



Health Protection Surveillance Centre

NATIONAL GUIDELINES FOR THE PREVENTION OF NOSOCOMIAL ASPERGILLOSIS

A Report of the Aspergillosis Subcommittee of the
Health Protection Surveillance Centre
Scientific Advisory Committee

January 2018

ISBN: 978-0-9565622-6-5



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive



Table of Contents

	Page
Abbreviations	3
Membership of the Aspergillosis Subcommittee	4
Terms of Reference	5
Acknowledgements	5
Foreword	6
Key recommendations	7
Chapter 1: Nosocomial Aspergillosis	8
1.1 Introduction	8
1.2 Literature Review	8
Chapter 2: At-Risk Patients and Risk Factors	10
2.1 Introduction	10
2.2 Classification of At-Risk Patients	13
Chapter 3: Preventive Measures to Control Invasive Aspergillosis	14
3.1 Introduction	14
3.2 Membership of the Multidisciplinary Team	14
3.3 Invasive Aspergillosis Risk Assessment	14
3.4 Invasive Aspergillosis Risk Assessment Process	15
3.5 Pressurised Ventilation Systems for Patient Isolation	19
3.5.1 Positive pressure room	19
3.5.2 Neutral pressure room	21
3.5.3 Negative pressure room	23
3.5.4 Management of existing ventilation systems	24
3.5.5 Room air filter units (fixed or portable)	24
3.5.6 Upgrade and refurbishment activities	24
3.6 Chemoprophylaxis and Prevention of Invasive Aspergillosis	26
Chapter 4: Surveillance and Diagnostic Strategies	28
4.1 Surveillance of Invasive Aspergillosis	28
4.1.1 Introduction	28
4.1.2 EORTC/MSG case definitions for invasive fungal infection	28
4.1.3 Recommendations	29
4.2 Clinical and Laboratory Diagnosis of Invasive Aspergillosis	29
4.3 Microbial Air Sampling	31
References	33
Appendix A: Nosocomial Invasive Aspergillosis Preventive Measures Compliance Checklist	38
Appendix B: Pre-Project Planning and Contractor Advice	39
Appendix C: Sample Construction Permit	45
Appendix D: Sample Template of a Hospital Policy Document	47
Appendix E: Ventilation and Environmental Control Measures for Isolation Rooms	48
Appendix F: Commissioning and Validation of Ventilation Equipment and Systems	53
Appendix G: General Air Filter Selection Guidelines	54
Appendix H: ISO 16890 - Air Filters for General Ventilation	59
Appendix I: Checklist of Action Points in the Event of a Suspected Cluster of Cases of Invasive Aspergillosis	61
Appendix J: Information Leaflet on Aspergillosis during Construction Activities	62
Appendix K: Frequently Asked Questions (FAQs)	63

List of Tables

Table 1:	Incidence of invasive aspergillosis in at-risk groups	11
Table 2:	Characteristics of 960 patients with invasive aspergillosis 2004-2008	13
Table 3:	Details of the type of construction project activity	15
Table 4:	Description of the required infection prevention and control precautions	16
Table 5:	Matrix of construction project activity type, patient risk group and class of required infection prevention and control precautions	18
Table 6:	Checklist prior to contractor handover following upgrade and refurbishment activities	25
Table 7:	Consensus guidelines on antifungal prophylaxis against invasive aspergillosis	27
Table 8:	Interpretation of air sampling data and recommendations	32
Table A1:	Engineering specifications for positive, neutral and negative pressure isolation rooms	52
Table A2:	Classification of EPA, HEPA and ULPA filters as per EN 1822	55
Table A3:	<i>Aspergillus</i> engineering and filter risk assessment table/matrix	58
Table A4:	ISO 16890 classification table	60
Table A5:	Filter classification based on EN 779:2012 and ISO 16890	60
Table A6:	ISO 16890 filter groups	60

List of Figures

Figure 1:	Simplified schematic representation of a positive pressure isolation room	20
Figure 2:	Simplified schematic representation of a neutral pressure isolation room	22
Figure 3:	Simplified schematic representation of a negative pressure isolation room	23
Figure A1:	Detailed illustrative example of a positive pressure isolation room	49
Figure A2:	Detailed illustrative example of a neutral pressure isolation room	50
Figure A3:	Detailed illustrative example of a negative pressure isolation room	51
Figure A4:	ISO 16890 filter classification	59

Abbreviations

ACH	Air changes per hour
AHU	Air handling unit
AML	Acute myelogenous leukaemia
ANC	Absolute neutrophil count
BDG	β -D-glucan
BEMS	Building Energy Management System
CFU	Colony forming units
CGD	Chronic granulomatous disorder
CT	Computerised tomography
COPD	Chronic obstructive pulmonary disease
DPC	Discrete particle counter
ECIL	European Conference on Infections in Leukaemia
ECMO	Extracorporeal membrane oxygenation
EORTC/MSG	European Organisation for Research and Treatment of Cancer and Mycoses Study Group
EPA	Efficiency particulate air (filter)
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GVHD	Graft-versus-host disease
HBN	Health Building Note
HBS	Health Business Services
HEPA	High-efficiency particulate air (filter)
HLA	Human leukocyte antigen
HPSC	Health Protection Surveillance Centre
HSCT	Haematopoietic stem cell transplant
HSSD	Hospital sterile supply department
HTM	Health Technical Memorandum
IA	Invasive aspergillosis
IARA	Invasive Aspergillosis Risk Assessment
IPCT	Infection Prevention and Control Team
ICU	Intensive care unit
IDSA	Infectious Disease Society of America
LCC	Life cycle costing
MDT	Multidisciplinary team
MLE	Minimum life efficiency
MRI	Magnetic resonance imaging
MPPS	Most penetrating particle size
NICU	Neonatal intensive care unit
NIOSH	National Institute for Occupational Safety and Health
OCT	Outbreak Control Team
ODI	Optical density index
Pa	Pascals
PATH	Prospective Antifungal Therapy Alliance
PPE	Personal protective equipment
PPVL	Positive pressure ventilated lobby
RIAI	Royal Institute of the Architects of Ireland
SCID	Severe Combined Immunodeficiency Syndrome
ULPA	Ultra low particulate air (filter)

Membership of the Aspergillosis Subcommittee

Professor Tom Rogers (Chair)

Professor of Clinical Microbiology, Trinity College and Consultant Microbiologist, St James's Hospital, Dublin

Dr Colette Bonner

Deputy Chief Medical Officer, Department of Health

Mr Gareth Davies

HSE - National Directorate of Estates

Dr Eoghan de Barra

Infectious Diseases Society of Ireland; until June 2012

Dr Lynda Fenelon

Consultant Microbiologist, St Vincent's University Hospital, Dublin

Margaret Fitzgerald PhD

Senior Surveillance Scientist, HSE - Health Protection Surveillance Centre

Mr Sean Mahon

Royal Institute of the Architects of Ireland

Dr Olive Murphy

Consultant Microbiologist, Bon Secours Hospital, Cork

Ms Angela O'Donoghue

Infection Prevention Society

Dr Niamh O'Sullivan

Consultant Microbiologist, Our Lady's Children's Hospital, Crumlin, Dublin

Mr Brendan Redington

HSE - National Directorate of Estates

Dr Alida Fe Talento

Lecturer in Clinical Microbiology, Trinity College Dublin and Temporary Consultant Microbiologist,
St James's Hospital, Dublin

From July 2012, in place of Dr de Barra

Terms of Reference

To review the recommendations of the 2002 national guidelines on the prevention of nosocomial invasive aspergillosis during construction/renovation activities and update if required.

Acknowledgements

The subcommittee would like to acknowledge the generous assistance of the following:

Ms Tracey Wall (Clinical Nurse Manager) and Mr Christy Connolly (Technical Engineer) for facilitating a guided tour of the intensive care unit at Our Lady's Children's Hospital, Crumlin. Mr Joe Hoare (Health Service Executive Estates West) for facilitating a guided tour of the intensive care and high dependency units and cardiac wards at the University Hospital, Limerick. Mr Kim Featherstone and Mr Niall McElwee (Estates) for facilitating a guided tour of the intensive care and leukaemia units at St James's Hospital, Dublin.

Dr Breida Boyle for sharing the St James's Hospital's "Infection Prevention and Control Recommendations for HCAI Invasive Aspergillosis during Construction Policy" document.

Ms Kirsty MacKenzie, Health Protection Surveillance Centre, for providing administrative support and for conducting the online survey on the original national guidelines for the prevention of nosocomial invasive aspergillosis during construction/renovation activities, 2002.

Mr Peter Hofmann, Consultant Clinical Scientist, Antimicrobial Resistance and Healthcare-associated Infections Reference Unit, Public Health England, UK, and Mr Malcolm Thomas, Consulting Engineer, Bristol UK for their helpful discussions and advice.

Foreword

The first version of the National Aspergillosis Prevention Guidelines were well received and since 2002 have helped to guide infection control practice in healthcare facilities where there is an ongoing risk of nosocomial aspergillosis.

Nevertheless, the risk of aspergillosis occurring as a complication of building or renovation works on the sites of healthcare facilities continues. In some cases there are major building projects occurring on existing hospital campuses where the population of immunocompromised patients is significant.

Therefore, it was felt that the original guidelines could be usefully reviewed and updated where appropriate. There have been some important changes in practice with relation to isolation facilities, antifungal therapies and fungal diagnostics. Added to this is the emergence of *A. fumigatus* strains with triazole resistance. All of these topics, and more, have been addressed taking note of recent publications that update our knowledge.

The continuing need for a multidisciplinary approach to prevention of aspergillosis is again emphasized, as is the importance of good communication between departments in advance of any potentially hazardous maintenance or new works. A grading system is presented which should facilitate risk assessment and identify appropriate preventive measures.

On this occasion the guidelines are only being published on the HPSC website and not in hard copy format, but this will enable any important updates to be made as new information becomes available.

I would like to thank the members of the committee for their continuing support, and also I thank Dr Margaret Fitzgerald who coordinated meetings, drafted updates and produced the final version of the guidelines.

Professor Tom Rogers

Chair of the Aspergillosis Subcommittee

Key Recommendations

- Measures should be taken to protect the growing populations of patients at-risk of acquiring *Aspergillus* infection as a consequence of hospital renovation, construction or demolition work in or near to clinical areas.
- 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.
- 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 risk assessment and appropriate preventive measures can be put in place to protect vulnerable patients.
- Contractors must agree to, and sign, a Construction Permit and be compliant with the local Infection Prevention and Control policy.
- 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.
- 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 specimens that are above baseline/expected rates.

Chapter 1: Nosocomial Aspergillosis

1.1 Introduction

Nosocomial aspergillosis is now well described and a better understanding of the disease and preventive strategies has resulted in a reduction in the incidence and mortality in certain high-risk populations, such as prolonged neutropenia, and haematopoietic stem cell transplantation, where appropriate preventive measures have been taken (1, 2). However, recent data have also identified changes in the epidemiology of aspergillosis with the recognition of a much broader group of at-risk patients including those with chronic obstructive pulmonary disease (COPD), burns, chronic granulomatous disorder (CGD), cystic fibrosis, neonates, and also some patients not typically regarded as immunocompromised (3). In terms of risk exposures, 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. However, other risk exposures for nosocomial aspergillosis may also be important and healthcare providers must ensure that all recognised risks are minimised.

1.2 Literature Review

Aspergillus species are ubiquitous fungi that commonly occur in soil, water, organically enriched debris and decaying vegetation (4). 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 (5). *Aspergillus flavus*, *A. terreus*, *A. nidulans* and *A. niger* invasive infections are relatively less common. In general, the host's innate immunity deals with the regular inhalation of *Aspergillus* spores. However, *Aspergillus*-related diseases can be associated with a spectrum of immune disorders and result in a wide variety of human illnesses ranging from colonisation of the bronchial tree and allergic type reactions to rapidly invasive and disseminated disease (6, 7). Invasive aspergillosis (IA) is primarily an infection of severely immunocompromised patients, i.e. patients with haematological malignancies undergoing intensive remission-induction chemotherapy, haematopoietic stem cell transplantation or solid organ transplant recipients (1, 8-14). However, over the last decade it has been increasingly recognised that patients without known immunocompromise who are critically ill or have severe COPD are at increased risk of IA (15-20). Underlying lung damage, malnutrition, the prolonged use of corticosteroids, and antibiotics are thought to have played a role in the emergence of IA in COPD patients (21).

Despite advances in our understanding of the interaction between *Aspergillus* species and the human host, and important advances in the diagnosis of IA, and in the use of antifungal agents (22), this disease remains difficult to diagnose and treat and case fatality associated with IA remains high (12, 23), thus, making prevention a priority in the management of at-risk patients. Recently, antifungal drug resistance, particularly affecting the triazole class, has been described and this development threatens future preventive and therapeutic options (24).

In the healthcare setting a number of environmental risks are recognised although some are better defined than others. One of the major environmental risks continues to be exposure to construction work and the relationship between construction activities and generation of *Aspergillus* and other mould spores is well described. Aspergillosis outbreaks have also been associated with improper operation and poor maintenance of sophisticated air ventilation systems. Dust generating activities such as maintaining the ventilation system, cleaning, vacuuming and dry mopping can also render *Aspergillus* spp. airborne. *Aspergillus* spores have also been detected in water systems (25); however, there have been no reported outbreaks of aspergillosis traced to water sources (12). In neonates, infection with *Aspergillus* has been linked primarily to cutaneous conditions. For example a case in a premature neonate has been associated with contaminated non-sterile disposable gloves used when delivering care (26).

Aspergillus spores are well adapted to airborne dissemination (27, 28). These spores 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. Airborne transmission is the principal route of transmission of *Aspergillus* within the hospital environment. 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 (29). 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 (30).

Nosocomial (i.e. hospital acquired) outbreaks of aspergillosis have become a well-recognised complication of construction, demolition or renovation work in or near hospital wards in which immunosuppressed patients are housed (31-33). Cases of aspergillosis may increase during hospital construction/renovation activities and hospital outbreaks of aspergillosis have been reported, for example, in transplantation units (34-37), haematology and oncology units (10, 13, 38-41), intensive care units (18, 42-45), a renal unit (46) and medical wards where immunosuppressed patients were housed (11, 47-48), and occasionally in non-immunosuppressed patients (17, 49).

In a review of nosocomial outbreaks of *Aspergillus* infection between 1966 and 2005, 53 outbreaks, affecting 458 patients, were identified (12). The majority of cases had an underlying haematological malignancy (65%) and this group also had the highest case fatality rate (57.6%). Although IA outbreaks occurred primarily in immunosuppressed patients, infection also occurred in patients without severe immunodeficiency including those with COPD. 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 immunosuppressed patients.

In the case of neonates, a recent report described a cluster of invasive cutaneous infections that occurred in a neonatal intensive care unit possibly due to the airborne contamination of incubators from a ventilation system (44). The risk and outcome in other paediatric patients have also recently been reviewed (50). In terms of adult patients in ICUs the risks and pathogenesis of IA remain poorly defined, although there is evidence that the incidence has increased over the last 10 years (16).

To date, the majority of the outbreaks reported have been related to contamination of the hospital air as a result of the dust and dirt raised during construction, demolition or renovation projects within or adjacent to the healthcare facility. Specific construction/maintenance activities included: (i) general construction and renovation work, (ii) disturbance of soil resulting from earth works associated with building construction and site development, (iii) removal of suspended ceiling tiles, (iv) removal of fibrous insulation material, (v) opening up of service distribution shafts.

Based on the current trends in medicine the number of at-risk patients will continue to increase in the coming years. It is also likely that, as our understanding of this disease increases, other vulnerable groups will be identified. In addition, hospitals that house these patients will have ongoing refurbishment and construction projects either within or near the hospital. Both of these factors will ensure that we continue to be challenged with protecting these patients and optimising diagnostic, therapeutic and preventive strategies.

Chapter 2: At-Risk Patients and Risk Factors

2.1 Introduction

Factors that impact on the risk for developing an invasive fungal infection include the patient's environmental exposure and/or colonisation with potentially pathogenic fungi, use of antifungal prophylaxis, as well as the net state of immunosuppression (51). The latter refers to the combined impact of immune suppressing factors, such as haematological diseases, anti-rejection therapies post-transplant, oncology chemotherapies, inherited and acquired immunodeficiency and a rapidly expanding range of immunosuppressing therapies for inflammatory disorders. Host immunity plays a major role in determining who may be at risk of developing IA. When a patient with a normal immune system is exposed to *Aspergillus* spp., macrophages kill the conidia while neutrophils are a defence against the mycelia (52). When the host is immunocompromised, an increased likelihood of invasion of tissue by *Aspergillus* spp. can occur (53).

The major risk factor for IA is prolonged and severe neutropenia, both disease- and therapy-induced. The risk of IA correlates strongly with the duration and degree of neutropenia. The overall incidence of IA has been in decline in centres implementing preventive measures. In a German centre, rates dropped from 24 cases per 100,000 patient days in 2003 to 4 cases per 100,000 patient days in 2007 coinciding with changes in antifungal prophylaxis (2). Graf *et al.* (2) found that 44% of cases of IA were classified as nosocomial. Most of this is likely related to the patients' immunosuppression and underlying illness rather than poor infection control. A similar seven-year study in France found 30% of cases to be nosocomial, with 80% of these cases occurring in areas of the hospital lacking a specific air treatment facility (1). Indeed all of the nosocomial cases in the Garnaud study (1) occurred in the absence of air treatment and/or during construction works. These studies support the need to identify patients at risk and put in place appropriate preventive measures. The incidence of IA in at-risk groups is shown in Table 1. However, not all cases of *Aspergillus* infection that present clinically as IA in the hospital are nosocomially acquired as patients may already be colonised with *Aspergillus* spp. prior to starting immunosuppressive therapy (54).

Haematopoietic stem cell transplant (HSCT) recipients are the population at highest risk. Over the last five to ten years a decreased incidence of IA has been seen in this group, due to improved preventive measures of isolation and antifungal prophylaxis (2). Other immunosuppressive conditions have frequently been reported as risk factors for construction related nosocomial fungal infections: graft-versus-host disease requiring treatment, prolonged neutropenia following cytotoxic chemotherapy, prolonged use of antibiotics, steroid therapy, and tumour necrosis factor α antagonists (54). 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.

