baseline *Aspergillus* levels may be established for both the construction zone and other areas which may be affected either by virtue of their proximity or the risk of airborne spread. Concern for a particularly high-risk patient cohort should prompt further environmental screening. It is recognised that airborne fungal spore counts can vary dramatically over a short time span, thus multiple samples will be required weekly for a minimum of four weeks prior to commencement of building works in order to establish a baseline [46].

Currently there are no numerical threshold guidelines available for *Aspergillus* counts however counts of <1cfu/m^3 for High Efficiency Particulate Air (HEPA) filtered rooms with > 99.95% efficiency, and <5cfu/m^3 in ward areas without air filtration have been suggested [4,5,9,16,42,46,47]. Microbiological air sampling should be continued whilst construction is ongoing. In the event of high *Aspergillus* air counts when compared to baseline, and/or a higher than expected frequency of isolation of *Aspergillus* spp. from respiratory specimens from patients in the same or adjacent clinical areas should prompt discussion and/or a

meeting with members of the MDT. It is essential to alert clinicians/wards and departments to the potentially increased risk of IA in their at-risk patients. Further investigations should focus on the air handling units (AHUs) in place and the possibility of ingress of outside air which may be contaminated as a result of ongoing construction/demolition or maintenance works. Preventive measures might include consideration of moving exposed patients to another part of the hospital and initiating or extending mould-active antifungal prophylaxis based on a risk assessment [23,42,48].

Mould-active antifungal prophylaxis

The standard practice of antifungal chemoprophylaxis is supported by several published reviews and meta-analyses of studies conducted in specific high-risk patient populations especially those receiving treatments for haematological malignancies [49,50]. Current recommendations regarding prophylaxis of IA are summarised in Table IV based on guidelines published by the Infectious Diseases Society of America (IDSA) [51], the European Conference on Infections in Leukaemia [52] and the European Society of Clinical Microbiology and Infectious Disease (ESCMID), European Confederation of Medical Mycology (ECMM) and European Respiratory Society (ERS) [53]. Some authorities recommend antifungal prophylaxis for selected solid organ transplant recipients [54,55], commenting that studies in these settings have been from non-randomised comparative trials with small patient numbers.

Several authors have published reports on the role of antifungal prophylaxis for the prevention of HCA-IA during construction/renovation work. Chabrol *et al* in their single centre experience showed a decreased incidence of IA in AML patients who received prophylaxis during building works near their haematology unit [56]. Prophylaxis with voriconazole formed part of a multi-faceted approach during major hospital construction contributing to the successful control of a HCA-IA outbreak in another centre [57]. Similarly, a retrospective single centre study showed that when an outbreak in haematology patients was experienced during hospital construction the addition of posaconazole prophylaxis to environmental control measures led to a reduction in further cases of IA [58]. A cost-effectiveness study on interventions for the prevention of IA during hospital construction revealed that the addition of antifungal prophylaxis to environmental control measures leads to higher costs. However it was shown to be more effective than environmental measures alone [59].

Patients receiving triazole prophylaxis should have therapeutic drug monitoring to ensure adequate serum concentrations are achieved and to allow for individualised optimised

dosing [52,53,60]. Given its global emergence, ongoing surveillance of triazole resistance in *A. fumigatus* is important [61]. A recent report on surveillance of *A. fumigatus* in a single centre during hospital demolition demonstrated that 15% (30/200) and 4% (6/152) of environmental and clinical isolates, respectively, were triazole-resistant [62]. Genotyping of the triazole-resistant isolates showed a polyclonal distribution [62].

Management of existing ventilation systems

Many areas of the hospital may have mechanical ventilation systems already in use. The specification of these units will have been determined at the time of their original design and subsequent installation. Upgrading may be required on existing installations depending on the patient type to be housed in these units, construction activity classification and overall risk assessment. It is important that all such units are reviewed at the time of planning, a risk assessment is undertaken and their appropriateness for the current situation is assessed. Temporary or permanent corrective measures may need to be in place as a consequence of the planned construction activity. These corrective measures should comply with local regulations and legislation such as the UK Health Technical Memorandum (HTM) 03 guidelines [63,64]. For healthcare facilities, relevant local engineering standards and technical guidelines must be referred to before designing the permanent correct solution. Where a room's environmental control system is made up of multiple components such as room-air, HEPA filter units, radiators, cooling units and toilet extract fans, indoor environmental conditions should be in accordance with relevant current indoor environmental control and building standards (e.g. HTMs/Health Building Notes (HBN)) [63–66].

Education and communication

Healthcare workers, cleaning staff, project managers, contractors and health and safety supervisors should be educated on the risk of invasive aspergillosis prior to construction taking place and during construction work whereby the infection control measures required to decrease its occurrence are explained. Clear communication through an institution-wide information campaign should also be provided. Patients and relatives should be provided with information leaflets.

II. Construction phase

Measures to reduce dust emission from the construction site

It is essential to utilise measures to minimise dust generation from construction or renovation sites which will ultimately depend on the type of construction activity (Supplementary Table I). An impermeable dust barrier from floor to slab/floor must be constructed and air-tightness ensured particularly if the works are proximal to clinical areas until the project is complete. Windows and doors should be sealed and a separate entrance away from patient traffic should be created for use by construction workers. Construction workers should wear protective clothing which should be removed when leaving the construction site. The direction of airflow between the construction zone and the existing hospital should be maintained in a clean to less clean direction by using a portable extract fan and to ensure this less clean air from the construction zone is exhausted directly to the outside where feasible and away from intake vents or filtered through a minimum of an F9 filter. Debris should be contained in covered containers and removed at the end of the work day. The work area should be cleaned and vacuumed with HEPA-filtered vacuums daily or more frequently if required [5,9,42,67].