More recently IA has been described in patients who do not have these traditional risk factors (3, 15-16). Nosocomial outbreaks have been reported amongst paediatric and adult patients in intensive care units (18, 50). IA is also increasingly being diagnosed in patients with COPD (55). COPD patients meeting stage III or IV of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for severity of COPD were at higher risk of IA (56). Though many of these infections are likely to be community rather than healthcare in origin, COPD patients with GOLD stage III and IV are at greater risk of acquiring IA in the intensive care unit, especially once mechanically ventilated (16).

Patients with extensive burns are also at risk of cutaneous *Aspergillus* infection which may progress to invasive disease (57).

Table 2 is an extract from data published by the Prospective Antifungal Therapy (PATH) registry (14). Cases of proven and probable IA were recorded prospectively between 2004 and 2008 in 25 centres in the United States and Canada. The absence of denominator data means there is no calculated incidence but it offers meaningful observations on the broad variety of patients in whom IA has been diagnosed and the relative frequencies between groups.

The timing of IA varies between the risk groups. For patients with acute leukaemia, 68% of IA may occur in the induction phase of chemotherapy, 27% during consolidation (58). Of the patients with IA post-HSCT in the same study, IA occurred in 19% at <40 days; 13% 40-99 days; and 68% $\geq$ 100 days. The PATH Registry (14) showed the median day of diagnosis of IA post-HSCT was 97 days. IA post solid organ transplant tends to occur over a broader time distribution, the majority in heart transplants being within 12 weeks of transplantation and at least 100 days after surgery for other transplants (58).

Table 1. Incidence of invasive aspergillosis in at-risk groups

Category	Risk Group	Incidence of IA %	Reference number
Haematopoietic stem cell transplantation	Allogeneic haematopoietic stem cell transplant recipients	2.5	59
		8.1	58
		8.8	60
		3.5	61
		15	62
		3.0	63
		11.4	64
		2.3-3.9	65
		7.3-10.5	66
	Autologous haematopoietic stem cell transplant recipients	0.9	58
		1.3	60
		1.2	61
		0.5	65
Solid organ transplantation	Lung transplant recipients	4.1	8
		4.5	67
		13.3	68
		6.6	69
		7.0	37
		7.6	70
		6.2*	71
		12.8	72
	Liver transplant recipients	0.8	58
		3.4	73
		0.77	74
		0.7	72
	Heart transplant recipients	4.8	58
		0.4	72
	Renal transplant recipients	0.3	58
		0.24	74
		1.3	75
		0.12	76
		0.4	72
Other	Intensive care patients	0.02	20
		0.52	18
	COPD patients	0.36	17
	ECMO [†] patients	2.6	77

*Median incidence based on review of literature

[†]ECMO=Extracorporeal membrane oxygenation

Table 2. Characteristics of 960 patients with invasive aspergillosis 2004-2008.

*This table was adapted from the Prospective Antifungal Therapy (PATH) Alliance registry data on the clinical epidemiology of IA (14)**

Patient characteristics	No. of patients	%
Age, mean years (range)	51.5 (<1-93)	-
Age group		
<18 years	35	3.6
18-65 years	763	79.5
>65 years	162	16.9
Underlying disease/treatment^a		
Haematological malignancy	464	48.3
Solid organ transplant	280	29.2
Haematopoietic stem cell transplant	268	27.9
Solid tumour	53	5.5
HIV/AIDS	14	1.5
Inherited immunodeficiency disorder	4	0.4
Other ^b	22	2.3
Immunologic risk^a		
ANC <500 cells/mm ³	324	33.8
Corticosteroid therapy	708	73.8
Immunosuppressive therapy	468	48.8
Type of haematological malignancy/disease^a		
Acute myelogenous leukaemia	144	31.0
Non-Hodgkin's lymphoma	79	17.0
Multiple myeloma	79	17.0
Acute lymphocytic leukaemia	56	12.1
Myelodysplastic syndrome	45	9.7
Chronic lymphocytic leukaemia	33	7.1
Hodgkin's lymphoma	21	4.5
Chronic myelogenous leukaemia	16	3.5
Aplastic anaemia	10	2.2
Other	17	3.7
Type of haematopoietic stem cell transplant		
Allogeneic: HLA-matched related	86	32.1
Allogeneic: HLA-matched unrelated	66	24.6
Allogeneic: haploidentical	13	4.9
Allogeneic: HLA mismatched	30	11.2
Autologous	73	27.2
Type of solid organ transplant^a		
Lung	185	66.1
Kidney	40	14.3
Liver	39	13.9
Heart	22	7.9
Pancreas	14	5.0
Small bowel	13	4.6
Heart and lung	2	0.7

*Note, includes both nosocomially- and community-acquired invasive aspergillosis

ANC = absolute neutrophil count

^a Not mutually exclusive; patients could have >1 characteristics within a category.

^b Contains non-transplant surgery and neonatal intensive care (NICU).

2.2 Classification of At-Risk Patients

At-risk patients may be categorised as outlined below. However, this list is not exhaustive and all patients should be individually risk assessed to determine if they are at risk of developing IA.

Group 1 - No evidence of risk¹

1. Staff members², 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 steroids³ 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 chemotherapy⁴
5. Dialysis patients

Group 3 - High risk

1. Patients with neutropenia for less than 14 days following chemotherapy
2. Adult acute lymphoblastic leukaemia patients on high dose steroid therapy³
3. Solid organ transplantation
4. Patients with Chronic Granulomatous Disorder (CGD)
5. Neonates in intensive care units
6. COPD patients meeting GOLD stage III and IV criteria⁵ and in intensive care or high dependency units
7. Patients with extensive burns

Group 4 - Very high risk

1. Allogeneic haematopoietic stem cell transplantation⁶
 - a. during the neutropenic period
 - b. with graft-versus-host disease requiring steroid $\pm$ other immunosuppressive therapy
2. Autologous haematopoietic stem cell transplantation⁶, i.e. during the neutropenic period
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 (including acute myeloid leukaemia)
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 $>1 \times 10^9/l$

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

Chapter 3: Preventive Measures to Control Invasive Aspergillosis

3.1 Introduction

There is now an acceptance that IA can be linked to demolition, excavation, construction and refurbishment activities within or adjacent to the hospital site. Over the last decade the adoption of control measures by healthcare facilities has been successful and has facilitated extensive hospital building works without a significant increase in aspergillosis. Indeed a literature review identifies little that is new in relation to prevention of aspergillosis during building works.

However, the variety of patients susceptible to IA has expanded, and with advanced medical technology this will become more extensive. The imperative to plan and ensure that optimum protection is afforded to all patient groups, based on their perceived risk is becoming more complicated and challenging. The preventive measures implemented will depend on the type of construction/renovation being undertaken in the hospital and the proximity of the at-risk patients to this site. This will be based on the results of a risk assessment.

The key measures for prevention remain:

- Risk assessment of patient susceptibility and the hazard posed by the construction/renovation activity
- Measures to reduce dust emission from the construction site
- Measures to protect at-risk patients.

3.2 Membership of the Multidisciplinary Team

Each project will require input from a multidisciplinary team (MDT). The membership will be determined by the size and scope of the works and should as a minimum include representation from the following:

- a. Management of the healthcare facility
- b. Project Team (HSE Estates, design team and hospital project team)
- c. Technical services/Maintenance/Site foreman
- d. Infection Prevention and Control Team (IPCT)
- e. Healthcare personnel from relevant clinical area(s)
- f. Health Business Services (HBS) Estates

3.3. Invasive Aspergillosis Risk Assessment

To facilitate the process, a formal **Invasive Aspergillosis Risk Assessment** (IARA) has been introduced to these guidelines. The IARA involves a multidisciplinary approach whereby the scope and hazards inherent in the building project are identified, the patient groups 'at-risk' are reviewed, then stratified, and the necessary safeguards are agreed.

Following the risk assessment by the MDT, a document should be compiled outlining the measures required to reduce risk of IA for that specific project as agreed by the MDT. This document should be circulated to relevant stakeholders prior to the commencement of a project and it forms the basis for the methods statement produced by the contractor. The contractor should not be permitted to work on the site until the method statement is available. Implementation of the recommended preventive measures should be assigned to the appropriate groups which extend from ward level to the project manager.

Compliance with the agreed recommended measures should be monitored by the relevant departments e.g. technical services, Infection Prevention and Control Team (IPCT) and cleaning staff. Prior to commencement of the project there should be agreement regarding the monitoring procedures, reporting arrangements and on the utilisation of a **Nosocomial Invasive Aspergillosis Preventive Measures Compliance Checklist** (Appendix A). Additional materials to assist with the pre-project planning stage are provided in Appendices B, C and D.

Any breaches to the agreed measures should be notified immediately to the designated person for that project who will in turn notify relevant groups such as the IPCT. 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 may 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 healthcare facility, the design team, and the IPCT, and be specified clearly in the contract documents. The instruction to cease must be implemented strictly in accordance with provisions of the contract. IPCTs and other stakeholders should be aware that all instructions to the contractor on site must be issued by the Employers' Representative under the public works contracts and by the architect under the Royal Institute of the Architects of Ireland (RIAI) contract.

A risk assessment of the patient population risk groups may need to be undertaken in consultation with the patients' primary care team and recommendations regarding further measures e.g. antifungal prophylaxis considered. An adverse incident form should be completed in the event of either a patient developing IA or a serious breach of safety precautions such that vulnerable patients required or were considered for antifungal prophylaxis.

3.4. Invasive Aspergillosis Risk Assessment Process

There are four steps to the risk assessment process.

Step One: Consider patient risk factors and assign to the correct at-risk group, Group 1-4 (see Section 2.2 for the classification of at-risk patients). If more than one risk group is identified within a specific cohort, select the higher risk group (Section 2.2).

Step Two: Detail the construction activity and assign type: A1, A2, B, C or D (Table 3).

Table 3. Details of the type of construction project activity

Type	Description of the activity
TYPE A1	Minor internal containable activities with no/minimal dust generation This includes, but is not limited to, inspection and non-invasive activities and small-scale activities that create minimal dust. These include, but are not limited to, activities that require removal of ceiling tiles for preliminary visual inspection (limited to 1 tile per 5m ²), painting (no sanding), wall covering, electrical trim work, minor plumbing and other maintenance activities that do not generate dust or require cutting of walls or access to ceilings other than for visual inspection.
TYPE A2	Minor internal small-scale works with some dust generation that can be contained This includes, but is not limited to, minor works on a small scale where dust containment is achieved by using dust barriers and a HEPA-filtered vacuum. Activities that require access to conduit spaces, cutting of walls, woodwork or ceilings where dust migration can be controlled, for example installation or repair of minor electrical work, ventilation components, telephone wires or computer cables. It also includes minor plumbing as well as minor drilling to allow for the erection of brackets and shelving.
TYPE B	Major internal containable activities Any work that generates a moderate level of dust or requires demolition or removal of any fixed building components or assemblies (e.g. counter tops, cupboards, sinks). These include, but are not limited to, activities that require sanding of walls for painting or wall covering, removal of floor-covering, ceiling tiles and stud work, new wall construction, minor duct work or electrical work above ceilings, major cabling activities, and any activity that cannot be completed within a single work shift. This type of activity includes extensive plumbing work. It also includes demolition or removal of a complete cabling system or plumbing and new construction that requires consecutive work shifts to complete.
TYPE C	Minor external non-containable activities External construction activities that generate moderate levels of dust or minor excavations. Such activities include, but are not limited to, digging trial pits and minor foundations, trenching, landscaping, minor construction and demolition work.
TYPE D	Major external non-containable activities External construction activities that generate large levels of dust. Such activities would include, but are not limited to, major soil excavation, demolition of buildings and any other construction activity not covered under Type C.

Step Three: Determine the construction site preventive measures and assign class, 0-III (Table 4).

Table 4. Description of the required infection prevention and control precautions by class
(Please refer to Table 5 for application of relevant Class of Preventive Measures required)

Class 0 Preventive Measures

Dust Control

- Immediately replace ceiling tiles displaced for preliminary visual inspection

Cleaning

- Wet mop and vacuum area as needed and when work is completed
- Wipe horizontal and vertical work surfaces with hot soapy water

Infection Prevention and Control Personnel

- Approval must be sought from IPCT for the construction activity

Patient Risk Reduction

- Minimise exposure of patients in at-risk Group 2 to the construction/renovation area
- Minimise dust and increase cleaning in patient area

Note: Class 0 preventive measures do not apply to Groups 3-4 at-risk patients.
For further details, please see matrix presented in Table 5.

Class I Preventive Measures

Dust Control

- Immediately replace ceiling tiles displaced for visual inspection
- Execute work by methods to minimise dust generation from construction or renovation activities
- Provide active means to minimise dust generation and migration into the atmosphere

Cleaning

- Wet mop and vacuum area as needed and when work is completed
- Wipe horizontal and vertical work surfaces with hot soapy water

Infection Prevention and Control Personnel

- Approval must be sought from IPCT for the construction activity and the permit to be issued
- In collaboration with cleaners and technical services, ensure that the construction zone remains sealed and that the cleaning is adequate at all times

Patient Risk Reduction

- Move at-risk patients (Groups 2-4) away from construction zone. If it is not possible to move, for example ICU patients, an impermeable dust barrier should be erected around the construction zone
- Minimise patients' exposure to the construction/renovation area
- Minimise dust and increase cleaning in patient area

Class II Preventive Measures

Dust Control

- Execute work by methods to minimise dust generation from construction or renovation activities
- Erect an impermeable dust barrier from floor to slab/floor
- Ensure windows and doors are sealed
- A separate entrance away from patient traffic should be created for use by construction workers
- Protective clothing should be worn by construction workers and removed when leaving the construction site
- Dust barrier should not be removed until the project is complete

Ventilation of Construction Zone

- Seal windows
- Maintain negative pressure within construction zone by using a portable extract fan
- Ensure air is exhausted directly to the outside where feasible and away from intake vents or filtered through a minimum of an F9 filter
- Ensure the ventilation system is functioning properly and is cleaned if contaminated by soil or dust after construction or renovation project is complete

Debris Removal and Cleaning

- Contain debris in covered containers or cover with either an impermeable or moistened sheet before transporting for disposal
- Remove debris at end of the work day
- An external chute will need to be erected if the construction is not taking place at ground level
- Vacuum work area with HEPA-filtered vacuums daily or more frequently if required

Infection Prevention and Control Personnel

- Approval must be sought from IPCT for the construction activity and the permit to be issued
- In collaboration with cleaners and technical services, ensure that the construction zone remains sealed and that the cleaning is adequate at all times

Patient Risk Reduction

- Move all patients from within the construction zone
- If possible move at-risk patients (Groups 2-4) who are adjacent or near to the construction zone
- Ensure that patients do not go near construction zone
- All windows, doors, air intake and exhaust vents should be sealed in areas of the hospital containing patients who are classified as at increased risk (Groups 2-4), if the construction or demolition work is considered likely to result in *Aspergillus*-contaminated air entering these areas
- High and very high-risk patients (Groups 3-4) should preferably be treated in HEPA-filtered, positive pressure isolation rooms or facilities. Where such facilities are not available, the local IPCT should perform a risk assessment to identify alternative options. This may include neutral pressure isolation rooms (also referred to as a room with positive pressure ventilated lobby (PPVL)) (79, 80). Although these facilities have been validated from an engineering perspective they have not yet been clinically validated for the prevention of nosocomial aspergillosis among at-risk patients, see section 3.5.1 and 3.5.2 for more details.

Traffic Control

- In collaboration with the Technical Services Manager, designate a traffic pattern for construction workers that avoids patient care areas and a traffic pattern for clean or sterile supplies, equipment, patients, staff and visitors that avoids the construction zone
- A traffic path should be designated for the removal of rubble from the construction site which preferably is separate to and away from all hospital-related traffic.

Class III Preventive Measures

Dust Control

- Execute work by methods to minimise dust generation from construction or renovation activities
- Provide active means to minimise dust generation and migration into the atmosphere. During dry weather soil must be regularly dampened for the period involving any ground works

Debris Removal and Cleaning

- Contain debris in covered containers or cover with an impermeable or moistened sheet before transporting for disposal
- Ensure no increased dust within hospital, increased cleaning may be necessary

Infection Prevention and Control Personnel

- Approval must be sought from IPCT for the construction activity and the permit to be issued
- In collaboration with technical services ensure that dust is minimised from the construction site and that the construction site measures are being adhered to
- Ensure that cleaning is adequate to minimise dust within the hospital

Patient Risk Reduction

- No specific requirement for Risk Group 1
- If possible move at-risk patients (Groups 2-4) who are adjacent or near to the construction zone
- Ensure that patients do not go near construction zone
- All windows, doors, air intake and exhaust vents should be sealed in areas of the hospital containing at-risk patients (Groups 2-4), if the construction or demolition work is considered likely to result in *Aspergillus*-contaminated air entering these areas
- High and very high-risk patients (Groups 3-4) should be preferably treated in HEPA-filtered, positive pressure isolation rooms or facilities. Where such facilities are not available the local IPCT should perform a risk assessment to identify alternative options. This may include neutral pressure isolation rooms (also referred to as a room with positive pressure ventilated lobby (PPVL)) (79, 80), although these facilities have been validated from an engineering perspective they have not yet been clinically validated for the prevention of nosocomial aspergillosis among at-risk patients, see section 3.5.1 and 3.5.2 for more details.

Traffic Control

- In collaboration with the Technical Services Manager, designate a traffic pattern for construction workers, that avoids patient care areas and a traffic pattern for clean or sterile supplies, equipment, patients, staff and visitors that avoids the construction zone
- A traffic path should be designated for the removal of rubble from the construction site which preferably is separate to and away from all hospital-related traffic.

Step Four: Verify risk assessment by checking the matrix in Table 5.

Table 5. Matrix of construction project activity type, patient risk group and class of required infection prevention and control precautions

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 (81)

Patient Risk Group	Construction Activity Type				
	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

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.

3.5 Pressurised Ventilation Systems for Patient Isolation

The risk of serious *Aspergillus* infection is recognised for a number of patient cohorts, as outlined in Chapter 2. These patients will typically reside in haem-oncology, haematopoietic stem cell transplant (HSCT), solid-organ transplant units and intensive care units. Protective isolation is designed to protect these immunocompromised patients from exogenously acquired infection and positive pressure isolation rooms or facilities are recommended. Over the last decade neutral pressure rooms have been advocated as they provide both source and protective isolation (79, 82); however, their efficacy for prevention of nosocomial aspergillosis has yet to be documented in the published literature. All these rooms use positive pressure ventilation i.e. air flows from the patient room or isolation room lobby to provide a barrier to the ingress of pathogens from the hospital corridor.

A simplified description of the pressurised ventilation systems used for patient isolation is provided below and should be read in conjunction with Appendices E, F, G and H. All pressurised ventilation units provide an additional layer of protection, once they are used in an appropriate manner. Monitoring filter changes and re-validation, at appropriate time intervals, are all essential components of a maintenance schedule.

3.5.1 Positive pressure room

Positive pressure rooms are designed to protect an immunocompromised patient from infectious diseases particularly those spread by the airborne route. The room is at a positive or higher pressure than the hospital corridor. The pressure differential is maintained by supplying a greater volume of air than is extracted via the exhaust vent within an airtight room. Typically the intake air is HEPA filtered, to provide additional protection, and delivered through a diffuser which facilitates air mixing. The positive pressure of 10 Pa relative to the corridor is difficult to maintain unless all openings within the room are properly sealed to avoid air leaks. Doors are a particular challenge and specialised designs are available to ensure an airtight seal. An isolation room lobby and an en-suite bathroom are usually incorporated.

Positive pressure rooms are recommended as they have been proven to protect vulnerable HSCT patients from fungal infection acquired by the airborne route (83). However, should the patient develop an airborne infectious disease (e.g. influenza) while in the room, they may pose a risk to other patients or staff in that unit. Each time a positive pressure room door is opened air leaks into the hospital environment from the room. The isolation room lobby acts as a barrier but cannot totally prevent egress of air. Accordingly the immunosuppressed patient with an airborne infection must then be moved to minimise risk to other patients.

It can be a conundrum where to place an immunosuppressed patient with an infectious disease spread by the airborne route. This type of patient requires both protective and source isolation. Newer concepts have been explored to avoid compromising optimum care of the patient while protecting other patients within the unit, hence the introduction of the neutral pressure room. Although, neutral pressure rooms (also referred to as a room with PPVL) have been validated from an engineering perspective (84), insufficient time has elapsed since their introduction in Ireland to allow for clinical validation of these facilities for the prevention of IA among at-risk patients. Furthermore, in supplement 1 of the UK Health Building Note 4, 2005 (79), although these facilities are described as suitable for both source and protective isolation, it is stated that the supplement does not describe the specialist facilities required in infectious disease units or on wards where severely immunocompromised patients are nursed. However, without an alternative option being available neutral pressure rooms are used for patients requiring both protective and source isolation. If a neutral pressure facility is not available, a single room without specialised ventilation is the preferred option.

Reversible positive/negative pressure ventilation

Older isolation units were sometimes designed with a reversible positive or negative pressure switch mechanism, so that the room could operate under either positive or negative pressure. Lack of training may result in the wrong option being selected and consequently this design has become defunct and is no longer recommended. However, where such rooms exist, they may be used provided appropriate standard operating procedures are in place. Regular training, education and diagrams are useful to ensure that the correct operation mode is always selected.

Positive Pressure Room

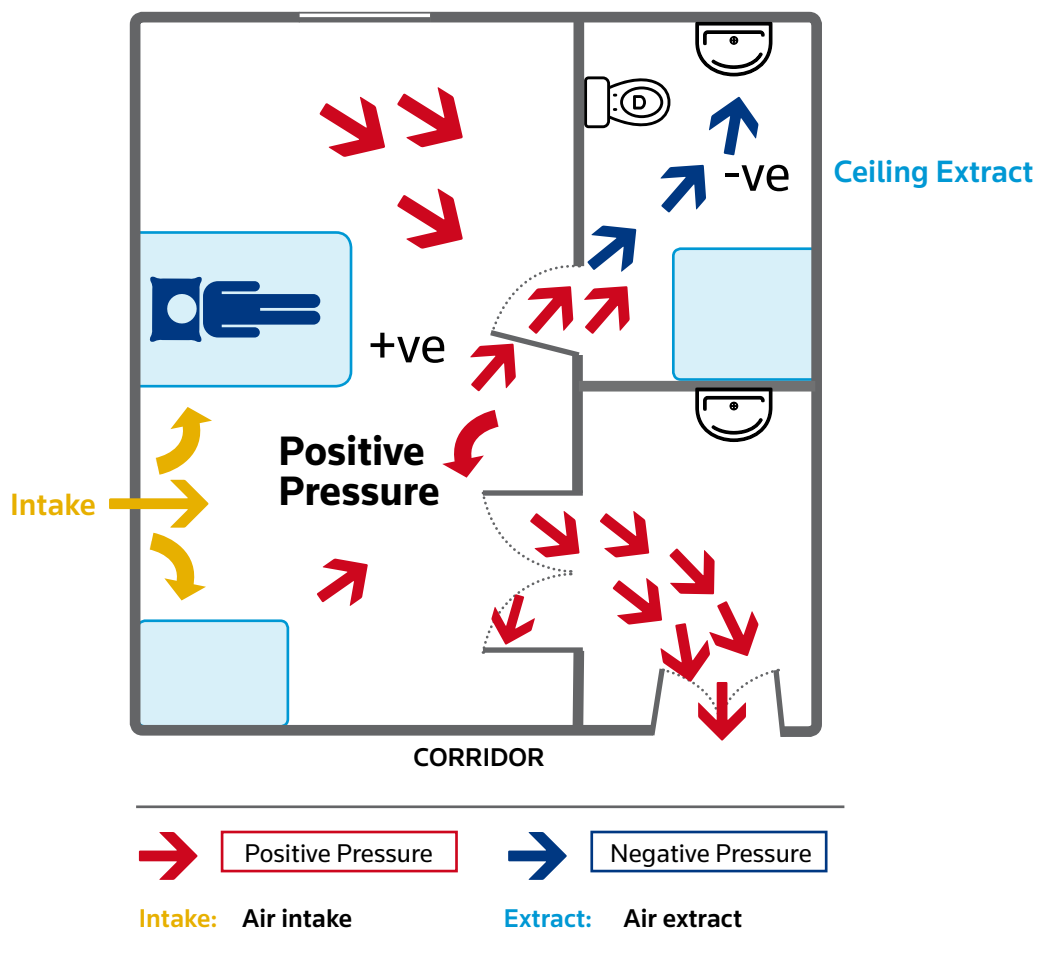


Figure 1. Simplified schematic representation of a positive pressure isolation room

Protective positive pressure: The patient is in a positive pressurised room. The air moves away from the patient to the hospital corridor and exterior. The patient is protected from air ingress from either the corridor or the outside.

This simplified schematic representation should be reviewed in conjunction with the more detailed diagram in Appendix E.

3.5.2 Neutral pressure room

The neutral pressure isolation room (i.e. a room with 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 prevents corridor air from entering the room. The patient room is at neutral pressure and there is a negative extract, typically via the bathroom. The air flows within a neutral pressure room are presented in Figure 2 and Appendix E, Figure A2. The essential elements of a neutral pressure room should be as per the UK Health Technical Memorandum (HTM) 03 and the Health Building Note (HBN) 04 requirements (79, 82, 85, 86):

- A neutral pressure room for the patient relative to the corridor
- A negative extract, typically via the en-suite bathroom
- The air flows, as illustrated in the diagram below (Figure 2)
- The positive pressure lobby has a positive pressure of +10 Pa relative to the corridor
- Air flows from the positive pressure anteroom via a pressure stabiliser to the room. The design must take account of highest and lowest ambient temperatures throughout the year to maintain a comfortable ambient temperature at all times
- HEPA-filtered intake and extract air required (subject to risk assessment); see Appendices E and F for further details
- The neutral pressure area which houses the patient must be well sealed. It is imperative that the side door, used to gain access with the bed, remains closed, except when the patient is being moved on the bed, and that it locks into position to maintain a seal
- The trunking in these rooms should include a scavenger device to remove noxious chemicals when medication is nebulised
- The intake and extract fans should be interlocked and both shut down, if one fails
- Alarms and pressure monitors should be visible and audible outside the room.

The engineering design and construction implementation is clearly of paramount importance to ensure specified function is achieved.

There have been anecdotal reports of organism entrapment within the neutral pressure rooms. This may reflect inefficient mixing of air within the patient room, leaving stagnant air pockets or insufficient extract. 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 local IPCT is best placed to give advice regarding utilisation of neutral pressure rooms following individual patient assessments.

Neutral Pressure Room

i.e. a room with positive pressure ventilated lobby (PPVL)

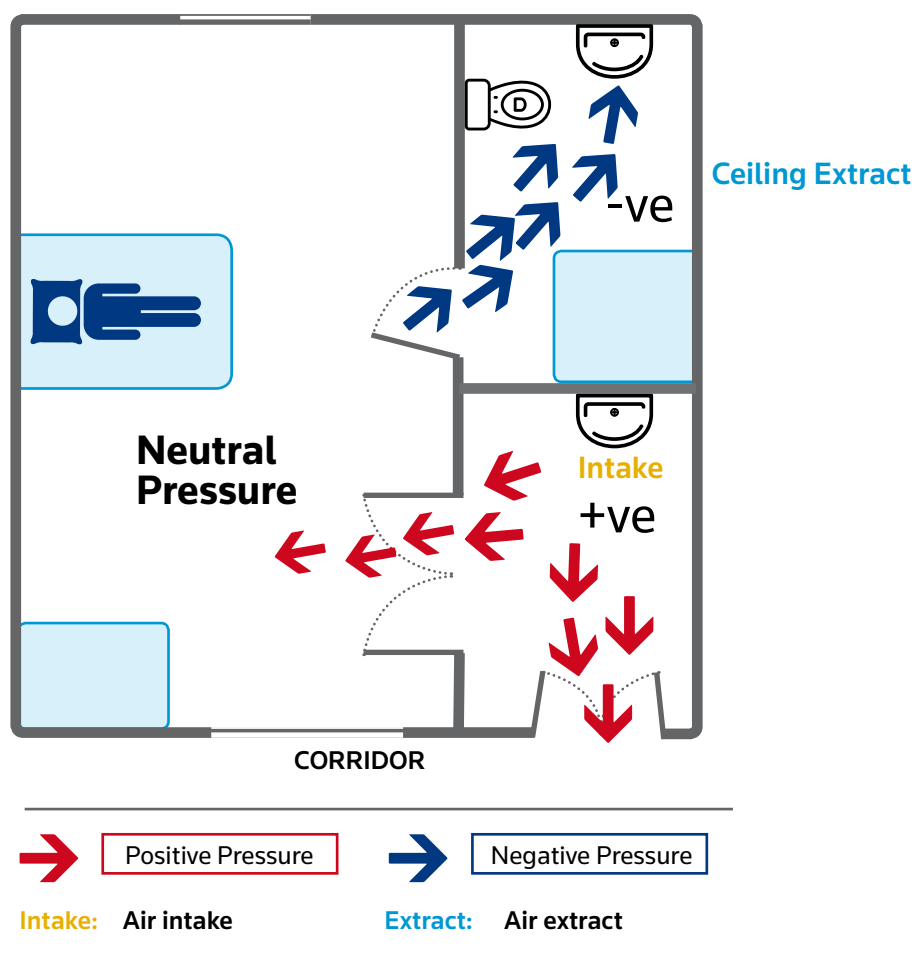


Figure 2. Simplified schematic representation of a neutral pressure isolation room.

Neutral pressure: The patient is in a neutral pressurised room as intake and extract are balanced. Engineering specification is vital, to ensure even mixing/dilution of air in the patient room.

The authors are not aware of clinical studies that confirm the efficacy of this type of isolation room (i.e. a room with PPVL) for the prevention of nosocomial aspergillosis, although they have been validated from an engineering perspective (84). Furthermore, in supplement 1 of the UK Health Building Note 4, 2005 (79), although these facilities are described as suitable for both source and protective isolation, it is stated that the supplement does not describe the specialist facilities required in infectious disease units or on wards where severely immunocompromised patients are nursed.

This simplified schematic representation should be reviewed in conjunction with the more detailed diagram in Appendix E.

3.5.3 Negative pressure room

Negative pressure ventilated rooms form *no part* of the strategy for the prevention of IA. A description of negative pressure ventilated rooms is included in this section to reiterate that they are unsuitable for immunocompromised patients, and also to facilitate an understanding of the neutral pressure room or reversible positive/negative pressure room. This room is designed for source isolation for a patient with an infectious disease, e.g. pulmonary tuberculosis, which may be spread by the airborne route.

The negative pressure relative to the hospital corridor is generated by extracting more air than is replaced by the air intake vent. This arrangement ensures that infectious aerosols, contaminated dust or skin squames are pulled away from the hospital ward to the exterior, thus preventing airborne microbes from leaking into the hospital corridor. The air extract is typically filtered to safeguard spread of infectious organisms outside the building. However, air will be pulled into the room each time the room door is opened potentially exposing the patient to airborne organisms from the hospital environment.

Therefore, this negative pressure arrangement is unsuitable for the immunocompromised patient.

Negative Pressure Room

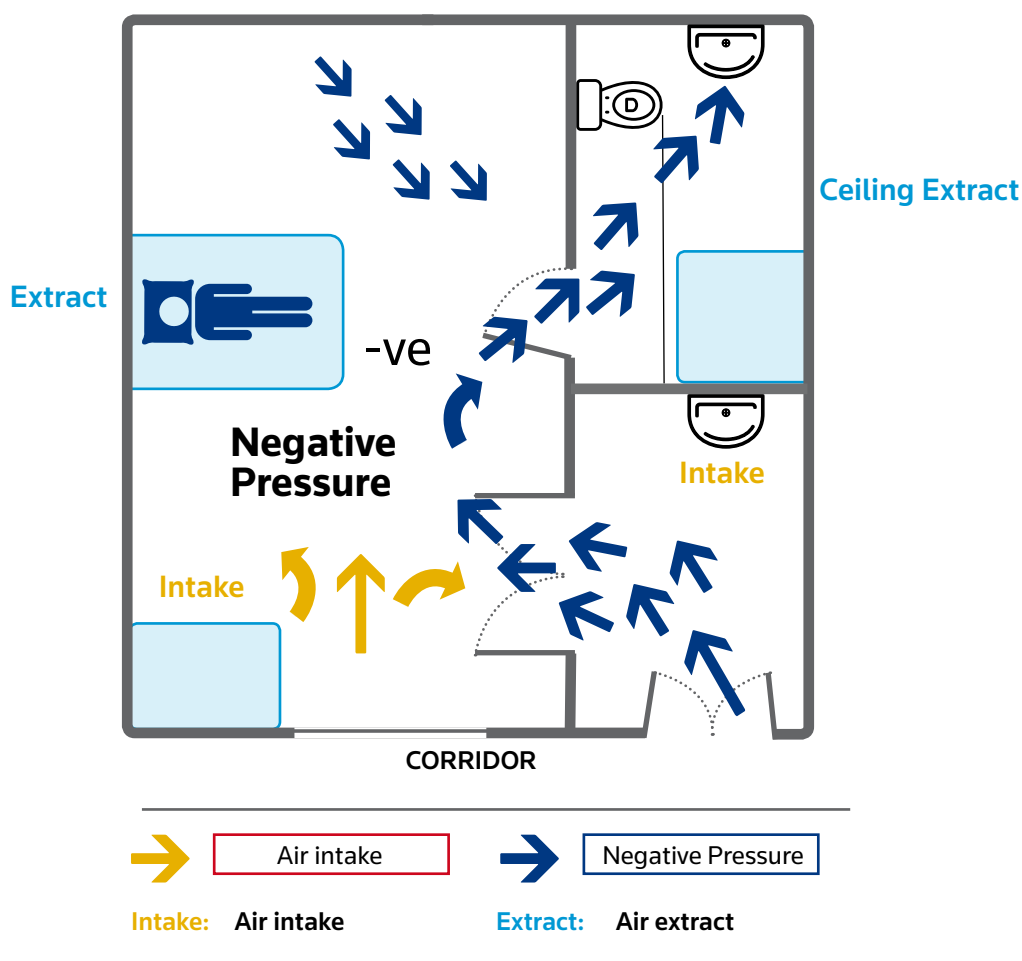


Figure 3. Simplified schematic representation of a negative pressure isolation room.

Negative pressure: The patient is in a negative pressurised room. The air is pulled away from the hospital corridor, thus protecting the hospital environment from airborne pathogens from an infectious patient.

This type of room is not suitable for protective isolation in an immunocompromised patient.

This simplified schematic representation should be reviewed in conjunction with the more detailed diagram in Appendix E.

3.5.4 Management of existing ventilation systems

Many areas of the hospital may have ventilation systems already in use. The specification of these units will have been determined at the time of their original development. Therefore, some of these units may not be appropriate for certain categories of patient in the event that additional building works and/or refurbishment are to be undertaken. It is possible that upgrading may be required depending on the patient type to be housed in these units. It is important that at the time of planning all such units are reviewed, a risk assessment is undertaken and their appropriateness for the current situation assessed. Please refer to Appendix G, Table A3, for a review of the required filter type based on patient category.

3.5.5 Room air filter units (fixed or portable)

Where windows are sealed as a consequence of construction activity in locations that were previously naturally ventilated there is a requirement to provide temporary mechanical ventilation for the duration of the construction activity. This requirement is driven primarily to comply with the Irish Building Control Regulations 2009, the Health and Safety Legislation 2005 and the Health and Safety Regulations 2007 (87-89). Room-air filter units (fixed or portable) can be installed where at-risk patients (Groups 1-2) are located while the windows remain sealed during construction. These units should only be provided as a temporary solution. Room-air HEPA-filtered units (fixed or portable) are generally not recommended for longer-term locations used for at-risk patients (Groups 3-4), but may be provided on a temporary basis. These room-air HEPA filter units may have potential uses in existing facilities as an interim, supplemental environmental control measure. Limitations in the design must be recognised. The design of such systems should also allow for easy access for scheduled preventive maintenance and cleaning.