Creating a protective environment

Because inhalation is the major route of acquisition of infection, an efficient and controlled ventilation system is essential in the prevention of nosocomial aspergillosis. The method by which patients are protected will depend on the IARA performed during the planning stage. If at all possible, patients should ideally be moved away from the construction area prior to commencing, and throughout the duration, of the construction works in order to decrease the risk of exposure to dust. It has been shown that the burden of airborne fungal spores is higher during the demolition stage when compared to the building work [68,69]. The IPCT and the patients' clinical team should assess the risk posed to the patients as detailed in the IARA. Patients at high and very high risk i.e. groups 3 and 4 (Table II) should preferably be treated in HEPA-filtered specialised ventilation isolation rooms (Supplementary Table IV). Based on published literature, positive pressure ventilated (PPV) rooms are currently recommended [4,40,42,70].

Positive pressure (PPV) rooms are designed to protect an immunocompromised patient from infectious diseases particularly those spread by the airborne route. PPV rooms have been

shown to protect vulnerable HSCT and acute leukaemia patients from fungal infections acquired by the airborne route [5,42,71,72].

Neutral pressure rooms have only been introduced into the healthcare setting over the last decade; consequently long-term “in use validation” of these rooms for all patient categories has not been established. The neutral pressure isolation room (i.e. a room with a Positive Pressure Ventilated Lobby, PPVL) has been designed to provide both protective and source isolation. The basic elements of the design are a positive pressure lobby with extensive air changes per hour (ACH), which helps prevent corridor air from entering the room. The patient room is at neutral pressure to the corridor and there is a negative extract, typically via the bathroom. To date, there has been no published report specifically investigating its effectiveness for protecting patients at risk for IA. Recently, Ryan *et al* compared the relative efficacy of PPVL and PPV rooms in reducing exposure to airborne mould elements in 2 hospitals in Ireland while in use. They showed the median *Aspergillus* spp. and total mould concentrations were similar in both room types which suggests that PPVL rooms provide protective isolation comparable to that of PPV rooms [73]. We note however that one of the PPVL rooms included did not have a properly designed positive pressure lobby. Clearly further studies are required to confirm their findings and for clinical validation of PPVL to provide protection against IA. Until then, the local IPCT is best placed to give advice regarding utilisation of PPVL rooms following individual patient assessments. Clear and good communication is required between HBS Estates and the local IPCT such that building and engineering controls are captured and agreed at project briefing stage for new capital works projects.

It is equally important to ensure that the essential elements of specialised ventilation rooms should be as per relevant technical guidelines such as the UK HTM 03-01 [63,64] and the HBN 04-01 supplements [65,66] requirements (Supplementary Table IV). Monitoring and documentation of compliance with these guidelines during construction work and contingencies should be in place in case of failure to meet the standards set.

Other measures to minimise exposure to airborne spores such as wearing surgical masks and limiting patient movements either for therapeutic or diagnostic reasons are also recommended [5,6,40,42,71].

Surveillance of nosocomial aspergillosis

It is imperative to maintain a high index of suspicion for the diagnosis of IA in the at-risk patients (Groups 2-4, Table II). This surveillance may be achieved through a diagnostic driven system using the European Organisation for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) revised definitions as a model for defining infections in high-risk patients [74]. Of note, these definitions were published 10 years ago. With the expansion of the type of patients at risk for IA, there clearly is a need for diagnostic criteria for other patient cohorts such as those with severe influenza requiring critical care and advanced COPD. Blot *et al* have validated a clinical diagnostic algorithm which may be useful for detection of IA in critical care patients [75]. Similarly, Bulpa *et al* have published diagnostic criteria for patients with COPD [76]. Bi-weekly serum galactomannan in high risked groups is suggested as a useful adjunct for detection of cases [58,69,77]. Nevertheless, cases should be reviewed at ward level and relevant microbiological, histological and post-mortem data should be checked regularly. Once a case of probable/proven IA has been identified, it is imperative to assess if the infection was healthcare or community-acquired. When confirmed to be nosocomial aspergillosis, a complete epidemiological investigation should be carried out immediately by a multidisciplinary team. The occurrence of two or more cases that are temporally related to each other or an incidence above the normal surveillance levels should prompt an investigation into the possibility of an environmental source. Genotypic analysis of *Aspergillus* spp. isolated from clinical and environmental samples should be considered to assist in identifying the possible source of the outbreak [78,79]. Such an approach has led to the detection of cases of suspected nosocomial IA [18,80].

III. Post construction Phase

The process for testing, commissioning and validation should be clearly set out in the contract documents, having been agreed in advance with the relevant IPCT advisors and the hospital management hospital maintenance manager along with HBS Estates representatives. The objective shall be to ensure that the Contractor achieves a satisfactory standard of construction and completion of all elements prior to issuing the Certificate for

Substantial Completion by the design team. The ventilation systems should be commissioned in accordance with relevant national guidance along with HTM 03-01 requirements [63,64] and HBN 04-01 supplements [65,66] where they apply. The AHU should be commissioned in accordance with relevant local technical guidelines such as the HTM 03-01 and the European standard EN 1886:2007 and EN 13053:2006+A1:2011 and witnessed by a competent independent third party [81,82].

Conclusion

Table V is a summary of the key measures recommended to prevent HCA-IA during construction/renovation work. Hospital construction works and the list of at-risk groups will continue to increase therefore it is important to ensure adherence to measures to prevent nosocomial IA at all times. It is important to emphasise that exposure to *Aspergillus* spp. and other moulds is not confined to the acute hospital setting. Continuing education and communication to the hospital staff and the patient are crucial for the prevention of invasive aspergillosis and/or other invasive mould infections. Further research on the role of PPVL isolation rooms and the critical minimum levels of airborne fungal spores to prevent IA are required.

References

[1] Garnaud C, Brenier-Pinchart M-P, Thiebaut-Bertrand A, Hamidfar R, Quesada J-L, Bosseray A, et al. Seven-year surveillance of nosocomial invasive aspergillosis in a French University Hospital. J Infect 2012;65:559–67. doi:10.1016/j.jinf.2012.08.006.

[2] Graf K, Khani SM, Ott E, Mattner F, Gastmeier P, Sohr D, et al. Five-years surveillance of invasive aspergillosis in a university hospital. BMC Infect Dis 2011;11:163. doi:10.1186/1471-2334-11-163.