For healthcare facilities, the HTM 03 guidelines must be referred to before designing the permanent correct technical solution (85, 86). System life cycle costs appraisal and an infection control risk assessment is required early in the design process to achieve the correct healthcare outcome. Maintenance costs, energy costs and noise levels when set at high speed need to be checked as part of this appraisal/risk assessment. It is essential that all of these systems are fail-safe and that the design is robust while complying with the engineering requirements of the relevant HTM/HBNs (79, 82, 85, 86).

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 HTM/HBNs (79, 82, 85, 86). Synergy between the various environmental control systems is not easily achieved; this needs to be considered early in the design phase.

3.5.6 Upgrade and refurbishment activities

The provision of additional isolation facilities should be considered when designing new healthcare buildings and renovating existing buildings. Long-term cost-benefit analysis should be factored into the infection prevention and control-related aspects of planning and design. Common pitfalls arise from a number of constraints e.g. the constraint to choose the cheapest products or design. The best products or designs may be more expensive initially but in the long term they will probably realise cost benefits as they may prevent outbreaks, last longer, require less maintenance and be more durable (90).

Refurbishment activities within existing hospital buildings are a particular challenge in relation to *Aspergillus* control. These works tend to release fungal spores from a variety of sources such as ceiling voids and ductwork. Partial refurbishments mean that ventilation filters and pipework may not be included within the scope of the project and are not a contractor's responsibility. It behoves the project team to realise that the area is not being returned in a 'turn key' state. The Contractor typically performs a builder's clean prior to hand-over. The project team should snag the area with technical services and the IPCT. The areas worthy of particular attention are outlined in Table 6.

Table 6. Checklist prior to contractor handover following upgrade and refurbishment activities

Area	Items to check
Drains	Are filters/traps <i>in situ</i> ?
Plumbing	Run water at all outlets and flush toilets. Ensure that any plumbed equipment is serviced and run cycles are operated regularly.
Sinks	Check tap handles are properly aligned. Ensure that water flow never runs directly into drains.
Pipework	Redundant pipework should ideally be removed, but if this is not feasible then it must be capped off, providing an adequate and robust seal.
Radiators	Inspect radiators and area behind each radiator to ensure they are visibly clean. Where radiator covers are used, ensure they are removed and area behind each radiator is visibly clean.
Ventilation units	Check that filters and their housings are clean and intact. Ensure new air supplies operate according to specification. For further details see Appendices E, F, G and H.
Rooms with specialised ventilation	Check that air flows are satisfactory and that there are no detectable leaks. Smoke tubes are useful for this purpose. Before use of smoke tubes, ensure fire alarms are covered (a surgical glove usually suffices) or inactivated prior to testing.
Ceiling void	Inspect and clean, as required.
Electrical cupboards	Open and inspect for cleanliness and incomplete seals around cables and ductwork.
General	Check that no raw wood is visible. If raw wood is detected arrange to varnish or paint. Ensure areas around pipework/ductwork/cables are properly sealed. Check gaps between floor and skirting-board, window ledges and windows, windows and walls.

The project team (hospital estates) should oversee the remedial works. A final clean should be organised when all works are completed. The first layer of plastic may be removed from the impermeable barrier prior to cleaning, but the area remains sealed off. It is vital that no further dust generating activity ensues after this point.

Commissioning by the IPCT should be conducted with air sampling and settle plates (see section 4.3). In the event of unsatisfactory results, re-cleaning is necessary and the use of portable ventilation units may be considered. These units must vent to the exterior of the building. Dry dusting several times a day may assist with ensuring that spores are airborne facilitating removal. Remember to run/flush water outlets and plumbed equipment on a regular basis. Hydrogen peroxide generating units have been utilised in some hospitals but are not validated in this context to remove *A. fumigatus* spores. Once the commissioning tests have been validated and passed, the hoarding may be removed and clinical activities resumed.

At-risk patients (Groups 2-4) should wear protective masks if it is necessary to transport them through or near to the construction zone. These masks should be capable of filtering *Aspergillus* spores such as particulate-filter respirators which give >95% filtration efficacy of 0.3 µm particle size. Masks should be used in association with the National Institute for Occupational Safety and Health (NIOSH) regulations.

3.6 Chemoprophylaxis and the Prevention of Invasive Aspergillosis

The 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 (91, 92).

Since the first edition of the National Guidelines for the Prevention of Nosocomial Invasive Aspergillosis during Construction/Renovation Activities were published in 2002 (93), national and international consensus guidelines have been published on the role of antifungal chemoprophylaxis in high-risk patient populations. The Infectious Diseases Society of America (IDSA) states that chemoprophylaxis may have a role in patients at high risk of IA. They and others have identified the following groups:

- Patients undergoing intensive chemotherapy for acute myeloid leukaemia (AML) or myelodysplastic syndrome
- Patients with GVHD after allogeneic HSCT
- Patients with ≥ 2 weeks of neutropenia or with a history of IA pre-engraftment
- Selected solid organ transplant recipients (94, 95)
- Rare cases of inherited immunodeficiency such as CGD.

Below, the recommendations regarding prophylaxis of IA are summarised, based on guidelines published by IDSA (96, 97) and the European Conference on Infections in Leukaemia (ECIL 5) (98). Readers are advised to refer to the full guidelines for further information and guidance.

In their 2016 recommendations for the management of aspergillosis, IDSA adopted the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, a systematic method of grading both the strength of the recommendation (weak or strong) and the quality of the evidence (very low, low, moderate and high) (96). In summary, IDSA recommends prophylaxis:

- For HSCT recipients with GVHD:
 - Posaconazole (strong recommendation; high quality evidence)
 - Itraconazole (strong recommendation; high quality evidence)
 - Voriconazole (strong recommendation; moderate quality evidence)
- For those with prolonged neutropenia at high risk of IA (e.g. patients undergoing intensive treatment for acute myelogenous leukaemia or myelodysplastic syndrome)
 - Posaconazole (strong recommendation; high quality evidence)
 - Voriconazole (strong recommendation; moderate quality evidence)
 - Micafungin (weak recommendation; low quality evidence)
- For lung transplant recipients:
 - Voriconazole, itraconazole or inhaled amphotericin B for 3 to 4 months after transplant (strong recommendation; moderate-quality evidence)

Using a standard scoring system for rating recommendations, the ECIL 5 guidelines similarly recommend posaconazole prophylaxis during induction chemotherapy and during GVHD treatment after allogeneic HSCT (both given grade A-I) (98). Itraconazole and voriconazole have each a B-I grade for both the initial neutropenic phase after allogeneic HSCT and during the GVHD phase; grading of voriconazole was based on results of two randomised controlled studies where it was compared with other triazoles for chemoprophylaxis (99, 100). However, there was no statistically significant reduction in IA in these studies.

Evidence to support the prophylactic use of the new triazole posaconazole comes from two independent clinical trials, both of which were in the setting of high-risk haematological malignancy treatment (101, 102). In both studies the patients on posaconazole had a reduced incidence of IA when compared with the comparison group. In the study of patients with acute myelogenous leukaemia (AML)/myelodysplasia there was a significant reduction in mortality (101). Patients receiving triazole prophylaxis should have therapeutic drug monitoring of serum concentrations (103).

Some authorities recommend antifungal prophylaxis for selected solid organ transplant recipients (94, 95), commenting that studies in these settings have typically been from non-randomised comparative trials with small

patient numbers. The use of itraconazole for long-term antifungal prophylaxis in CGD is well established (104) and posaconazole is a possible alternative agent. Acquired itraconazole resistance has been reported in CGD patients who received prolonged courses of prophylaxis (105).

Antifungal prophylaxis **is not recommended** for patients outside of those identified belonging to a high-risk group (96, 98). However, in the event of a possible outbreak of aspergillosis in a patient group not belonging to a high-risk group, e.g. cardiothoracic patients, antifungal prophylaxis should be considered and expert advice sought. It should be noted that the suspension formulation of oral posaconazole may take one week to achieve steady state serum concentrations. The recently licensed delayed release tablet formulation of posaconazole has improved bioavailability compared to the earlier suspension formulation and need only be administered once daily after a loading dose.

Table 7. Consensus guidelines on antifungal prophylaxis against invasive aspergillosis
(Grading of evidence is shown in the right hand column in brackets)

Guideline	Patient group	Antifungal agent(s)
Infectious Diseases Society of America (IDSA, 2016) (96)	HSCT patients* with GVHD	Posaconazole (strong recommendation; high quality evidence) Itraconazole (strong recommendation; high quality evidence) Voriconazole (strong recommendation; moderate quality evidence)
	For those with prolonged neutropenia	Posaconazole (strong recommendation; high quality evidence) Voriconazole (strong recommendation; moderate quality evidence) Micafungin (weak recommendation; low quality evidence)
	Lung transplant recipients	Voriconazole, itraconazole or inhaled amphotericin B for 3 to 4 months after transplant (strong recommendation; moderate quality evidence)
European Conference on Infections in Leukaemia ECIL 5 (98) *	Induction chemotherapy in acute myeloid leukaemia patients	Posaconazole (AI) Itraconazole (BI) Aerosolised liposomal amphotericin B with fluconazole (BI)
	Allogeneic HSCT* (Pre-engraftment)	Voriconazole (BI) Itraconazole (BI) Aerosolised liposomal amphotericin B with fluconazole (BII) Posaconazole oral (BII) Micafungin (CI) Intravenous polyene (CII)
	Allogeneic HSCT* with GVHD	Posaconazole oral (AI) Itraconazole (BI) Voriconazole (BI) Micafungin (CII) Liposomal amphotericin (CII)

*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) and the European Conference on Infections in Leukaemia (ECIL)

Chapter 4: Surveillance and Diagnostic Strategies

4.1 Surveillance of Invasive Aspergillosis

4.1.1 Introduction

Although many reports have been published on outbreaks of IA during building work (see Chapter 1), data on its true incidence in Ireland and worldwide are lacking. A number of multi-centre prospective surveillance studies in North America, Europe and the Asia-Pacific Region reviewing the epidemiology of IA in both immunocompromised and non-immunocompromised patients have been published recently. The PATH Alliance® conducted a prospective surveillance of invasive fungal infections among patients hospitalised in North America from 2004-2008 and reported an incidence of 13.3% (1,001/7,526) of IA (14, 106). In Europe, a prospective three-year surveillance study of IA in France reported a median incidence per hospital of 0.27 cases per 1,000 admissions (58) while an 18 month surveillance study in southern Italy on patients with haematologic malignancies reported an incidence of 2.1% (10/475) (107). Data on IA in the Asia-Pacific region is scant; however, a recent review revealed that IA is the most common mould infection in this region with cases of IA in patients with no known predisposing conditions for this infection (108). However, these reports used different criteria for diagnosis and different denominators for their incidence rates thus making it difficult to draw generalisations. In Ireland, while healthcare facilities conduct local surveillance on IA, national data on IA are not collated as it is not a notifiable disease, unless in an outbreak situation which is reported to the regional Department of Public Health.

It is imperative to maintain a high index of suspicion for the diagnosis of nosocomial aspergillosis in the at-risk patients (Groups 2-4). This surveillance should 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 (78). Relevant clinical cases should be reviewed at ward level and relevant microbiological, histological and post-mortem data should be checked regularly.

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 (see Appendix I). Such an approach has led to the detection of cases of suspected nosocomial IA (14, 41). The occurrence of two or more cases that are temporally related to each other should be notified to the regional Department of Public Health.

4.1.2 EORTC/MSG case definitions for invasive fungal infection

The EORTC/MSG Consensus Group published revised definitions of invasive fungal disease (78). These definitions are primarily intended for use in research studies and are as follows:

Proven invasive fungal infection

Microscopic analysis in sterile material: histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which hyphae are seen accompanied by evidence of associated tissue damage.

Culture on sterile material: recovery of *Aspergillus* by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen and urine.

Probable invasive fungal infection (all three criteria must be met)

1. Host factors (one of the following):

- Recent history of neutropenia ($<0.5 \times 10^9$ neutrophils/l [<500 neutrophils/mm³] for >10 days) temporally related to the onset of the fungal disease
- Receipt of an allogeneic stem cell transplant
- 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
- Treatment with other recognised T-cell immunosuppressants, such as cyclosporine, TNF- α blockers, specific monoclonal antibodies or recognised analogues during the past 90 days
- Inherited severe immunodeficiency (such as CGD or SCID)

2. Clinical criteria (one of the following)

- Lower respiratory tract fungal disease
The presence of one of the following on CT: dense well circumscribed lesion(s) with or without a halo sign, air crescent sign, cavity
- Tracheobronchitis
Tracheobronchial ulceration, nodule, pseudomembrane, plaque or eschar seen on bronchoscopic analysis
- Sinonasal infection
Imaging showing sinusitis plus at least one of the following three signs: acute localised pain (including pain radiating to the eye), nasal ulcer with black eschar, extension from the paranasal sinus across bony barriers, including into the orbit.
- CNS infection
One of the following two signs: focal lesions on imaging and meningeal enhancement on MRI or CT

3. Mycological criteria (one of the following)

- Direct test (cytology, direct microscopy, or culture)
Mould in sputum, bronchoalveolar lavage fluid, bronchial brush or sinus aspirate samples, indicated by one of the following: presence of fungal elements indicating a mould and recovery by culture
- Indirect tests
Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF or β -D-glucan (BDG) detected in serum

Possible invasive fungal infection

Presence of host factors and clinical features but in the absence of or with negative mycological findings.

4.1.3 Recommendations

It is recommended that healthcare facilities perform local active surveillance on patients at-risk (Groups 2- 4) for IA to establish baseline levels. If levels digress, then prompt investigation should be instigated. It is important to be vigilant when the following situations occur:

1. When renovation or construction works are ongoing in the healthcare facility
2. When defects/breaches in the hospital's ventilation system are suspected or identified;
3. When a suspected/confirmed outbreak of nosocomial aspergillosis occurs.

Once a case of probable/proven IA has been identified, it is imperative to assess if the infection was healthcare acquired or community acquired. When confirmed to be nosocomial aspergillosis, a complete epidemiological investigation should be carried out immediately by a multidisciplinary team. Genotypic analysis of *Aspergillus* spp. isolated from clinical and environmental samples should be considered to assist in identifying the possible source of the outbreak (109).

4.2 Clinical and Laboratory Diagnosis of Invasive Aspergillosis

Although the EORTC/MSG case definitions are a useful tool for surveillance and research studies, they are not recommended or intended for use in evaluating patients in clinical practice; a significant number of patients with eventually proven fungal infection may be excluded by these strict criteria. A systematic review of the clinical and laboratory diagnosis of IA is beyond the scope of this document, and there are, as yet, no published systematic reviews in the international literature.

The diagnosis of IA is fraught with difficulties. The gold standard, histopathological diagnosis, will not be performed in most cases and although *Aspergillus* spp. may be readily cultured on standard media, it frequently is not isolated from patients with disseminated IA. Conversely, the presence of *Aspergillus* spp. in cultures from the lung (sputum, bronchoalveolar lavage, biopsy) may represent airway colonisation and does not necessarily indicate disease.

Recently, Blot *et al.* (110) reported on a multi-centre observational histopathology controlled study to validate an alternative clinical algorithm to discriminate *Aspergillus* colonisation from what they termed putative IA in critically ill

patients. The authors concluded that this algorithm may be useful to discriminate colonisation from putative IA and probably encompasses a larger proportion of the true burden of IA in intensive care patients. However, one major drawback is the requirement of an *Aspergillus*-positive culture as entry criterion whereas IA may develop in the absence of positive cultures (110).

The clinical algorithm developed by Blot *et al.* (110) is as follows:

Proven IA

Idem EORTC/MSG criteria

Putative IA (all four criteria must be met):

1. *Aspergillus* positive lower respiratory tract specimen culture (= entry criterion)
2. Compatible signs and symptoms (one of the following):
 - Fever refractory to at least 3 days of appropriate antibiotic therapy
 - Recrudescence fever after a period of defervescence of at least 48 hours while still on antibiotics and without apparent cause
 - Pleuritic chest pain
 - Pleuritic rub
 - Dyspnoea
 - Haemoptysis
 - Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support
3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs
4. Either 4a or 4b
 - 4a. Host risk factors (one of the following conditions)
 - Neutropenia (absolute neutrophil count $<500/\text{mm}^3$) preceding or at the time of ICU admission
 - Underlying haematological or oncological malignancy treated with cytotoxic agents
 - Glucocorticoid treatment (prednisone equivalent, $>20 \text{ mg/d}$)
 - Congenital or acquired immunodeficiency
 - 4b. Semi-quantitative *Aspergillus*-positive culture of broncho-alveolar lavage fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae

Aspergillus respiratory tract colonisation

When ≥ 1 criterion necessary for a diagnosis of putative IA is not met, the case is defined as *Aspergillus* colonisation.

Characteristic radiological features such as the halo or air crescent sign are not always diagnostic of IA. Surrogate markers of IA such as serum galactomannan and BDG may be useful. In a recent systematic review of the diagnostic utility of galactomannan used as a sole test, the reviewers found that the diagnostic utility of this test depended on the cut-off optical density index (ODI) used: varying the cut-off from 0.5 ODI to 1.5 resulted in sensitivities of 64-78%, and specificities of 81-95% (111). The authors noted that these numbers should be interpreted with caution as the results were heterogeneous.

Galactomannan antigen has also been detected in CSF samples from patients with CNS aspergillosis and in bronchoalveolar lavage fluid specimens from patients with invasive pulmonary aspergillosis (112-115). Serum galactomannan may also be used for therapeutic monitoring, however, its use in this context remains investigational (116, 117). PCR-based diagnosis may have some utility in the detection of amplified *Aspergillus* genetic material (118), this test has been the subject of a recent Cochrane review (119). Combining non-culture-based diagnostics (e.g. PCR and GM or GM and BDG) may improve the overall predictive value of these systems. A useful review of the diagnosis of aspergillosis is incorporated into the most recent IDSA Guidelines for the treatment of aspergillosis (96).

4.3 Microbial Air Sampling

Environmental air sampling 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 screening. It is recognised that airborne microbial counts can vary dramatically over a short time span, thus multiple samples will be required weekly for a minimum of four weeks in order to establish a true *Aspergillus* baseline. In areas where air handling units (AHUs) are installed, these should be turned on for a sufficient time period prior to taking the air samples.