[3] Stevens DA, Melikian GL. Aspergillosis in the “nonimmunocompromised” host. Immunol Invest 2011;40:751–66. doi:10.3109/08820139.2011.614307.

[4] Haiduven D. Nosocomial aspergillosis and building construction. Med Mycol 2009;47:210–6. doi:10.1080/13693780802247694.

[5] Suleyman G, Alangaden GJ. Nosocomial Fungal Infections: Epidemiology, Infection Control, and Prevention. Infect Dis Clin North Am 2016;30:1023–52. doi:10.1016/j.idc.2016.07.008.

[6] Partridge-Hinckley K, Liddell GM, Almyroudis NG, Segal BH. Infection control measures to prevent invasive mould diseases in hematopoietic stem cell transplant recipients. Mycopathologia 2009;168:329–37. doi:10.1007/s11046-009-9247-z.

[7] Lavergne R-A, Chouaki T, Hagen F, Toublanc B, Dupont H, Jounieaux V, et al. Home Environment as a Source of Life-Threatening Azole-Resistant Aspergillus fumigatus in Immunocompromised Patients n.d. doi:10.1093/cid/ciw664.

[8] Schweer K, Jakob B, Liss B, Christ H, Fischer G, Vehreschild M, et al. Domestic mould exposure and invasive aspergillosis—air sampling of *Aspergillus* spp. spores in homes of hematological patients, a pilot study. Med Mycol 2016;54:576–83. doi:10.1093/mmy/myw007.

[9] National Guidelines for the prevention of nosocominal aspergillosis. A Report of the Aspergillosis Subcommittee of the Health Protection Surveillance Centre Scientific Advisory Committee 2018. https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/infectioncontrolandhai/guidelines/Aspergillus Guidelines 2018.pdf (accessed September 9, 2018).

[10] Tilton RC and McGinnis MR. Opportunistic fungi. In: B.J. Howard, editor. Clin. Pathog. Microbiol., St. Louis, MO: C.V. Mosby Co.; 1987, p. 609–23.

[11] Samson, RA, Varga JDP. Morphology and reproductive mode of Aspergillus fumigatus. In: Latge, JP SW, editor. Aspergillus fumigatus, ASM Press Washington DC; 2009, p. 7–13.

[12] Rotstein C, Cummings KM, Tidings J, Killion K, Powell E, Gustafson TL, et al. An outbreak of invasive aspergillosis among allogeneic bone marrow transplants: a case-control study. Infect Control 1985;6:347–55.

[13] Perraud M, Piens MA, Nicoloyannis N, Girard P, Sepetjan M, Garin JP. Invasive nosocomial pulmonary aspergillosis: risk factors and hospital building works. Epidemiol Infect 1987;99:407–12.

[14] Anderson K, Morris G, Kennedy H, Croall J, Michie J, Richardson MD, et al. Aspergillosis in immunocompromised paediatric patients: associations with building hygiene, design, and indoor air. Thorax 1996;51:256–61.

[15] Oren I, Haddad N, Finkelstein R, Rowe JM. Invasive pulmonary aspergillosis in neutropenic patients during hospital construction: before and after chemoprophylaxis and institution of HEPA filters. Am J Hematol 2001;66:257–62. doi:10.1002/ajh.1054.

[16] Vonberg RP, Gastmeier P. Nosocomial aspergillosis in outbreak settings. J Hosp Infect 2006;63:246–54. doi:10.1016/j.jhin.2006.02.014.

[17] Chang CC, Cheng AC, Devitt B, Hughes AJ, Campbell P, Styles K, et al. Successful control of an outbreak of invasive aspergillosis in a regional haematology unit during hospital construction works. J Hosp Infect 2008;69:33–8.

doi:10.1016/j.jhin.2008.02.010.

[18] Steinbach WJ, Marr KA, Anaissie EJ, Azie N, Quan SP, Meier-Kriesche U, et al. Clinical Epidemiology of 960 Patients with Invasive Aspergillosis from the PATH Alliance registry. J Infect 2012. doi:10.1016/j.jinf.2012.08.003.

[19] Meersseman W, Vandecasteele SJ, Wilmer A, Verbeken E, Peetermans WE, Van Wijngaerden E. Invasive aspergillosis in critically ill patients without malignancy. Am J Respir Crit Care Med 2004;170:621–5. doi:10.1164/rccm.200401-093OC.

[20] Meersseman W, Lagrou K, Maertens J, Van Wijngaerden E. Invasive aspergillosis in the intensive care unit. Clin Infect Dis 2007;45:205–16. doi:10.1086/518852.

[21] Guinea J, Torres-Narbona M, Gijon P, Munoz P, Pozo F, Pelaez T, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. Clin Microbiol Infect 2010;16:870–7. doi:10.1111/j.1469-0691.2009.03015.x.

[22] Espinel-Ingroff A, Arendrup MC, Pfaller MA, Bonfietti LX, Bustamante B, Canton E, et al. Interlaboratory variability of Caspofungin MICs for Candida spp. Using CLSI and EUCAST methods: should the clinical laboratory be testing this agent? Antimicrob Agents Chemother 2013;57:5836–42. doi:10.1128/aac.01519-13.

[23] Pelaez T, Munoz P, Guinea J, Valerio M, Giannella M, Klaassen CHW, et al. Outbreak of invasive aspergillosis after major heart surgery caused by spores in the air of the intensive care unit. Clin Infect Dis 2012;54:e24–31.

[24] Wessolossky M, Welch VL, Sen A, Babu TM, Luke DR. Invasive Aspergillus infections in hospitalized patients with chronic lung disease. Infect Drug Resist 2013;6:33–9. doi:10.2147/IDR.S43069.

[25] Baddley JW, Stephens JM, Ji X, Gao X, Schlamm HT, Tarallo M. Aspergillosis in Intensive Care Unit (ICU) patients: epidemiology and economic outcomes. BMC Infect Dis 2013;13:29. doi:10.1186/1471-2334-13-29.