Detection of bacteria, fungi or their spores is usually performed by impaction on solid agar surfaces and sedimentation on settle plates. There are a variety of machines available for general bioaerosol sampling but slit or centrifugal samplers are most commonly employed within the healthcare setting. A calibration certificate is provided with the machine. The certificate must be renewed at least annually and bi-annually, if used daily. SAS hand-held air samplers are also commonly used for air sampling and have the convenience of ready portability.

The sampler may be set to sample a defined volume of air which is typically 1,000 litres within a clean zone or 200 litres within normal environmental areas. Calculations enable the organism counts to be expressed as colony forming units (CFU) per m³ (1,000 litres = 1m³). Conversion tables are provided with each machine to correct for the statistical probability of multiple particles passing through the same hole in the slit sample. The media may be changed depending on the organism sought, but Tryptone Soya agar is suitable for most purposes and Sabourauds agar may be utilised for fungi.

The operator must avoid contamination of the samples, during clean zone environmental screening by using the time delay switch and wearing a theatre scrub suit. The machine heads are sent for sterilisation to the hospital sterile supply department (HSSD) following use, but may be decontaminated using alcohol wipes and reused when screening within a single area.

The use of settle plates is not generally recommended if only fungal spores are being sought as they may remain airborne indefinitely. However, within a building project settle plates may be useful and do not require any specialised equipment. For example, comparing *Aspergillus* counts between a ward or unit with controlled ventilation to those in an area outside the controlled zone can help identify evidence of ingress of fungal spores. Results are expressed as CFU but this sampling method does not permit a quantification of air volume sampled. These results should be read in conjunction with airborne counts obtained from air sample testing.

Table 8. Interpretation of air sampling data and recommendations

Adapted and with modifications from publication by Morris et al. (120)

Levels of fungal spores vary by several orders of magnitude during the course of a day due to:

- Activity levels in any one particular area
- Fluctuations in temperature
- Fluctuations in humidity
- Fluctuations in air flow
- Changes in light level

A single air sample will often underestimate the fungal contamination in the air and multiple air samples should be obtained.

No strict numerical guidelines are available for *Aspergillus* counts, which are appropriate for assessing whether the contamination in a particular location is acceptable or not but the following threshold levels have been recorded:

- Outdoor air (Note: seasonal variation recognised):
 - *Aspergillus*: 5-10 CFU/m³
- HEPA-filtered air (>99.95% efficiency and >10 ACH): <1 CFU/m³
- In ward area with no air filtration: <5.0 CFU/m³

Other authorities (121) recommend for:

- Protected environments (including rooms or areas with HEPA filtration): no *Aspergillus* CFUs
- Other clinical areas: *Aspergillus* ≤2 CFU/m³

Further investigation of sources of contamination is warranted in the following circumstances:

- Total indoor counts are greater than outdoor counts
- Comparison of indoor and outdoor levels of fungal organisms show one of the following:
 - Organisms are present in the indoor sample and not in the outdoor sample
 - The predominant organisms found in the indoor sample is different from the predominant organism in the outdoor sample
 - A monoculture of an organism is found in the indoor sample. It may be absent from samples taken in other areas of the building
 - Persistently high counts

If persistently high counts are recorded, or nosocomial invasive aspergillosis suspected or confirmed, identify source of contamination by sampling:

- Dust
- Fabrics
- Ventilation ducts/screens/fans
- Ceiling voids
- Kitchen areas
- Excreta of roosting birds in close proximity of windows

Action in the event of high *Aspergillus* air counts 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 (see Section 3.2). It is essential to alert clinicians/wards and departments to the need for further investigations which should focus on the air handling systems in place, 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 antifungal prophylaxis based on a risk assessment (121-123). Also see Appendix I.

References

- Garnaud C, Brenier-Pinchart MP, Thiebaut-Bertrand A, Hamidfar R, Quesada JL, Bosseray A, Lebeau B, Mallaret MR, Maubon D, Saint-Raymond C, Pinel C, Hincly V, Plantaz D, Cornet M, Pelloux H. Seven-year surveillance of nosocomial invasive aspergillosis in a French University Hospital. *J Infect.* 2012; 65(6): 559-67.
- Graf K, Khani SM, Ott E, Mattner F, Gastmeier P, Sohr D, Ziesing S, Chaberny IF. Five-years surveillance of invasive aspergillosis in a university hospital. *BMC Infect Dis.* 2011; 11:163.
- Stevens DA and Melikian GL. Aspergillosis in the 'nonimmunocompromised' host. *Immunol Invest.* 2011; 40(7-8): 751-66.
- Tilton RC and McGinnis MR. Opportunistic fungi. In: *Clinical and Pathogenic Microbiology*. B. J.Howard, ed. St Louis, MO: C.V. Mosby Co. 1987; p609-623.
- Samson RA, Varga J, Dyer PS. Morphology and reproductive mode of *Aspergillus fumigatus*. In: *Aspergillus fumigatus* Editors J-P Latge and WJ Steinbach ASM Press Washington DC. 2009; p7-13.
- Hope WW, Walsh TJ, Denning DW. The invasive and saprophytic syndromes due to *Aspergillus* spp. *Medical Mycology.* 2005; 43(Suppl 1): S207-238.
- Segal BH. Aspergillosis. *N Engl J Med.* 2009; 360(18): 1870-1884.
- Rotstein C, Cummings KM, Tidings J, Killion K, Powell E, Gustafson TL, Higby D. An outbreak of invasive aspergillosis among allogeneic bone marrow transplants: a case-control study. *Infect Control.* 1985; 6: 347-355.
- 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: 407-412.
- Anderson K, Morris G, Kennedy H, Croall J, Michie J, Richardson MD, Gibson B. Aspergillosis in immunocompromised paediatric patients: associations with building hygiene, design, and indoor air. *Thorax.* 1996; 51: 256-261.
- 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 Haematol.* 2001; 66: 257-262.
- Vonberg RP, Gastmeier P. Nosocomial aspergillosis in outbreak settings. *J Hosp Infect.* 2006; 63(3): 246-54.
- Chang CC, Cheng AC, Devitt B, Hughes AJ, Campbell P, Styles K, Low J, Athan E. Successful control of an outbreak of invasive aspergillosis in a regional haematology unit during hospital construction works. *J Hosp Infect.* 2008; 69(1): 33-8.
- Steinbach WJ, Marr KA, Anaissie EJ, Azie N, Quan SP, Meier-Kriesche HU, Apewokin S, Horn DL. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. *J Infect.* 2012; 65(5): 453-64.
- 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(6): 621-5.
- Meersseman W, Lagrou K, Maertens J, Van Wijngaerden E. Invasive aspergillosis in the intensive care unit. *Clin Infect Dis.* 2007; 45(2): 205-16.
- Guinea J, Torres-Narbona M, Gijón P, Muñoz P, Pozo F, Peláez T, de Miguel J, Bouza E. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. *Clin Microbiol Infect.* 2010; 16(7): 870-7.
- Peláez T, Muñoz P, Guinea J, Valerio M, Giannella M, Klaassen CH, Bouza E. Outbreak of invasive aspergillosis after major heart surgery caused by spores in the air of the intensive care unit. *Clin Infect Dis.* 2012; 54(3): e24-31. doi: 10.1093/cid/cir771
- 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: 33-39.
- 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
- Ader F, Bienvenu AL, Rammaert B, Nseir S. Management of invasive aspergillosis in patients with COPD: rational use of voriconazole. *Int J Chron Obstruct Pulmon Dis.* 2009; 4: 279-87.
- Sherif R, Segal BH. Pulmonary aspergillosis: clinical presentation, diagnostic tests, management and complications. *Curr Opin Pulm Med.* 2010; 16(3): 242-250.
- 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(4): 531-40.
- 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(4): 153-7.
- Anaissie EJ, Stratton SL, Dignani MC, Lee CK, Summerbell RC, Rex JH, Monson TP, Walsh TJ. Pathogenic moulds (including *Aspergillus* species) in hospital water distribution systems: a 3-year prospective study and clinical implications for patients with hematologic malignancies. *Blood.* 2003; 101: 2542-2546.
- Stock C, Veyrier M, Raberin H, Fascia P, Rayet I, Lavocat MP, Teyssier G, Berthelot P. Severe cutaneous aspergillosis in a premature neonate linked to non sterile disposable glove contamination? *Am J Infect Control.* 2012; 40(5): 465-7.
- Rhame FS. Prevention of nosocomial aspergillosis. *J Hosp Infect* 1991; 18 (Suppl. A): 466-472.
- 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(3): 259-64.
- Walsh TJ and Dixon DM. Nosocomial aspergillosis: environmental microbiology, hospital epidemiology, diagnosis and treatment. *Eur J Epidemiol.* 1989; 5: 131-142.
- Rhame FS, Streifel AJ, Kersey JH, McGlave PB. (1984) Extrinsic risk factors for pneumonia in the patient at high risk of infection. *Am J Med.* 1984; 76: 42-52.

31. Haiduven D. Nosocomial aspergillosis and building construction. *Med Mycol.* 2009; 47(Suppl 1): S210-6.
32. Weber DJ, Peppercorn A, Miller MB, Sickbert-Bennett E, Rutala WA. Preventing healthcare-associated *Aspergillus* infections: review of recent CDC/HICPAC recommendations. *Med Mycol.* 2009; 47 (Suppl 1): S199-209.
33. 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(3): 433-44.
34. Arnow PM, Andersen RL, Mainous PD, Smith EJ. Pulmonary aspergillosis during hospital renovation. *Am Rev Respir Dis.* 1978; 118: 49-53.
35. Lentino JR, Rosenkranz MA, Michaels JA, Kurup VP, Rose HD, Rytel MW. Nosocomial aspergillosis: a retrospective review of airborne disease secondary to road construction and contaminated air conditioners. *Am J Epidemiol.* 1982; 116: 430-437.
36. Barnes RA, Rogers TR. Control of an outbreak of nosocomial aspergillosis by laminar air-flow isolation. *J Hosp Infect.* 1989; 14: 899-894.
37. Raviv Y, Kramer MR, Amital A, Rubinovitch B, Bishara J, Shitrit D. Outbreak of aspergillosis infections among lung transplant recipients. *Transpl Int.* 2007; 20(2): 135-40.
38. Loo VG, Bertrand C, Dixon C, Vityé D, DeSalis B, McLean AP, Brox A, Robson HG. Control of construction-associated nosocomial aspergillosis in an antiquated hematology unit. *Infect Control Hosp Epidemiol.* 1996; 17: 360-364.
39. Iwen PC, Davis JC, Reed EC, Winfield BA, Hinrichs SH. Airborne fungal spore monitoring in a protective environment during hospital construction, and correlation with an outbreak of invasive aspergillosis. *Infect Control Hosp Epidemiol.* 1994; 15: 303-306.
40. Thio CL, Smith D, Merz WC, Streifel AJ, Bova G, Gay L, Miller CB, Perl TM. 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(1): 18-23.
41. Kidd SE, Ling LM, Meyer W, Orla Morrissey C, Chen SC, Slavin MA. Molecular epidemiology of invasive aspergillosis: lessons learned from an outbreak investigation in an Australian hematology unit. *Infect Control Hosp Epidemiol.* 2009; 30(12): 1223-6.
42. Humphreys H, Johnson EM, Warnock DW, Willatts SM, Winter RJ, Speller DCE. An outbreak of aspergillosis in a general ITU. *J Hosp Infect.* 1991; 18:167-177.
43. Flynn PM, Williams BG, Hetherington SV, Williams BF, Giannini MA, Pearson TA. *Aspergillus terreus* during hospital renovation. *Infect Control Hosp Epidemiol.* 1993; 14: 363-365.
44. Singer S, Singer D, Rüchel R, Mergeryan H, Schmidt U, Harms K. Outbreak of systemic aspergillosis in a neonatal intensive care unit. *Mycoses.* 1998; 41(5-6): 223-7.
45. Etienne KA, Subudhi CP, Chadwick PR, Settle P, Moise J, Magill SS, Chiller T, Balajee SA. Investigation of a cluster of cutaneous aspergillosis in a neonatal intensive care unit. *J Hosp Infect.* 2011; 79(4): 344-8.
46. Sessa A, Meroni M, Battini G, Pitingolo F, Giordano F, Marks M, Casella P. Nosocomial outbreak of *Aspergillus fumigatus* infection among patients in a renal unit? *Nephrol Dial Transplant.* 1996; 11: 1322-1324.
47. 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: 411-412.
48. Dewhurst AG, Cooper MJ, Khan SM, Pallett AP, Dathan JRE. Invasive aspergillosis in immunosuppressed patients: potential hazard of hospital building work. *BMJ.* 1990; 301: 802-804.
49. Guarro J, Solé M, Castany R, Cano J, Teixidó A, Pujol I, Gené J, Castro A, Sarda P. Use of random amplified microsatellites to type isolates from an outbreak of nosocomial aspergillosis in a general medical ward. *Med Mycol.* 2005; 43(4): 365-71.
50. Brissaud O, Guichoux J, Harambat J, Tandonnet O, Zaoutis T. Invasive fungal disease in PICU: epidemiology and risk factors. *Ann Intensive Care.* 2012; 2(1): 6. doi: 10.1186/2110-5820-2-6.
51. Shoham S, Marr KA. Invasive fungal infections in solid organ transplant recipients. *Future Microbiol.* 2012; 7(5): 639-55.
52. Morton CO, Bouzani M, Loeffler J, Rogers TR. Direct interaction studies between *Aspergillus fumigatus* and human immune cells; what have we learned about pathogenicity and host immunity? *Frontiers in Immunology.* 2012; 3: 413. doi: 10.3389/fmicb.2012.00413
53. Marr KA, Patterson T, Denning DW. Aspergillosis: pathogenesis clinical manifestations and therapy. *Infect Dis Clin North Am.* 2002; 16: 875-894.
54. 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(Suppl1): i5-i14
55. Xu H, Li L, Huang WJ, Wang LX, Li WF, Yuan WF. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: a case control study from China. *Clin Microbiol Infect.* 2012; 18(4): 403-8.
56. Ader F. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: an emerging fungal disease. *Curr Infect Dis Rep.* 2010; 12(6): 409-16.
57. Murray CK, Loo FL, Hospenthal DR, Cancio LC, Jones JA, Kim SH, Holcomb JB, Wade CE, Wolf SE. Incidence of systemic fungal infection and related mortality following severe burns. *Burns.* 2008; 34(8): 1108-12.
58. Lortholary O, Gangneux JP, Sitbon K, Lebeau B, de Monbrison F, Le Strat Y, Coignard B, Dromer F, Bretagne S; French Mycosis Study Group. Epidemiological trends in invasive aspergillosis in France: the SAI network (2005-2007). *Clin Microbiol Infect.* 2011; 17(12): 1882-9.
59. Neofytos D, Treadway S, Ostrander D, Alonso CD, Dierberg KL, Nussenblatt V, Durand CM, Thompson CB, Marr KA. Epidemiology, outcomes, and mortality predictors of invasive mold infections among transplant recipients: a 10-year, single-center experience. *Transpl Infect Dis.* 2013; 15(3): 233-42.
60. Panackal AA, Li H, Kontoyiannis DP, Mori M, Perego CA, Boeckh M, Marr KA. Geoclimatic influences on invasive aspergillosis after hematopoietic stem cell transplantation. *Clin Infect Dis.* 2010; 50(12): 1588-97.

61. Rubio PM, Sevilla J, González-Vicent M, Lassaletta A, Cuenca-Estrella M, Díaz MA, Riesco S, Madero L. 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(9): 642-6.
62. Mikulska M, Raiola AM, Bruno B, Furfaro E, Van Lint MT, Bregante S, Ibatci A, Del Bono V, Bacigalupo A, Viscoli C. 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(6): 361-70.
63. Carvalho-Dias VM, Sola CB, Cunha CA, Shimakura SE, Pasquini R, Queiroz-Telles Fd. Invasive aspergillosis in hematopoietic stem cell transplant recipients: a retrospective analysis. *Braz J Infect Dis*. 2008; 12(5): 385-9
64. 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(8): 1041-50.
65. Morgan J, Wannemuehler KA, Marr KA, Hadley S, Kontoyiannis DP, Walsh TJ, Fridkin SK, Pappas PG, Warnock DW. 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.
66. 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(13): 4358-66.
67. 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(6): 537-45.
68. Pasqualotto AC, Xavier MO, Sánchez LB, de Oliveira Costa CD, Schio SM, Camargo SM, Camargo JJ, Sukiennik TC, Severo LC. Diagnosis of invasive aspergillosis in lung transplant recipients by detection of galactomannan in the bronchoalveolar lavage fluid. *Transplantation*. 2010; 90(3): 306-11.
69. Iversen M, Burton CM, Vand S, Skovfoged L, Carlsen J, Milman N, Andersen CB, Rasmussen M, Tvede M. Aspergillus infection in lung transplant patients: incidence and prognosis. *Eur J Clin Microbiol Infect Dis*. 2007; 26(12): 879-86.
70. 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(5): 359-65.
71. 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(3): 258-66.
72. Minari A, Husni R, Avery RK, Longworth DL, DeCamp M, Bertin M, Schilz R, Smedira N, Haug MT, Mehta A, Gordon SM. The incidence of invasive aspergillosis among solid organ transplant recipients and implications for prophylaxis in lung transplants. *Transpl Infect Dis*. 2002; 4(4): 195-200.
73. Pacholczyk M, Lagiewska B, Lisik W, Wasiak D, Chmura A. Invasive fungal infections following liver transplantation - risk factors, incidence and outcome. *Ann Transplant*. 2011; 16(3): 14-6.
74. Ju MK, Joo DJ, Kim SJ, Chang HK, Kim MS, Kim SI, Kim YS. Invasive pulmonary aspergillosis after solid organ transplantation: diagnosis and treatment based on 28 years of transplantation experience. *Transplant Proc*. 2009; 41(1): 375-8.
75. Sharifpour F, Rezaeetalab F, Naghibi M. Pulmonary fungal infections in kidney transplant recipients: an 8-year study. *Transplant Proc*. 2009; 41(5): 1654-6.
76. Einollahi B, Lessan-Pezeshki M, Pourfarziani V, Nemati E, Nafar M, Pour-Reza-Gholi F, Hassan Ghadyani M, Samadian F, Ahmadpoor P, Aslani J. Invasive fungal infections following renal transplantation: a review of 2410 recipients. *Ann Transplant*. 2008; 13(4): 55-8.
77. Aubron C, Pilcher D, Leong T, Cooper DJ, Scheinkestel C, Pellegrino V, Cheng AC. Aspergillus spp. isolated in critically ill patients with extracorporeal membrane oxygenation support. *Scand J Infect Dis*. 2013; 45(9): 715-21.
78. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lortholary O, Kauffman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Muñoz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobel JD, Sorrell TC, Viscoli C, Wingard JR, Zaoutis T, Bennett JE; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. 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(12): 1813-21.
79. Department of Health, United Kingdom. Health Building Note 04-01, Supplement 1 - Isolation facilities in acute settings. 2005.
80. 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(6): 329-37.
81. Association for Professionals in Infection Control and Epidemiology (APIC). Infection Control Risk Assessment Matrix of Precautions for Construction & Renovation [updated 2005; cited 2 April 2014]. Available from: <http://apicwv.org/docs/IARA-matrix.pdf>
82. Department of Health, United Kingdom. Health Building Note 04-01, Supplement 1 - Isolation facilities for infectious patients in acute settings. 2013. Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/148503/HBN_04-01_Supp_1_Final.pdf
83. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young JA, Boeckh MJ; Center for International Blood and Marrow Research; National Marrow Donor program; European Blood and Marrow Transplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Disease Canada; Centers for Disease Control and Prevention. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009; 15(10): 1143-238.

84. Fletcher A, Booth W, Arribas BB. Validation of a neutral pressure isolation room BSRIA Ltd., UK. 2007. Proceedings of Clima 2007 Wellbeing Indoors. Available at: http://www.inive.org/members_area/medias/pdf/Inive%5Cclima2007%5CA09%5CA09I1375.pdf
85. Department of Health, United Kingdom. Health Technical Memorandum (HTM) 03-01: Specialist ventilation for healthcare premises: Part A – Design and validation. 2007. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/144029/HTM_03-01_Part_A.pdf
86. Department of Health, United Kingdom. Health Technical Memorandum (HTM) 03-01: Specialist ventilation for healthcare premises: Part B – Operational management and performance verification. 2007. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/144030/HTM_03-01_Part_B.pdf
87. Environment, Heritage and Local Government. Building Regulations 2009. Technical Guidance Document F, Ventilation. Available at: <http://www.environ.ie/en/Publications/DevelopmentandHousing/BuildingStandards/FileDownload,1647,en.pdf>
88. Health and Safety Authority (HAS). Safety, Health and Welfare Act 2005 (No. 10 of 2005). Available at: http://www.hsa.ie/eng/Topics/Managing_Health_and_Safety/Safety,_Health_and_Welfare_at_Work_Act_2005/
89. Health and Safety Authority (HAS). Guide to the Safety, Health and Welfare at work (general application Regulations 2007, Regulation 6: Ventilation of Enclosed Places of Work. Available at: http://www.hsa.ie/eng/Publications_and_Forms/Publications/General_Application_Regulations/gen_apps_workplace.pdf
90. National Services Scotland. Scottish Health Facilities Note 30 (SHFN 30) Version 3. Infection Control in the Built Environment: Design and Planning. 2007. Available at: <http://www.hfs.scot.nhs.uk/publications/shfn-30-v3.pdf>
91. Rogers TR, Slavin MA, Donnelly JP. Antifungal prophylaxis for haematological malignancies: are we there yet? *Br J Haem.* 2011; 153: 681-697.
92. Ziakis P, Kourbeti I, Mylonakis E. Systemic antifungal prophylaxis after hematopoietic stem cell transplantation: a meta-analysis. *Clinical Therapeutics.* 2014; 36: 292-306.
93. Health Protection Surveillance Centre (HPSC) (formerly the National Disease Surveillance Centre; NDSC), Ireland. National guidelines for the prevention of nosocomial invasive aspergillosis during construction/renovation activities. 2002.
94. Singh NM, Husain S, and the AST Infectious Diseases Community of Practice. Aspergillosis in solid organ transplantation. *American Journal of Transplantation.* 2013; 13: 228-241.
95. Muñoz P, Valerio M, Palomo J, Giannella M, Yañez JF, Desco M, Bouza E. Targeted antifungal prophylaxis in heart transplant recipients. *Transplantation.* 2013; 96(7): 664-669.
96. Patterson TF, Thompson III GR, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JH, Bennett JE. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 updated by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016; 63 (4): e1-60
97. Freifeld A, Bow E, Sepkowitz K, Boeckh M, Ito J, Mullen C, Raad I, Rolston K, Young J-AH, Wingard J. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011; 52(4): e56-93. doi: 10.1093/cid/cir073.
98. European Conference on Infections in Leukaemia (ECIL). Update of the ECIL guidelines for antifungal therapy in leukaemia and HSCT patients (ECIL-5), 2013. Available at: <http://mikologija.org.rs/2014/wp-content/uploads/2016/06/ECIL5-Antifungal-Therapy.pdf> and at <https://www.ebmt.org/Contents/Resources/Library/ECIL/Pages/ECIL.aspx>
99. Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, Baden LR, Gersten ID, Mendizabal AM, Leather HL, Confer DL, Maziarz RT, Stadtmauer EA, Bolaños-Meade J, Brown J, Dipersio JF, Boeckh M, Marr KA; Blood and Marrow Transplant Clinical Trials Network. Randomized, double blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood.* 2010; 116: 5111-5118.
100. Marks DI, Pagliuca A, Kibbler CC, Glasmacher A, Heussel CP, Kantecki M, Miller PJ, Ribaud P, Schlamm HT, Solano C, Cook G; IMPROVIT Study Group. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem cell transplantation. *Br J Haematol.* 2011; 155: 318-327.
101. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, Greinix H, Morais de Azevedo W, Reddy V, Boparai N, Pedicone L, Patino H, Durrant S. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med.* 2007; 356(4): 335-47.
102. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med.* 2007; 356(4): 348-59.
103. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother.* 2013;doi:10.1093/jac/dkt508
104. Falcone EL, Holland SM. Invasive fungal infection in chronic granulomatous disease: insights into pathogenesis and management. *Curr Opin Infect Dis.* 2012; 25(6): 658-669.
105. Vermeulen E, Lagrou K, Verweij PE. Azole resistance in *Aspergillus fumigatus*: a growing public health concern. *Curr Opin Infect Dis* 2013; 26(6): 493-500.

106. Azie N, Neofytos D, Pfaller M, Meier-Kriesche HU, Quan SP, Horn D. The PATH (Prospective Antifungal Therapy) Alliance® registry and invasive fungal infections: update 2012. *Diagn Microbiol Infect Dis.* 2012; 73(4): 293-300.
107. Montagna MT, De Giglio O, Napoli C, Lovero G, Caggiano G, Delia M, Pastore D, Santoro N, Specchia G. Invasive fungal infections in patients with hematologic malignancies (aurora project): lights and shadows during 18-months surveillance. *Int J Mol Sci.* 2012; 13(1): 774-87.
108. Slavin MA, Chakrabarti A. Opportunistic fungal infections in the Asia-Pacific region. *Med Mycol.* 2012; 50(1): 18-25.
109. Guinea J, Garcia de Viedma D, Pelaez T, Escibano P, Munoz P, Meis J, Klaassen CHW, Bouza E. Molecular epidemiology of *Aspergillus fumigatus*: an in-depth genotypic analysis of isolates involved in an outbreak of invasive aspergillosis. *J Clin Micro.* 2011; 49(10): 3498-3503.
110. Blot SI, Taccone FS, Van den Abeele A, Bulpa P, Meersseman W, Brusselsaers N, Dimopoulos G, Paiva JA, Misset B, Rello J, Vandewoude K, Vogelaers D and the AspiCU Study investigators. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients, *Am J Respir Crit Care Med.* 2012; 186(1): 56-64.
111. Leeflang MM, Debets-Ossenkopp YJ, Visser CE, Scholten RJ, Hooft L, Bijlmer HA, Reitsma JB, Bossuyt PM, Vandenbroucke-Grauls CM. Galactomannan detection for invasive aspergillosis in immunocompromized patients. *Cochrane Database Syst Rev.* 2008; (4): CD007394. doi: 10.1002/14651858.CD007394.
112. Becker MJ, Lugtenburg EJ, Cornelissen JJ, Van Der Schee C, Hoog- steden HC, De Marie S. Galactomannan detection in computerized tomography-based broncho-alveolar lavage fluid and serum in haematological patients at risk for invasive pulmonary aspergillosis. *Br J Haematol* 2003; 121: 448-57.
113. Machetti M, Zotti M, Veroni L, Mordini N, Van Lint MT, Bacigalupo A, Paola D, Viscoli C. Antigen detection in the diagnosis and management of a patient with probable cerebral asper- gillosis treated with voriconazole. *Transpl Infect Dis.* 2000; 2: 140-4.
114. Musher B, Fredricks D, Leisenring W, Balajee SA, Smith C, Marr KA. *Aspergillus* galactomannan enzyme immunoassay and quantitative PCR for diagnosis of invasive aspergillosis with bronchoalveolar lavage fluid. *J Clin Microbiol.* 2004; 42: 5517-22.
115. Viscoli C, Machetti M, Gazzola P, De Maria A, Paola D, Van Lint MT, Gualandi F, Truini M, Bacigalupo A. *Aspergillus* galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. *J Clin Microbiol.* 2002; 40: 1496-9.
116. Boutboul F, Alberti C, Leblanc T, Sulahian A, Gluckman E, Derouin F, Ribaud P. Invasive aspergillosis in allogeneic stem cell transplant recipients: Increasing antigenemia is associated with progressive disease. *Clin Infect Dis.* 2002; 34: 939-43.
117. Anaissie EJ. Trial design for mold-active agents: time to break the mold—aspergillosis in neutropenic adults. *Clin Infect Dis.* 2007; 44: 1298-306.
118. Donnelly JP. Polymerase chain reaction for diagnosing invasive as- pergillosis: getting closer but still a ways to go. *Clin Infect Dis.* 2006; 42: 487-9.
119. Cruciani M, Mengoli C, Loeffler J, Donnelly P, Barnes R, Jones BL, Klingspor L, Morton O, Maertens J. Polymerase chain reaction blood tests for the diagnosis of invasive aspergillosis in immunocompromised people. *Cochrane Database Syst Rev.* 2015; 10: CD009551. doi: 10.1002/14651858.CD009551.pub3.
120. Morris G, Kokki MH, Anderson K, Richardson MD. Sampling of *Aspergillus* spores in air. *J Hosp Infect.* 2000; 44: 81-92.
121. SF2H-SFMM. Risk of fungal infections, and construction work in hospitals. Identification of risks and implementation of management precautions. 2011. Available at: https://sf2h.net/wp-content/uploads/2016/04/SF2H-SFMM_fungal-infections-guidelines-2011.pdf
122. Reboux G, Gbaguidi-Haore H, Bellanger AP, Demonmerot F, Houdrouge K, Deconinck E, Bertrand X, Millon L. 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.
123. Peláez T, Muñoz P, Guinea J, Valerio M, Giannella M, Klaassen CH, Bouza E. Outbreak of invasive aspergillosis after major heart surgery caused by spores in the air of the intensive care unit. *Clin Infect Dis.* 2012; 54(3): e24-31.
124. EN 1886:2007. Ventilation for buildings. Air handling units. Mechanical performance. Available at: https://standards.cen.eu/dyn/www/?p=204:110:0:::FSP_PROJECT,FSP_ORG_ID:21763,6138&cs=1F3A95F1A7AEA000F529FC0463D7E7177
125. EN 13053:2006+A1:2011. Ventilation for buildings. Air handling units. Rating and performance for units, components and sections. Available at: https://standards.cen.eu/dyn/www/?p=204:110:0:::FSP_PROJECT,FSP_ORG_ID:36865,6138&cs=195B5AEFB475F05C00EECDC4483B32A50

Appendix A: Nosocomial invasive aspergillosis preventive measures compliance checklist

Name of project: _____		Date project commenced: _____					
Name of ward/unit being monitored: _____		Monitored by*: _____					
Standard	Date of inspection						
	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy
Patient risk reduction							
Windows/vents sealed							
Restricted access to site							
No "at-risk" patients exposed							
FFP2 masks used, if required							
Other							
Traffic control							
Dust control							
Ventilation							
Debris removal							
Cleaning							
Comments							
Signature							

*Name of team or person assigned the responsibility to monitor compliance in a particular ward/unit, e.g. Infection Prevention and Control Nurse

Appendix B: Pre-Project Planning and Contractor Advice

Invasive aspergillosis (IA) is linked to demolition, excavation, construction and refurbishment activities either within or adjacent to the hospital site. Meticulous planning can prevent a surge in IA among immunocompromised patients during these works. The local Infection Prevention and Control Team (IPCT) must be involved at all stages of new hospital builds, or hospital refurbishments, including preparing the brief, design, planning, construction and commissioning, and be represented on the Project Team coordinating the new build or refurbishment.

Planning Stage

Outline the extent and scope of the activity or project. Obtain input from the Environmental Control Group or the IPCT, Health Business Services (HBS) Estates, as appropriate. The following points should be considered:

- Can immunocompromised patients be moved away from active site?
 - If not, will building works have to be completed in separate phases?
 - If yes, consider the time lag to allow for cleaning and microbiological surveillance
- Provisionally identify where hoarding might be erected for each phase
- Consider ventilation aspects:
 - Will intake ducts have to be inactivated, adapted, filtered or capped off?
 - Additional maintenance of ventilation system with more frequent changes of primary and secondary filters will be required
 - Are adequate positive or neutral pressure rooms available for all patients requiring protective isolation?
- Will patient services have to be curtailed?
- Consider potential sites for builder's compound
- Consider route for builder's supplies and removal of waste
- Determine builder's entry and exit points
- Identify patient/staff/public routes maintaining segregation from building site
- Consider additional cleaning required.

Any measures identified above should be incorporated into Preliminary Health and Safety Plan.

Tender Process

Tender documents must specify compliance with:

- Aspergillosis guidelines and all contractual requirements
- Health and Safety Regulations
- Outline contractor responsibilities
- Mandated attendance at Aspergillosis/Infection Control, and Health and Safety induction sessions.

The main contractor is responsible for all subcontractors. The main contractor must ensure subcontractors' comprehension of *Aspergillus*, Health and Safety, and Fire regulations. Construction site personnel will not be permitted to enter the hospital or use the hospital facilities. When entry is essential then protective boiler suits and over-shoes must be worn.

The constraints of working on an active hospital site should be made clear. Activities include damping of site during high dust generating works, covering waste skips, maintaining a clean compound free of extraneous debris as per guidelines outlined in this document.

Construction Phase

General

Aspergillus is transmitted as airborne fungal spores which originate in organic soil and decaying vegetation, and which are carried in air currents and on dust⁷ particles as well as on persons or objects moving from one place to another.

The Contractor shall ensure that any person required to work in zones of the working hospital are provided with the following, in addition to basic personal protective equipment; clean disposable overalls, overshoes, electric vacuum with HEPA filter, fungicidal barrier sticky/tacky mats and proper washing facilities. The Contractor shall ensure that all persons are required, in the safety statement of each Employer, to change, wash and clean the soles of their shoes prior to carrying out any such work.

The Contractor shall ensure that dust levels do not exceed the maximum levels set out in the footnote and shall in all cases ensure that adequate retention measures are in place and maintained to ensure the minimum practicable dust transmission to areas retained in use by the Employer. In the event of dust transmission to areas retained in use by the Employer, the Contractor shall at no expense to the Employer take such action as the Employer's representative may consider reasonable in the circumstances to minimise the risk.

The Contractor shall maintain the site in a clean condition at all times, and shall not allow situations to arise in which cleaning will result in higher dust concentration than required for the proper execution of the works. Organic refuse and spoil shall be removed from the site where not required – and all top soil to be moved shall be dampened if necessary to minimise resulting dust generation.

The Contractor shall be obliged to conduct the works to minimise the risk of spread of *Aspergillus*, on the basis that this is a dust- and airborne spore which occurs naturally in organic materials and soils, and he shall do everything necessary to reduce the risk of its spread insofar as practicable throughout the period of the works, and especially during excavation, site works, demolition and cutting. Measures shall be based on dust control in this context and as otherwise required and on tactile barriers in general and on special procedures where direct intervention in hospital areas is required. The Contractor shall ensure that site staff do not use hospital facilities, save where necessary, and shall ensure that through Safety Statements, instruction, and general notices, all persons on-site are fully informed in relation to *Aspergillus* risk and are obliged to take all reasonably practicable measures to avoid such risk, and shall cooperate with the Hospital representatives on an on-going basis in respect of the same.

Method statements (permits to work or Infection Prevention and Control permit) will be required for each phase and additional safeguards may be requested by the hospital.

⁷ Dust: means any product of a construction process which forms a powder or cloud and is injurious to health or is in a substantial concentration, including cement, wood, stone, silica, fillers and plastics.

Categories & Concentrations: Concentrations of dust in any particular category shall be limited to the concentrations set out in HSE (UK): EH 40/2005, Workplace Exposure Limits. "workplace exposure limits" in respect of the categories listed specify that no concentrations of inhalable dust shall exceed 10mg/m³ of air averaged over 8 hours or any respirable dust in excess of 4mg/m³ averaged over 8 hours.

The following shall be considered as a general guideline for Contractors, in progressing any Minor Internal Containable Construction Activities:

Personal Hygiene and Work Organisation:

- Wear a clean change of clothing and shoes or overshoes and overalls when working in the clinical area.
- All equipment should be put in place before starting the job to avoid unnecessary exits through the ward corridor/clinical areas.
- Possess relevant signed permits and agreed method statements as specified above.