[26] van de Veerdonk FL, Kolwijck E, Lestrade PP, Hodiamont CJ, Rijnders BJ, van Paassen J, et al. Influenza-Associated Aspergillosis in Critically Ill Patients. Am J Respir Crit Care Med 2017. doi:10.1164/rccm.201612-2540LE.

[27] Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018;6:782–92. doi:10.1016/S2213-2600(18)30274-1.

[28] Sherif R, Segal BH. Pulmonary aspergillosis: clinical presentation, diagnostic tests, management and complications. Curr Opin Pulm Med 2010;16:242–50. doi:10.1097/MCP.0b013e328337d6de.

[29] Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive aspergillosis following

hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. Clin Infect Dis 2007;44:531–40. doi:10.1086/510592.

[30] Mayr A, Lass-Flörl C. Epidemiology and antifungal resistance in invasive Aspergillosis according to primary disease: review of the literature. Eur J Med Res 2011;16:153–7.

[31] Rhame FS. Prevention of nosocomial aspergillosis. J Hosp Infect 1991;18 Suppl A:466–72.

[32] Hansen D, Blahout B, Benner D, Popp W. Environmental sampling of particulate matter and fungal spores during demolition of a building on a hospital area. J Hosp Infect 2008;70:259–64. doi:10.1016/j.jhin.2008.07.010.

[33] Walsh TJ, Dixon DM. Nosocomial aspergillosis: environmental microbiology, hospital epidemiology, diagnosis and treatment. Eur J Epidemiol 1989;5:131–42.

[34] Rhame FS, Streifel AJ, Kersey JH, McGlave PB. Extrinsic risk factors for pneumonia in the patient at high risk of infection. Am J Med 1984;76:42–52.

[35] Weber DJ, Peppercorn A, Miller MB, Sickbert-Benett E, Rutala WA. Preventing healthcare-associated Aspergillus infections: review of recent CDC/HICPAC recommendations. Med Mycol 2009;47 Suppl 1:S199-209. doi:10.1080/13693780802709073.

[36] Kanamori H, Rutala WA, Sickbert-Bennett EE, Weber DJ. Review of fungal outbreaks and infection prevention in healthcare settings during construction and renovation. Clin Infect Dis 2015;61:433–44. doi:10.1093/cid/civ297.

[37] Shoham S, Marr KA. Invasive fungal infections in solid organ transplant recipients. Future Microbiol 2012;7:639–55. doi:10.2217/fmb.12.28.

[38] Pagano L, Akova M, Dimopoulos G, Herbrecht R, Drgona L, Blijlevens N. Risk assessment and prognostic factors for mould-related diseases in immunocompromised patients. J Antimicrob Chemother 2011;66 Suppl 1:i5-14. doi:10.1093/jac/dkq437.

[39] Chang CC, Ananda-Rajah M, Belcastro A, Mcmullan B, Reid A, Dempsey K, et al. Consensus guidelines for implementation of quality processes to prevent invasive fungal disease and enhanced surveillance measures during hospital building works, 2014. Intern Med J 2014;44:1389–97. doi:10.1111/imj.12601.

[40] Centers for Disease Control and Prevention, Infectious Disease Society of America, American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Reports Morb Mortal Wkly Report Recomm Reports 2000;49:1–125, CE1-7.

[41] Sehulster L, Chinn RYW, CDC, HICPAC. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Reports

Morb Mortal Wkly Report Recomm Reports 2003;52:1–42.

[42] SF2H-SFMM. Risk of fungal infections, and construction work in hospitals 2011. http://www.eunetips.eu/fileadmin/pdf/spi.fr.sf2h-sfmm_fungal_infections_vdef.pdf (accessed May 19, 2018).

[43] Health Building Note 00-09: Infection control in the built environment. 2012.

[44] CDC. Guidelines for Environmental Infection Control in Health-Care Facilities Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). n.d.

[45] Bartley J. Infection Control Risk Assessment Matrix of Precautions for Construction & Renovation. Construction 2009:1–5.

[46] Morris G, Kokki MH, Anderson K, Richardson MD. Sampling of Aspergillus spores in air. J Hosp Infect 2000;44:81–92. doi:10.1053/jhin.1999.0688.

[47] Health Protection Surveillance Centre National Guidelines for the Prevention of Nosocomial aspergillosis during hospital construction/renovation: A report of the Aspergillus Subcommittee of Health Protection Surveillance Centre Scientific Advisory Committ 2018. http://www.hpsc.ie/a-z/respiratory/aspergillosis/guidance/Aspergillus Appendix D 2018.pdf (accessed May 16, 2018).

[48] Reboux G, Gbaguidi-Haore H, Bellanger AP, Demonmerot F, Houdrouge K, Deconinck E, et al. A 10-year survey of fungal aerocontamination in hospital corridors: a reliable sentinel to predict fungal exposure risk? J Hosp Infect 2014;87:34–40. doi:10.1016/j.jhin.2014.02.008.

[49] Rogers TR, Slavin MA, Donnelly JP. Antifungal prophylaxis during treatment for haematological malignancies: are we there yet? Br J Haematol 2011;153:681–97. doi:10.1111/j.1365-2141.2011.08650.x.

[50] Ziakas PD, Kourbeti IS, Mylonakis E. Systemic antifungal prophylaxis after hematopoietic stem cell transplantation: a meta-analysis. Clin Ther 2014;36:292–306.e1. doi:10.1016/j.clinthera.2013.11.010.

[51] Patterson TF, Thompson Iii GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America n.d. doi:10.1093/cid/ciw326.

[52] Maertens JA, Girmenia C, Brüggemann RJ, Duarte RF, Kibbler CC, Ljungman P, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrob Chemother 2018:1–10. doi:10.1093/jac/dky286.

[53] Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017

ESCMID-ECMM-ERS guideline. Clin Microbiol Infect 2018;24 Suppl 1:e1–38. doi:10.1016/j.cmi.2018.01.002.

[54] Singh NM, Husain S. Aspergillosis in Solid Organ Transplantation Infectious Diseases Community of Practice n.d. doi:10.1111/ajt.12115.