Dust Control:

- Disturbance of ceiling tiles carries a significant risk of generating a lot of dust that is difficult to control. If ceiling tiles must be disturbed in a clinical area (for visual inspection, feeding through cables or clipping cables), the room/area should if at all possible be vacated for the duration of the work and patients should not return to the area until the ceiling tiles are replaced and the area is cleaned.
- Immediately replace ceiling tiles displaced for visual inspection, feeding through cables or clipping cables.
- Execute work using methods to minimise dust generation from construction or renovation activities. When drilling or chasing walls, **'drills, chasing tools with optional attachment, for dust catching'** must be used and must be approved by 'Maintenance or Infection Control Personnel' in advance of works commencing.
- Cutting of items such as ceiling tiles must be done outside the clinical areas wherever possible, in designed compound or in location agreed with maintenance department.
- Cutting small openings i.e. <50 mm in plasterboards, ceilings, or walls shall where possible be done from the least risk, clinical side e.g. corridor. The higher risk side e.g. patient room, clean utility shall have local dust screen fitted prior to work commencing. Cleaning shall be as outlined. Use tools to minimise dust generation and have agreed method with infection control and maintenance staff.
- Works under the contract shall be completed under a daily work permit from the maintenance department. This shall assist in ensuring that the contractor is fully prepared to carry out daily schedules of work and provide for alternative arrangements as necessary to progress the contract in conjunction with scheduled and emergency clinical activity. Staff at local level shall also cooperate with the Contractor to progress works in conjunction with clinical activity. In the interests of infection prevention and control, patient privacy and speedy completion of the contract, the Contractor must liaise on an ongoing basis with staff locally.
- Debris leaving the building area must be completely enclosed and the outside of the bag/container must be free from dust.
- Debris must be removed from the building area without exposing staff or patients.

Cleaning:

- Vacuum cleaner must have a HEPA filter. The filter should be changed regularly.
- Change/empty the vacuum cleaner bag daily.
- Vacuum dry floors and wet mop as needed and promptly when work is completed
- Wipe dust from adjacent horizontal ledges and vertical edges promptly with soapy water and dry-off.
- Change mop-head daily and before working in a new area.
- Do not leave the mop in water, wring out after each use.
- The ward vacuum cleaner and mops **must not** be used as these are segregated for use in clinical or infectious areas.

Minor Internal Containable Construction Activities (with some dust generation) – Type A2

- Each area **must** be vacated before work commencing. Windows and doors must be closed and sealed. If the area for works cannot be sealed off by closing and sealing windows and doors, erect an impermeable dust barrier in the work area, and provide sticky/tacky mats.
- Remove furniture, equipment, and supplies before commencing work, if possible. Any equipment, furniture, or supplies that cannot be removed from the area must be protected from dust and debris. These will all have to be cleaned on completion of work.
- All areas will need to be cleaned and disinfected when work is finished.
- Patients must not return to the area vacated until the work is complete, all debris has been removed and the area has been cleaned.

Major Internal Containable Activities – Type B

- If renovating a pre-existing building ensure full decant of all furniture, equipment and supplies prior to commencement.
- Hoarding to be provided in order to seal off all areas from the active construction site. Hoarding should be cut off site, so that only minor adjustments are required to fit it within the hospital. The hoarding should extend from floor to slab ceiling and provide one hour's fire resistance. The hospital side should have a wipe clean surface, which may be a painted or have a varnished finish, subject to fire safety requirements. All joints must be sealed. Place two separate layers of plastic sheeting on the builder's side. The first layer will be removed, following the builder's clean at the end of the project and the second, following the terminal clean.
- The Contractor shall generally provide fungicidal shoe cleaning sticky/tacky mats approved by the hospital Infection Control Officer, on a walk over access basis at all site exits to be maintained to a proper saturation level with an approved fungicide at all times.
- Pedestrian entry and exit to and from the site shall be separated. The foregoing provision is not deemed necessary in the case of contractors' dedicated routes which do not cross lands outside the construction zone at any particular stage of the works.
- Arrangements made to isolate ventilation, heating and waste shafts, as required.
- Seal windows.
- Negative pressure to be maintained where feasible within building site – portable commercial extract units to be provided and at minimum F9 filter to be provided on extract ventilation.

Minor External Non-Containable Construction Activity – Type C

The Contractor shall be obliged to conduct the works to minimise the risk of spread of *Aspergillus*.

The Contractor shall ensure that site staff do not use hospital facilities, unless by prior arrangement, and shall ensure that through Safety Statements, instruction and general notices that all persons on site are fully informed in relation to *Aspergillus* risk and are obliged to take all reasonably practicable measures to avoid such risk and shall cooperate with the nominated Hospital contact and the Hospital Infection Control Officer on an on-going basis in respect of the same.

Major External Non-Containable Construction Activity – Type D

The Contractor shall ensure that all containers, skips or vehicles entering or leaving the site and containing soil, debris or any material which may generate dust, are enclosed on all sides and sprayed down with water or are covered with dampened dust proof sheets.

The Contractor shall in particular and without prejudice to the generality of this appendix:

- Ensure that site traffic and hospital traffic remain separated throughout the period of risk.
- Cover all vehicles carrying friable or granulated material, in order to contain dust.
- Carry out random particle counter dust level checks at agreed locations and report these to the Project Manager at regular intervals of one week or as otherwise directed. All such records shall be maintained by the Contractor for the purposes of inspection during the course of the works.
- Spray excavation works, demolished works or other dust generating works during dry weather or where dust is likely to be generated, to include works. The Contractor shall provide cold water, at regular intervals throughout

the site for local watering of the site to control dust transmission.

- Vehicular exits to non-dedicated routes shall provide a drain grid, over which all vehicles shall pass and shall be hosed by a person maintained for that purpose, to ensure that wheels are clean and dust is dampened in all cases.
- The Contractor shall manage the programme for the installation of all site services by specialist subcontractors to ensure that, where all such site services are to be installed in trenches formed by the Contractor, such works shall be carried out immediately on the forming of such trenches by the Contractor. The Contractor shall further ensure that all such site services trenches are temporarily covered with a concrete topping on completion of the services installation where such trenches would otherwise remain open for any duration during the course of the works.

The Contractor shall maintain the site in a clean condition at all times, and shall not allow situations to arise in which cleaning will result in higher dust concentration than required for the proper execution of the works. Organic refuse and spoil shall be removed from the site where not required – and all top soil to be moved shall be damped if necessary to minimise resulting dust generation.

The Contractor shall be obliged to conduct the works to minimise the risk of spread of *Aspergillus*, on the basis that this is a dust and airborne spore which occurs naturally in/on inorganic materials and soils and adheres to inorganic dust. It can also adhere to clothing, shoes and vehicles. The Contractor shall do everything necessary to reduce the risk of its spread insofar as practicable throughout the period of the works, and especially during excavation, site works, demolition and cutting. Measures shall be based on dust control in this context and as otherwise required and on tactile barriers in general and on special procedures where direct intervention in hospital areas is required.

The Contractor shall ensure that site staff do not use hospital facilities, unless by prior arrangement, and shall ensure that through Safety Statements, instruction and general notices that all persons on site are fully informed in relation to *Aspergillus* risk and are obliged to take all reasonably practicable measures to avoid such risk, and shall cooperate with the nominated Hospital contact and Hospital Infection Control Officer on an on-going basis in respect of the same.

The costs of general implementation of this Appendix shall be deemed to be included in the contract sum.

Education

Educate healthcare workers on:

- The risk of invasive aspergillosis in the categorised at-risk groups during construction work.
- The infection control measures to decrease its occurrence.

Educate project managers, contractors, design teams and health and safety supervisors on:

- The preventive measures that should be implemented during construction and renovation activities.
- The importance of ensuring that this information is given to the construction workers and its significance understood in order to aid with compliance.

Educate supervisors of cleaning staff/contract cleaners on:

- Basic principles of *Aspergillus* spore contamination of the environment.
- Cleaning measures to prevent environmental contamination.
- The importance of ensuring that this information is given to the operatives and its significance understood in order to aid with compliance.

Inform at-risk patients (Groups 2-4) and the relatives of these patients of:

- The risks of nosocomial aspergillosis infection.

An information leaflet on aspergillosis should be provided (Appendix J). The purpose of this leaflet is to inform patients, relatives of patients, healthcare workers and those involved in the activities of construction, of the risk of aspergillosis during construction work. This leaflet should be considered as introductory information only. It is also recommended that each hospital prepare an additional information leaflet for at-risk patients when leaving hospital, outlining the

risks and the precautionary measures to be taken at home in order to prevent IA. This latter leaflet is supplementary to the one provided in Appendix J and should be tailored to the hospital's specific patient population.

General

- Communication lines to be clearly designated for the Contractor and hospital on a twenty-four hour basis.
- Regular meetings to monitor progress and discuss problems.
- Initiate increased cleaning, ensuring use of HEPA-filtered vacuums, wet mops etc.
- Initiate increased vigilance of ventilation systems.
- Provide weekly progress reports for staff and public.
- When the construction and commissioning of a new hospital building or a major refurbishment project is completed, the work must be signed-off by the relevant Contractors, Design Team Project Team and the Hospital Manager/CEO.
- The final documentation should include evidence that advice was sought from the Infection Prevention and Control Team at all relevant stages of the project.

Appendix C: Sample Construction Permit

Construction Permit		
Permit No:	Permit Expiration Date:	Project Start Date:
Location of Construction:		Estimated Duration:
Contractor:	Contact Person:	Tel:
CEO Approval:		
Name:	Signed:	Tel:
Hospital Technical Services Manager Approval:		
Name:	Signed:	Tel:
Infection Prevention and Control Personnel Approval:		
Name:	Signed:	Tel:

Construction/Renovation Activity

Type A2 - Minor Internal Containable Activities

This includes, but is not limited to, minor works on a small scale where dust containment is achieved by using dust barriers and a HEPA-filtered vacuum. Activities that require access to conduit spaces, cutting of walls, woodwork or ceilings where dust migration can be controlled, for example installation or repair of minor electrical work, ventilation components, telephone wires or computer cables. It also includes minor plumbing as well as minor drilling to allow for the erection of brackets and shelving.

Type B - Major Internal Containable Activities

Any work that generates a moderate level of dust or requires demolition or removal of any fixed building components or assemblies (e.g. counter tops, cupboards, sinks). These include, but are not limited to, activities that require sanding of walls for painting or wall covering, removal of floor-covering, ceiling tiles and stud work, new wall construction, minor duct work or electrical work above ceilings, major cabling activities, and any activity that cannot be completed within a single work shift. This type of activity includes extensive plumbing work. It also includes demolition or removal of a complete cabling system or plumbing and new construction that requires consecutive work shifts to complete.

Type C - Minor External Non-Containable Activities

External construction activities that generates moderate levels of dust or minor excavations. Such activities include, but are not limited to, digging trial pits and minor foundations, trenching, landscaping and minor construction and demolition work.

Type D - Major External Non-Containable Activities

External construction activities that generate large levels of dust. Such activities would include, but are not limited to, major soil excavation, demolition of buildings and any other construction activity not covered under Type C.

Population Risk Groups

Group 1 - No Evidence of Risk

- Staff members/service providers/contractors
- All patients not listed in Groups 2-4 below

Group 2 - Increased Risk

- Patients on prolonged courses of high dose steroids or tumour necrosis factor α antagonists
- Severely immunosuppressed AIDS patients
- Patients undergoing mechanical ventilation
- Non-neutropenic patients on chemotherapy
- Dialysis patients

Group 3 - High Risk

- Neutropenia for less than 14 days following chemotherapy
- Adult acute lymphoblastic leukaemia on high dose steroid therapy
- Solid organ transplantation
- Chronic Granulomatous Disorder
- Neonates in intensive care units
- COPD patients meeting GOLD stage III and IV criteria and in intensive care or high dependency units
- Patients with extensive burns

Group 4 - Very High Risk

- Allogeneic haematopoietic stem cell transplantation:
 - during the neutropenic period
 - with graft-versus-host disease requiring steroid $\pm$ other immunosuppressive therapy
- Autologous haematopoietic stem cell transplantation, i.e. during the neutropenic period
- Non-myeloablative transplantation
- Children with severe combined immunodeficiency syndrome (SCID)
- Prolonged neutropenia for greater than 14 days following chemotherapy or immunosuppressive therapy (including acute myeloid leukaemia)
- Aplastic anaemia patients

Recommendations for Infection Control Preventive Measures

Class I

Class I Preventive Measures are recommended for Minor Internal Containable Construction Activities (Type A2)

Dust Control

- Immediately replace ceiling tiles displaced for visual inspection
- Execute work by methods to minimise dust generation from construction or renovation activities
- Provide active means to minimise dust generation and migration into the atmosphere

Cleaning

- Wet mop and vacuum area as needed and when work is completed
- Wipe horizontal and vertical work surfaces with hot soapy water

Infection Prevention and Control Personnel

- Approval must be sought from IPCT for the construction activity and the permit to be issued
- In collaboration with cleaners and technical services, ensure that the construction zone remains sealed and that the cleaning is adequate at all times

Patient Risk Reduction

- Move at-risk patients (Groups 2-4) away from construction zone. If it is not possible to move, e.g. ICU patients, an impermeable dust barrier should be erected around the construction zone
- Minimise patients' exposure to the construction/renovation area
- Minimise dust and increase cleaning in patient area

Class II

Class II Preventive Measures are recommended for Major Internal Containable Construction Activities (Type B)

In addition to the Class I measures outlined above, the following measures should be also implemented for Type B activities

Dust Control

- Execute work by methods to minimise dust generation from construction or renovation activities
- Erect an impermeable dust barrier from floor to slab/floor
- Ensure windows and doors are sealed
- A separate entrance away from patient traffic should be created for use by construction workers
- Protective clothing should be worn by construction workers and removed when leaving the construction site
- Dust barrier should not be removed until the project is complete

Ventilation of Construction Zone

- Seal windows
- Maintain negative pressure within construction zone by using a portable extract fan
- Ensure air is exhausted directly to the outside where feasible and away from intake vents or filtered through a minimum of an F9 filter
- Ensure the ventilation system is functioning properly and is cleaned if contaminated by soil or dust after construction or renovation project is complete

Debris Removal and Cleaning

- Contain debris in covered containers or cover with either an impermeable or moistened sheet before transporting for disposal
- Remove debris at end of the work day
- An external chute will need to be erected if the construction is not taking place at ground level
- Vacuum work area with HEPA-filtered vacuums daily or more frequently if required

Infection Prevention and Control Personnel

- Approval must be sought from IPCT for the construction activity and the permit to be issued
- In collaboration with cleaners and technical services, ensure that the construction zone remains sealed and that the cleaning is adequate at all times

Class II cont'd

Patient Risk Reduction

- Move all patients from within the construction zone
- If possible move at-risk patients (Groups 2-4) who are adjacent or near to the construction zone
- Ensure that patients do not go near construction zone
- All windows, doors, air intake and exhaust vents should be sealed in areas of the hospital containing patients who are classified as at increased risk (Groups 2-4), if the construction or demolition work is considered likely to result in *Aspergillus*-contaminated air entering these areas
- High and very high-risk patients (Groups 3-4) should preferably be treated in HEPA-filtered, positive pressure isolation rooms or facilities or if not available, do a risk assessment to identify alternative options (see Section 3.4 on Class II preventive measures)

Traffic Control

- In collaboration with the Technical Services Manager, designate a traffic pattern for construction workers that avoids patient care areas and a traffic pattern for clean or sterile supplies, equipment, patients, staff and visitors that avoids the construction zone
- A traffic path should be designated for the removal of rubble from the construction site which preferably is separate to and away from all hospital-related traffic.

Class III

Class III Preventive Measures are recommended for all External Non-Containable Construction Activities (Type C & D)

Dust Control

- Execute work by methods to minimise dust generation from construction or renovation activities
- Provide active means to minimise dust generation and migration into the atmosphere. During dry weather soil must be regularly dampened for the period involving any ground works

Debris Removal and Cleaning

- Contain debris in covered containers or cover with an impermeable or moistened sheet before transporting for disposal
- Ensure no increased dust within hospital, increased cleaning may be necessary

Infection Prevention and Control Personnel

- Approval must be sought from IPCT for the construction activity and the permit to be issued
- In collaboration with technical services ensure that dust is minimised from the construction site and that the construction site measures are being adhered to
- Ensure that cleaning is adequate to minimise dust within the hospital

Patient Risk Reduction

- No specific requirement for Risk Group 1
- If possible move at-risk patients (Groups 2-4) who are adjacent or near to the construction zone
- Ensure that patients do not go near construction zone
- All windows, doors, air intake and exhaust vents should be sealed in areas of the hospital containing at-risk patients (Groups 2-4), if the construction or demolition work is considered likely to result in *Aspergillus*-contaminated air entering these areas
- High and very high-risk patients (Groups 3-4) should preferably be treated in HEPA-filtered, positive pressure isolation rooms or facilities or if not available, do a risk assessment to identify alternative options (see Section 3.4 on Class III preventive measures)

Traffic Control

- In collaboration with the Technical Services Manager, designate a traffic pattern for construction workers, that avoids patient care areas and a traffic pattern for clean or sterile supplies, equipment, patients, staff and visitors that avoids the construction zone.
- A traffic path should be designated for the removal of rubble from the construction site which preferably is separate to and away from all hospital-related traffic.

Appendix D: Sample Template of a Hospital Policy Document

A sample template policy document has been developed for use by hospitals (based on this guideline) and it is available for download from the HPSC website at:

<http://www.hpsc.ie/a-z/respiratory/aspergillosis/guidance/>

Appendix E:

Ventilation and Environmental Control Measures for Isolation Rooms

Isolation is used to separate patients who pose an infection risk to others or for immunocompromised patients who are susceptible to infection from other sources. This is achieved by placing the patient in a single room with en-suite facilities. The pressure in the room is dependent on whether the patient needs source isolation or protective isolation. The majority of patients requiring isolation can be cared for in enhanced single rooms with en-suite facilities that have an extract system. Only a small number of patients will need an isolation suite. Source isolation is required when a patient can present as a risk of infection to others. Source isolation prevents the spread of microorganisms from an infected patient to others, by placing the infected patient in a negative pressure room relative to the corridor. These rooms should have a lobby and an en-suite facility.