[55] Muñoz P, Valerio M, Palomo J, Giannella M, Yañez JF, Desco M, et al. Targeted antifungal prophylaxis in heart transplant recipients. Transplantation 2013;96:664–9. doi:10.1097/TP.0b013e31829e6d7b.

[56] Chabrol A, Cuzin L, Huguet F, Alvarez M, Verdeil X, Linas MD, et al. Prophylaxis of invasive aspergillosis with voriconazole or caspofungin during building work in patients with acute leukemia 2010;95:996–1003. doi:10.3324/haematol.2009.012633.

[57] Chang CC, Cheng AC, Devitt B, Hughes AJ, Campbell P, Styles K, et al. Successful control of an outbreak of invasive aspergillosis in a regional haematology unit during hospital construction works. J Hosp Infect 2008;69:33–8. doi:10.1016/j.jhin.2008.02.010.

[58] Combariza JF, Toro LF, Orozco JJ. Effectiveness of environmental control measures to decrease the risk of invasive aspergillosis in acute leukaemia patients during hospital building work. J Hosp Infect 2017;96:336–41. doi:10.1016/j.jhin.2017.04.022.

[59] Combariza JF, Toro LF, Orozco JJ, Arango M. Cost-effectiveness analysis of interventions for prevention of invasive aspergillosis among leukemia patients during hospital construction activities. Eur J Haematol 2017:1–7. doi:10.1111/ejh.12991.

[60] Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother 2014;69:1162–76. doi:10.1093/jac/dkt508.

[61] Verweij PE, Ananda-Rajah M, Andes D, Arendrup MC, Bruggemann RJ, Chowdhary A, et al. International expert opinion on the management of infection caused by azole-resistant Aspergillus fumigatus. Drug Resist Updat 2015;21–22:30–40. doi:10.1016/j.drup.2015.08.001.

[62] Wirmann L, Ross B, Reimann O, Steinmann J, Rath P-M. Airborne Aspergillus fumigatus spore concentration during demolition of a building on a hospital area and patient risk determination for invasive aspergillosis including azole resistance. J Hosp Infect 2018. doi:10.1016/j.jhin.2018.07.030.

[63] Heating and ventilation systems Health Technical Memorandum 03-01: Specialised ventilation for healthcare premises Part B n.d. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/144030/HTM_03-01_Part_B.pdf (accessed May 16, 2018).

[64] Heating and ventilation systems Health Technical Memorandum 03-01: Specialised

ventilation for healthcare premises Part A n.d. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/144029/HTM_03-01_Part_A.pdf (accessed May 16, 2018).

[65] Health Building Note 04-01 Supplement 1 Isolation facilities for infectious patients in acute settings 2013. http://www.nationalarchives.gov.uk/doc/open-government-licence/ (accessed November 7, 2018).

[66] Department of Health UK. Health Building Note 04-01, Supplement 1 - Isolation facilities in acute settings. 2005.

[67] Loschi M, Thill C, Gray C, David M, Bagatha MF, Chamseddine A, et al. Invasive Aspergillosis in Neutropenic Patients During Hospital Renovation: Effectiveness of Mechanical Preventive Measures in a Prospective Cohort of 438 Patients. Mycopathologia 2015;179:337–45. doi:10.1007/s11046-015-9865-6.

[68] Pilmis B, Thepot-Seegers V, Angebault C, Weiss E, Alaabouche I, Bougnoux ME, et al. Could we predict airborne Aspergillus contamination during construction work? Am J Infect Control 2017;45:39–41. doi:10.1016/j.ajic.2016.08.003.

[69] Barreiros G, Akiti T, Magalhães ACG, Nouér SA, Nucci M. Effect of the implosion and demolition of a hospital building on the concentration of fungi in the air. Mycoses 2015;58:707–13. doi:10.1111/myc.12418.

[70] Eckmanns T, Rüden H, Gastmeier P. The influence of high-efficiency particulate air filtration on mortality and fungal infection among highly immunosuppressed patients: a systematic review. J Infect Dis 2006;193:1408–18. doi:10.1086/503435.

[71] Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15:1143–238. doi:10.1016/j.bbmt.2009.06.019.

[72] Humphreys H. Positive-pressure isolation and the prevention of invasive aspergillosis. What is the evidence? J Hosp Infect 2004;56:93–100. doi:10.1016/j.jhin.2003.10.011.

[73] Ryan L, O'Mara N, Tansey S, Slattery T, Hanahoe B, Vellinga A, et al. A 2-year comparative study of mold and bacterial counts in air samples from neutral and positive pressure rooms in 2 tertiary care hospitals. Am J Infect Control 2018;46:590–3. doi:10.1016/j.ajic.2017.10.019.

[74] De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, 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) C. Clin Infect Dis 2008;46:1813–21. doi:10.1086/588660.

[75] Blot SI, Taccone FS, Van Den Abeele AM, Bulpa P, Meersseman W, Brusselaers N,

et al. A Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients. Am J Respir Crit Care Med 2012;186:56–64.

[76] Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. Eur Respir J 2007;30:782–800. doi:10.1183/09031936.00062206.

[77] Kaya H, Ozaki J, Okumura H. Usefulness of <i>Aspergillus</i> Galactomannan Antigen Testing and the Prediction of an Outbreak during Hospital Reconstruction. Intern Med 2018. doi:10.2169/internalmedicine.0269-17.

[78] Guinea J, Garcia de Viedma D, Pelaez T, Escribano P, Munoz P, Meis JF, et al. Molecular epidemiology of Aspergillus fumigatus: an in-depth genotypic analysis of isolates involved in an outbreak of invasive aspergillosis. J Clin Microbiol 2011;49:3498–503. doi:10.1128/jcm.01159-11.

[79] Loeffert ST, Melloul E, Gustin M-P, Hénaff L, Guillot C, Dupont D, et al. Investigation of the Relationships Between Clinical and Environmental Isolates of Aspergillus fumigatus by Multiple-locus Variable Number Tandem Repeat Analysis During Major Demolition Work in a French Hospital. Clin Infect Dis 2018. doi:10.1093/cid/ciy498.

[80] Kidd SE, Ling LM, Meyer W, Morrissey CO, Chen SCA, Slavin MA. Molecular Epidemiology of Invasive Aspergillosis: Lessons Learned from an Outbreak Investigation in an Australian Hematology Unit. Infect Control Hosp Epidemiol 2009;30:1223–6. doi:10.1086/648452.

[81] EN 13053:2006+A1:2011. Ventilation for buildings.Air handling units. Rating and performance for units, components and sections n.d. https://standards.cen.eu/dyn/www/f?p=204:110:0::::FSP_PROJECT,FSP_ORG_ID:36865,6138&cs=195B5AEFB475F05C00EECDC4483B32A50 (accessed May 16, 2018).

[82] EN 1886:2007. Ventilation for buildings. Air handling units. Mechanical performance n.d. https://standards.cen.eu/dyn/www/f?p=204:110:0::::FSP_PROJECT,FSP_ORG_ID:21763,6138&cs=1F3A95F1A7AEA000F529FC0463D7E7177 (accessed May 16, 2018).

[83] Neofytos D, Treadway S, Ostrander D, Alonso CD, Dierberg KL, Nussenblatt V, et al. Epidemiology, outcomes, and mortality predictors of invasive mold infections among transplant recipients: A 10-year, single-center experience. Transpl Infect Dis 2013;15:233–42. doi:10.1111/tid.12060.

[84] Lortholary O, Gangneux JP, Sitbon K, Lebeau B, de Monbrison F, Le Strat Y, et al. Epidemiological trends in invasive aspergillosis in France: the SAIF network (2005-2007). Clin Microbiol Infect 2011;17:1882–9. doi:10.1111/j.1469-0691.2011.03548.x.

[85] Panackal AA, Li H, Kontoyiannis DP, Mori M, Perego CA, Boeckh M, et al.

Geoclimatic Influences on Invasive Aspergillosis after Hematopoietic Stem Cell Transplantation. Clin Infect Dis 2010;50:1588–97. doi:10.1086/652761.

[86] Rubio PM, Sevilla J, González-Vicent M, Lassaletta A, Cuenca-Estrella M, Díaz MA, et al. Increasing incidence of invasive aspergillosis in pediatric hematology oncology patients over the last decade: A retrospective single centre study. J Pediatr Hematol Oncol 2009;31:642–6. doi:10.1097/MPH.0b013e3181acd956.

[87] Mikulska M, Raiola AM, Bruno B, Furfaro E, Van Lint MT, Bregante S, et al. Risk factors for invasive aspergillosis and related mortality in recipients of allogeneic SCT from alternative donors: an analysis of 306 patients. Bone Marrow Transplant 2009;44:361–70. doi:10.1038/bmt.2009.39.

[88] Carvalho-Dias VMH, Sola CBS, Cunha CA da, Shimakura SE, Pasquini R, Queiroz-Telles F de. Invasive aspergillosis in hematopoietic stem cell transplant recipients: a retrospective analysis. Braz J Infect Dis 2008;12:385–9.

[89] Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of Invasive Mold Infections in Allogeneic Stem Cell Transplant Recipients: Biological Risk Factors for Infection According to Time after Transplantation. Clin Infect Dis 2008;47:1041–50. doi:10.1086/591969.

[90] Morgan J, Wannemuehler KA, Marr KA, Hadley S, Kontoyiannis DP, Walsh TJ, 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.

[91] 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. doi:10.1182/blood-2002-05-1496.

[92] Peppel RJ Van De, Visser LG, Dekkers OM, Boer MGJ De. The burden of Invasive Aspergillosis in patients with haematological malignancy: a meta-analysis and systematic review. J Infect 2018. doi:10.1016/j.jinf.2018.02.012.

[93] Pinney MF, Rosenberg AF, Hampp C, Schain D, Akindipe O, Baz M. Invasive Fungal Infections in Lung Transplant Recipients Not Receiving Routine Systemic Antifungal Prophylaxis: 12-Year Experience at a University Lung Transplant Center. Pharmacotherapy 2011;31:537–45. doi:10.1592/phco.31.6.537.

[94] Pasqualotto AC, Xavier MO, Sánchez LB, de Oliveira Costa CDA, Schio SM, Camargo SM, et al. Diagnosis of invasive aspergillosis in lung transplant recipients by detection of galactomannan in the bronchoalveolar lavage fluid. Transplantation 2010;90:306–11. doi:10.1097/TP.0b013e3181e49bc1.

[95] Iversen M, Burton CM, Vand S, Skovfoged L, Carlsen J, Milman N, et al. Aspergillus infection in lung transplant patients: incidence and prognosis. Eur J Clin Microbiol

Infect Dis 2007;26:879–86. doi:10.1007/s10096-007-0376-3.

[96] Raviv Y, Kramer MR, Amital A, Rubinovitch B, Bishara J, Shitrit D. Outbreak of aspergillosis infections among lung transplant recipients. Transpl Int 2007;20:135–40. doi:10.1111/j.1432-2277.2006.00411.x.

[97] Solé A, Morant P, Salavert M, Pemán J, Morales P, Valencia Lung Transplant Group. Aspergillus infections in lung transplant recipients: risk factors and outcome. Clin Microbiol Infect 2005;11:359–65. doi:10.1111/j.1469-0691.2005.01128.x.

[98] Singh N, Husain S. Aspergillus infections after lung transplantation: clinical differences in type of transplant and implications for management. J Heart Lung Transplant 2003;22:258–66.

[99] Minari A, Husni R, Avery RK, Longworth DL, DeCamp M, Bertin M, et al. The incidence of invasive aspergillosis among solid organ transplant recipients and implications for prophylaxis in lung transplants. Transpl Infect Dis 2002;4:195–200.

[100] Pacholczyk M, Lagiewska B, Lisik W, Wasiak D, Chmura A. Invasive fungal infections following liver transplantation - risk factors, incidence and outcome. Ann Transplant n.d.;16:14–6.

[101] Ju MK, Joo DJ, Kim SJ, Chang HK, Kim MS, Kim SI, et al. Invasive pulmonary aspergillosis after solid organ transplantation: diagnosis and treatment based on 28 years of transplantation experience. Transplant Proc 2009;41:375–8. doi:10.1016/j.transproceed.2008.11.006.

[102] Sharifipour F, Rezaeetalab F, Naghibi M. Pulmonary fungal infections in kidney transplant recipients: an 8-year study. Transplant Proc 2009;41:1654–6. doi:10.1016/j.transproceed.2009.02.072.

[103] Einollahi B, Lessan-Pezeshki M, Pourfarziani V, Nemati E, Nafar M, Pour-Reza-Gholi F, et al. Invasive fungal infections following renal transplantation: a review of 2410 recipients. Ann Transplant 2008;13:55–8.

[104] Aubron C, Pilcher D, Leong T, Cooper DJ, Scheinkestel C, Pellegrino V, et al. Aspergillus sp. isolated in critically ill patients with extracorporeal membrane oxygenation support. Scand J Infect Dis 2013;45:715–21. doi:10.3109/00365548.2013.797598.

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Table I. Incidence of invasive aspergillosis in at-risk groups

Category	Risk Group	% Incidence of IA	Study Design [Reference number]	Number of patients
Haematopoietic stem cell transplantation	Allogeneic haematopoietic stem cell transplant recipients	2.5	Retrospective single center [83]	106
		8.1	Prospective multicentre [84]	393
		8.8	Retrospective multicentre [85]	4213
		3.5	Retrospective single centre [86]	20
		15	Prospective single centre [87]	306
		3.0	Retrospective single centre [88]	61
		11.4	Retrospective single centre [89]	163
		2.3-3.9	Prospective multicentre [90]	8731
		7.3-10.5	Prospective single centre [91]	327
		7.66-9.23	Systematic review 49 articles [92]	16815
	Autologous haematopoietic stem cell transplant recipients	0.9	Prospective multicentre [84]	393
		1.3	Retrospective multicentre [85]	4213
		1.2	Retrospective single centre [86]	20
		0.5	Prospective multicentre [90]	8731
Solid organ transplantation	Lung transplant recipients	4.1	Retrospective single centre [12]	46
		4.5	Retrospective single centre [93]	242
		13.3	Prospective single centre [94]	60
		6.6	Retrospective single centre [95]	362
		7.0	Retrospective single centre [96]	115
		7.6	Retrospective single centre [97]	251
		6.2*	Review, 40 studies [98]	159
		12.8	Retrospective single centre [99]	2046
	Liver transplant recipients	0.8	Prospective multicentre [84]	393
		3.4	Retrospective single centre [100]	175
		0.77	Retrospective single centre [101]	3215
		0.7	Retrospective single centre [99]	2046
	Heart transplant recipients	4.8	Prospective multicentre [84]	393
		0.4	Retrospective single centre [99]	2046
	Renal transplant recipients	0.3	Prospective multicentre [84]	393
		0.24	Retrospective single centre [101]	3215
		1.3	Retrospective single centre [102]	595
		0.12	Retrospective single centre [103]	2410

		0.4	Retrospective single centre [100]	175
Other	Intensive care patients	0.02	Retrospective multicentre cohort study [25]	412
		0.52	Prospective single centre [23]	Approximately 600
	Severe influenza intensive care patients	19%	Retrospective multicentre [27]	432
	COPD patients	0.36	Retrospective single centre [21]	239
	ECMO† patients	2.6	Retrospective single centre [104]	151

*Median incidence based on review of literature
†ECMO=Extracorporeal membrane oxygenation

Table II. Categorisation of at-risk groups for Invasive Aspergillosis

Group 1 - No evidence of risk[1]

1. Staff members[2], service providers and contractors
2. All patients not listed in Groups 2-4 below

Group 2 - Increased risk

1. Patients on prolonged courses of high dose steroids[3] or tumour necrosis factor α (TNF- α) antagonists, particularly those hospitalised for prolonged periods
2. Severely immunosuppressed AIDS patients
3. Patients undergoing mechanical ventilation
4. Non-neutropenic patients on chemotherapy[4]
5. Dialysis patients

Group 3 - High risk

1. Patients with neutropenia for less than 14 days following chemotherapy
2. Autologous haematopoietic stem cell transplantation[6], i.e. during the neutropenic period
3. Adult acute lymphoblastic leukaemia patients on high dose steroid therapy[3]
4. Solid organ transplantation
5. Patients with Chronic Granulomatous Disorder (CGD)
6. Neonates in intensive care units
7. COPD patients meeting GOLD stage III and IV criteria[5], patients with severe influenza and in intensive care or high dependency units
8. Patients with extensive burns

Group 4 - Very high risk

1. Allogeneic haematopoietic stem cell transplantation[6]
    a. during the neutropenic period
    b. with graft-versus-host disease requiring steroid ± other immunosuppressive therapy
2. Acute myeloid leukaemia
3. Non-myeloablative transplantation
4. Children with severe combined immunodeficiency syndrome (SCID)
5. Prolonged neutropenia for greater than 14 days following chemotherapy or immunosuppressive therapy
6. Aplastic anaemia patients

Note: Cystic fibrosis patients should also be considered. Each cystic fibrosis patient is assigned to one of the above four categories depending on the stage of his/her illness.

[1] Assuming no known immunocompromise

[2] Staff should be informed of pending construction projects, and staff concerned re immunocompromise should be referred to Occupational Health

[3] Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks (De Pauw *et al*, 2008) (78)

[4] ANC count >1 x 10^9/l

[5] Furthermore, wards with a high occupancy of COPD patients (e.g. respiratory wards) meeting GOLD stage III and IV criteria should be risk assessed on the basis of the patients' levels of immunosuppression, and the threat posed to the patients by the construction activity. However, the guideline group recognise it is not possible to risk assess all COPD patients meeting GOLD stage III and IV criteria who are dispersed throughout the hospital.

[6] Includes bone marrow transplantation patients

Table III. Matrix of construction project activity type, patient risk group and class of required infection prevention and control precautions

	Construction Activity Type				
Patient Risk Group	**TYPE A1**	**TYPE A2**	**TYPE B**	**TYPE C**	**TYPE D**
Group 1 – No evidence of risk	**0**	**I**	**I**	**III**	**III**
Group 2 – Increased risk	**0**	**I**	**II**	**III**	**III**
Group 3 – High risk	**I**	**I**	**II**	**III**	**III**
Group 4 – Very high risk	**I**	**I**	**II**	**III**	**III**

This matrix was adapted from Infection Control Risk Assessment Matrix of Precautions for Construction & Renovation from the Association of Professionals in Infection Control and Epidemiology [4]

Note 1: Engagement with the IPCT is required irrespective of type of construction activity.

Note 2: This is a guide and if specific risk issues are identified, an individual risk assessment of that issue may be required.

Table IV. Summary of Consensus guidelines on antifungal prophylaxis against invasive aspergillosis (Grading of evidence is shown in brackets)*

Type of Patient	**European Conference on Infections in Leukaemia (ECIL, 2018)** [52]	**Infectious Diseases Society of America (IDSA, 2016)** [51]	**European Society of Clinical Microbiology and Infectious Disease-European Confederation of Medical Mycology-European Respiratory Society (ESCMID-ECMM-ERS, 2018)** [53]
Induction Chemotherapy in acute myeloid leukaemia	Posaconazole (AI) Itraconazole (BI) Aerosolised liposomal amphotericin B with fluconazole (BI) Voriconazole BII	Posaconazole (strong recommendation; high quality evidence) Voriconazole (strong recommendation; moderate quality evidence)	Posaconazole (AI) Aerosolised liposomal amphotericin B with fluconazole (BI) Voriconazole (CII)
Induction chemotherapy in Acute lymphoblastic leukaemia	No recommendations	No recommendations	Liposomal amphotericin B (BII)
Allogeneic haematopoietic stem cell transplant (HSCT) recipients, neutropenic phase	Voriconazole (BI) Itraconazole (BI) Posaconazole (BII) Aerosolised liposomal amphotericin B with fluconazole (BII) Micafungin (CI) Intravenous polyene (CII)	No recommendations	Posaconazole oral (BII) Aerosolised liposomal amphotericin B with fluconazole(BII) Micafungin (CI) Voriconazole (CI) Itraconazole (DI)
Allogeneic HSCT recipients with graft versus host disease (GVHD)	Posaconazole (AI) Itraconazole (BI) Voriconazole (BI) Micafungin (CII) Liposomal amphotericin B (CII)	Posaconazole (strong recommendation; high quality evidence) Itraconazole (strong recommendation; high quality evidence) Voriconazole (strong recommendation; moderate	Posaconazole oral (AI) Voriconazole (CII) Itraconazole (CII) Micafungin (CIII)

		quality evidence)	
Patients with prolonged neutropenia (Hematologic disorders with poorly functioning neutrophils (eg, aplastic anaemia and variants thereof, MDS), acute leukaemia with repeated and/or prolonged neutropenia, or a history of IA prior to transplantation)	Posaconazole (AI) Itraconazole (BI) Aerosolised liposomal amphotericin B with fluconazole (BI) Voriconazole BII	Posaconazole (strong recommendation; high quality evidence) Voriconazole (strong recommendation; moderate quality evidence) Micafungin (weak recommendation; low quality evidence)	Posaconazole oral (AI) Aerosolised liposomal amphotericin B with fluconazole(BI) ABLC (CII) Micafungin (CII) Liposomal Amphotericin B (CII) Voriconazole (CII) Itraconazole (DII)
Lung transplant recipients	No recommendations	Voriconazole, itraconazole or inhaled amphotericin B for 3 to 4 months after transplant (strong recommendation; moderate quality evidence)	No recommendations

*Note: not all the recommendations in these guidelines are licenced indications/approvals for use
For the most up to date guidelines, please refer to the relevant websites of the Infectious Diseases Society of America (IDSA), the European Conference on Infections in Leukaemia (ECIL), the European Society of Clinical Microbiology and Infectious Disease (ESCMID), the European Confederation of Medical Mycology (ECMM) and the European Respiratory Society (ER

Table V. Summary of Key Recommendations for the prevention of nosocomial IA during Construction/Renovation in Acute Care settings

Planning and pre-construction phase

Measures should be taken to protect patients at risk of acquiring *Aspergillus* infection as a consequence of hospital renovation, construction or demolition work in or near to clinical areas.

Hospital management must give sufficient notice (appropriate to the complexity of the project) to all interested parties including the IPCT of any planned activities before they start so that a comprehensive Invasive Aspergillosis Risk Assessment is performed and appropriate preventive measures can be put in place to protect vulnerable patients.

The hospital Infection Prevention and Control Team (IPCT) should take the lead in informing management of the risks involved by drafting local policies based on national and international guidelines.

Contractors must agree to, and sign, a Construction Permit and be compliant with the local Infection Prevention and Control policy.

Surveillance of fungal spore burden by microbiological air sampling should be performed prior to the build to establish baseline levels and throughout the duration of the construction/renovation activity

Education and communication to hospital staff on the measures to prevent nosocomial IA

Construction Phase

Major internal or external works may require transfer of at-risk patients to another part of the hospital if the environment cannot be protected from ingress of airborne fungal spores.

Affected clinical areas should be monitored for ingress of dust in spite of preventive measures, and in the highest risk groups air sampling should be used to monitor fungal counts.

High-efficiency particulate air (HEPA)-filtered positive pressure facilities are preferred for the protection of high and very high-risk patients during major internal, and non-containable external activities.

In consultation with the clinical team(s) involved, consideration should be given to prescribing antifungal drug prophylaxis in selected patients based on a risk assessment.

Microbiological air sampling should continue throughout this phase

Patients should be monitored throughout the project for clinical, radiological and mycological evidence that would suggest a diagnosis of invasive pulmonary aspergillosis.

The Microbiology laboratory should inform the IPCT of any increase in isolation of *Aspergillus* spp. from respiratory and air sampling specimens that are above baseline/expected rates.

Post-Construction Phase

Commissioning and validation should be performed by a competent third party and meet international standards