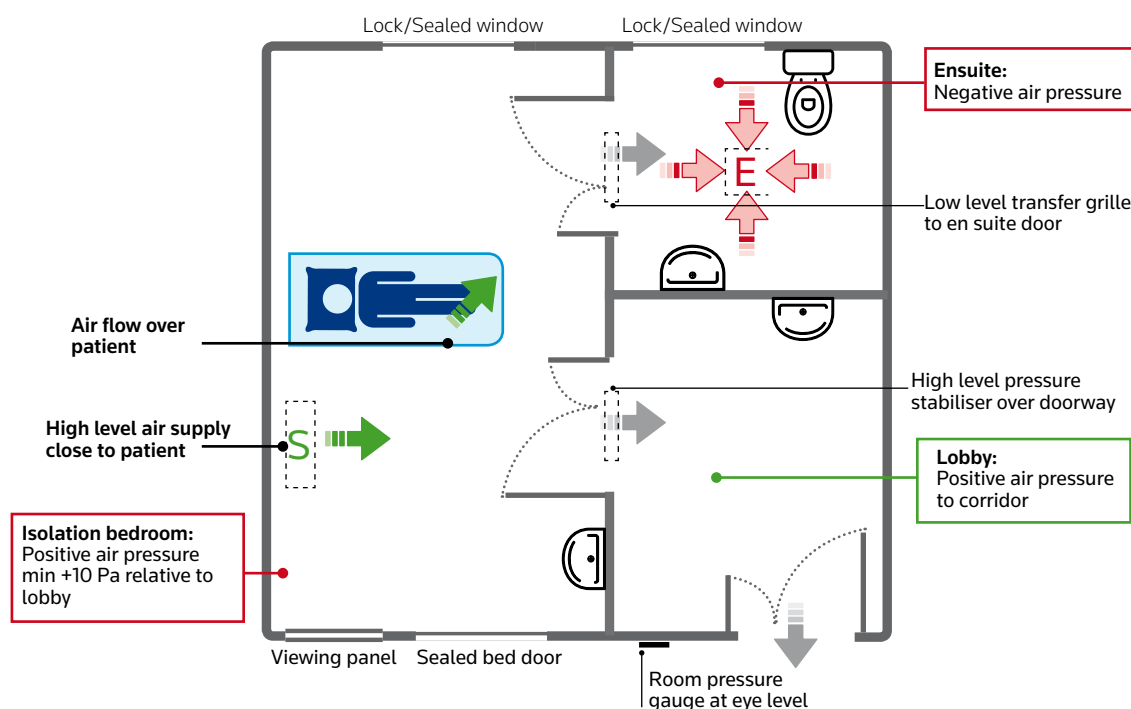
Protective isolation is required when immunosuppressed patients are particularly susceptible to infection and therefore these patients should be placed in a room or facility with positive pressure ventilation relative to the corridor. These rooms should have a lobby and have an en-suite facility. The lobby provides an additional level of protection to the patient from the corridor environment. Alternatively, protective isolation may be achieved using a neutral pressure isolation room, although this type of isolation facility has not yet been clinically validated for protection of immunocompromised patients from nosocomial aspergillosis. The neutral pressure room with a positive pressure ventilated lobby (PPVL) is a relatively recent concept under HBN04-01 Supplement 1, 2005 (79) and it appears to have a wider application, offering protective and source isolation. However, careful consideration and risk assessment should be undertaken when using this facility in an immunocompromised patient with an infectious disease transmissible by aerosols. The authors are not aware of for example, of evidence of its clinical efficacy in protecting staff or nearby patients from acquiring tuberculosis from a source case. For patients with tuberculosis negative pressure isolation rooms are the preferred option.

It is essential that all isolation units are fail safe and that the design is robust while complying with the engineering requirements of HTM03, HBN04-01 Supplement 1 2005 and 2013 (79, 82, 85, 86). As a minimum requirement, the air permeability should be no worse than that required under the building regulations. This is a variable value with a minimum required air permeability of less than $10\text{m}^3/\text{hr}/\text{m}^2$ at a reference pressure of 50 Pa. Alternatively the suite will be considered fit for purpose if at a test pressure of +50 and -50 Pa, it has an average leakage rate of not more than one litre per second of air per m^3 of envelope volume. It is essential that the monitoring of these mechanical systems is implemented in accordance with HTM03 in that a mechanical device such as a magnehelic gauge and an electronic device such as a pressure transducer are installed and linked to the Building Energy Management System (BEMS).

Positive pressure isolation room

Positive pressure isolation rooms are for high-risk immunocompromised patients and are designed to minimise fungal spore counts by maintaining adequate filtration of the incoming air usually by a central air handling unit (AHU) filtration system which shall incorporate an HEPA filter for high-risk applications. The supply air to the room shall be on one side of the room, across the patient and exhausted on the opposite side of the room, preferably at low level. The room must be at least +10 Pa relative to the corridor and pressure tested to ± 50 Pa and achieves 10-12 ACH.

POSITIVE PRESSURE ISOLATION ROOM



Dedicated supply and extract system to positive pressure isolation room

Figure A1. Detailed illustrative example of a positive pressure isolation room

Neutral pressure isolation room

HBN04-01 Supplement 1, 2005 (79) describes how an enhanced single room with en-suite facilities and a ventilated lobby can provide an isolation suite for patients who have airborne infections (source isolation) or who need to be protected from them (protective isolation).

The positive pressure lobby ensures that air from the corridor does not enter the isolation room, and that air from the room does not escape into the corridor. This simple design enables the suite to be used for both source and protective isolation without the need for switchable ventilation or special training for staff. The ventilated lobby ensures that air entering the bedroom is the clean ventilation supply from the lobby. Air from the corridor is blocked by the ventilation supply in the lobby. The patient in the bedroom is protected from the air from the corridor and potentially the contaminated air from the bedroom is prevented from escaping into the corridor by the ventilated lobby, so the patient will not present a risk of infection to others. Because the lobby simultaneously prevents unfiltered air entering the room and potentially contaminated air escaping from it, the room can be potentially used to isolate both infectious patients and those at risk of being infected by others.

The use of personal protective equipment (PPE) will be determined by the local infection control policy. Facilities for putting on and removing PPE, and washing hands, are provided in the lobby. The risk of contaminants being dislodged from the used PPE by the ventilation system and blown out into the corridor is considered negligible. However, a hand-wash basin and disposal bin are also provided in the bedroom close to the exit door so that PPE can be removed in the bedroom should local policy require it. In addition, if the ventilation system fails the layout of the suite still ensures a degree of protection. The general specification for single rooms is provided in HBN04-01 Supplement 1, 2005 and 2013 (79, 82).

The lobby enhancements and modifications recommended for isolating patients as per HBN04-01 Supplement 1, 2005 (79) are as follows:

- A clinical hand-wash basin
- Wall-mounted soap dispensers
- Disinfectant hand-rub dispensers

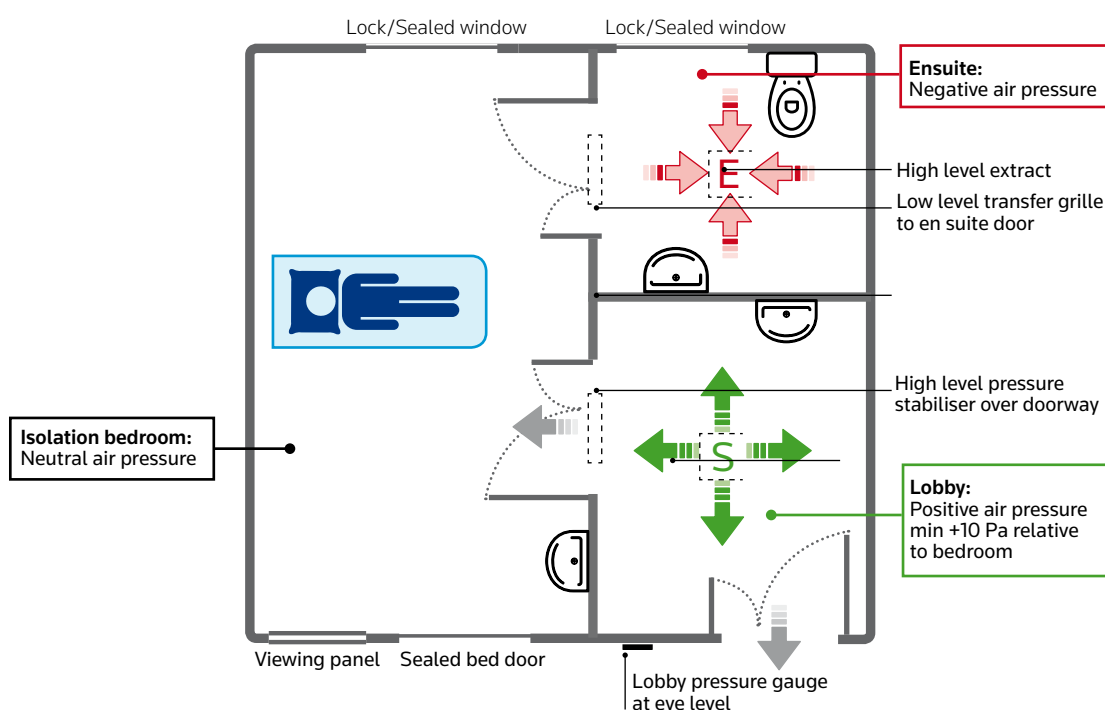
- Disposable towel holders
- Wall-mounted plastic apron and glove dispensers
- Storage for other clean PPE items
- A clinical waste bin for disposal of used PPE
- A bin for disposing of paper towels and other non-clinical items

Good patient observation facilities are essential and also the facility for the patient to be able to see out of the room enhances patient comfort.

Under HBN04-01 Supplement 1, 2005 (79), the extract terminal should be fitted at a high level in the en-suite room. An additional terminal at low level adjacent to the bed-head in the bedroom is recommended in this document for the neutral pressure room with a PPVL.

The authors are not aware of clinical studies that confirm the efficacy of this type of isolation room (i.e. a room with PPVL) for the prevention of nosocomial aspergillosis, although they have been validated from an engineering perspective (84). Furthermore, in supplement 1 of the UK Health Building Note 4, 2005 (79), although these facilities are described as suitable for both source and protective isolation, it is stated that the supplement does not describe the specialist facilities required in infectious disease units or on wards where severely immunocompromised patients are nursed.

NEUTRAL PRESSURE ISOLATION ROOM



Dedicated supply and extract system to neutral pressure isolation room

Figure A2. Detailed illustrative example of a neutral pressure isolation room

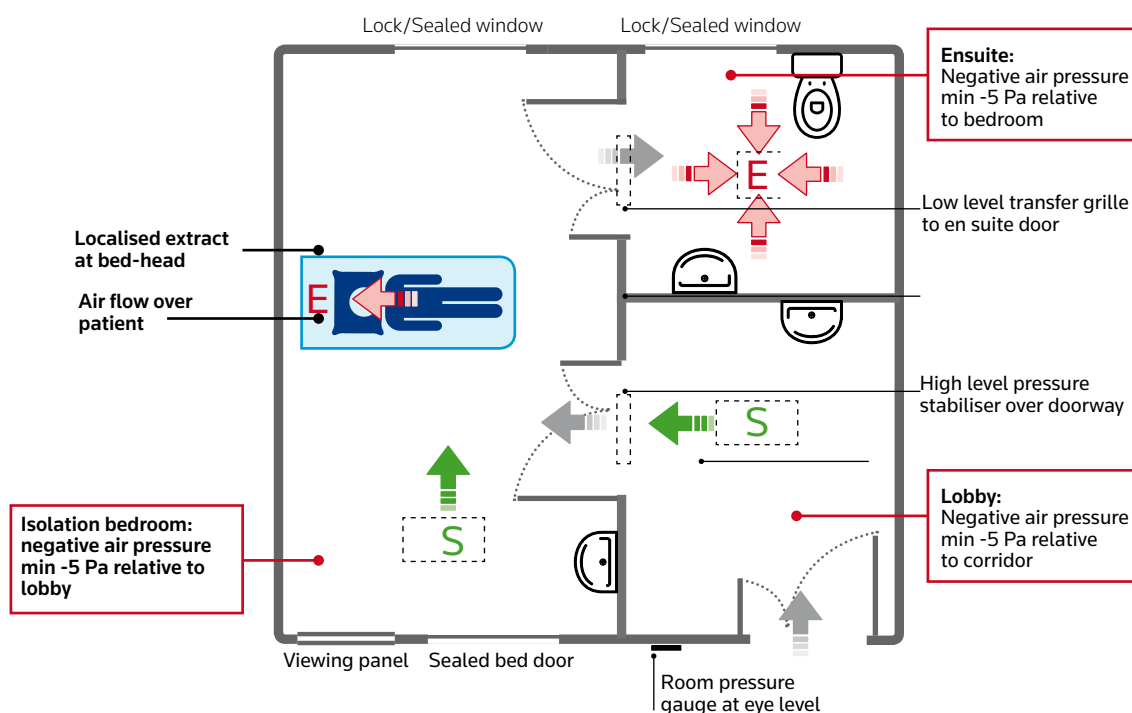
Negative pressure isolation room

Negative pressure isolation rooms are unsuitable for the protection of immunocompromised patients and form no part of the strategy for the prevention of IA.

Acute care in-patient facilities need at least one room equipped to house patients with airborne infectious disease e.g. pulmonary tuberculosis. A negative pressure room is a requirement to assist in the prevention of spread of infection to others. The room must be at least -10 Pa relative to the corridor pressure tested to ± 50 Pa and achieves 10-12 ACH. The en-suite must be negative to the bedroom and achieve 10 ACH. If the patient does not require protection from the corridor air, the lobby should be at negative pressure relative to the corridor. HBN04-01 Supplement 1, 2013 (82) requires the inflow of air into the room (negative pressure) preventing the escape of contaminated air to surrounding areas and the ventilation in the room dilutes airborne pathogens. For a negative pressure room there is a negative pressure cascade from the corridor to the room. The supply air to the patient space shall be filtered with an F7 primary filter and F9 secondary filter in accordance with EN 779:2012 and ISO 16890.⁸ To determine if HEPA filtration of the supply air is necessary, an infection control risk assessment is required. The overall engineering requirements shall be in accordance with HTM03 and HBN04-01 Supplement 1, 2013 (82, 85, 86). Air from negative pressure rooms must be exhausted directly to outside in accordance with the engineering requirements set out in HBN04-01 Supplement 1, 2013 (82). This 2013 document also requires there is a negative pressure cascade from the corridor to the room.

Provided the entrance lobby is positive relative to the patient's isolation room, staff members are provided with greater protection in terms of applying PPE once the exhaust air from the patient space is exhausted to outside and a minimum of 10-12 ACH is achieved within the patient space. Negative pressure anterooms or entrance lobbies relative to the patient space and corridor are not recommended as healthcare workers must mask prior to entering the anteroom.

NEGATIVE PRESSURE ISOLATION ROOM



Dedicated supply and extract system to negative pressure isolation room

Figure A3. Detailed illustrative example of a negative pressure isolation room

For each of these three isolation room options (positive, neutral or negative) the ventilation system must be designed on the basis that all of its constituent parts work together to form an integrated system. A failure of either the supply or extract fan will be indicated at a designated nurse station and in the maintenance department. The suite should be tested following initial commissioning and thereafter retested at least annually for conformity with the appropriate standard. Hospitals should prioritise the building of airborne isolation rooms where they are required.

⁸ The new test standard ISO 16890 for filter testing and assessment, replaced EN779:2012 at the end of 2016, with a transition period of 18 months, after this period EN779:2012 will be withdrawn

Switchable ventilation systems which can switch the room pressure (positive/negative) have been used in the past but are no longer recommended because of the risk to people inside and outside the room, in the event of an incorrect setting.

The number of positive, neutral or negative pressure rooms required should be determined by a risk assessment of the facility by the IPCT with reference to infection prevention and control and engineering standards.

Table A1. Engineering specifications for positive, neutral and negative pressure isolation rooms

	Positive Pressure Room (79)	Neutral Pressure Room (79)	Negative Pressure Room (82)
Purpose	Protective isolation	Protective and source isolation	Source (airborne infection) isolation
Pressure differentials	+10 Pa relative to the corridor	Zero pressure differential between the patient room and the corridor	-10 Pa relative to the corridor
Air changes per hour (ACH)	10-12 ACH	10-12 ACH	10-12 ACH
Filtration efficiency of outdoor air supply	F7 primary/F9 secondary filters to EN 779:2012, ISO 16890. H13 HEPA to EN 1822:2009. See filter matrix Table A3 for details on filters to use.	F7 primary/F9 secondary to EN 779:2012, ISO 16890. H13 HEPA to EN 1822:2009. See filter matrix Table A3 for details on filters to use.	Minimum F7 primary filter/F9 secondary filter to EN 779:2012, ISO 16890. See filter matrix Table A3 for details on filters to use.
Room airflow direction	Out to adjacent areas	Patient room is neutral to the corridor but air flow is toward the extract grille in the en-suite and low level extract grille in the bedroom	Into the patient room from entrance lobby
Clean to less clean airflow in the patient room	Away from the patient. Airflow direction from clean to less clean. Ceiling mounted supply air at the foot of the bed to help prevent draughts/noise. Low level extract grille recommended (85).	As per HBN04-01 Supplement 1, 2005 (79)	Towards the patient. Localised extract at the bed-head. Airflow direction from clean to less clean. Ceiling mounted supply air at the foot of the bed to help prevent draught. Low level extract grille recommended (85).
Pressure differential	+10 Pa relative to the corridor	Patient space is neutral relative to the corridor	-10 Pa relative to the corridor
Engineering, environmental, temperature, humidity, noise	As per HTM03, HBN04-01 Supplement 1 2005 requirements (79, 85)	As per HBN04-01 Supplement 1 2005 requirements (79)	HBN04-01 Supplement 1 2013 requirements (82)
Isolation lobby, anteroom	The lobby is 10 Pa positive relative to the corridor and the bedroom	The lobby is 10 Pa positive relative to the corridor and the bedroom	Negative pressure relative to the corridor (-5 Pa) but positive relative to the patient room. HBN04-01 Supplement 1, 2013 (82) requires a negative pressure cascade from the corridor to the room.
Isolation room en-suite	Negative to the patient room. 10 ACH required	Negative to the patient room. 10 ACH required	Negative to the patient room. 10 ACH required. HBN04-01 Supplement 1, 2013 (82) require en-suite extract to handle 67% of the isolation room extract requirements
Leakage, Pressure Test	±50 Pa, average leakage not greater than 1 l/s/m ³ of envelope volume	±50 Pa, average leakage not greater than 1 l/s/m ³ of envelope volume	±50 Pa, average leakage not greater than 1 l/s/m ³ of envelope volume

Note: the new test standard ISO 16890 for filter testing and assessment replaced EN 779:2012 at the end of 2016, with a transition period of 18 months, after this period EN 779:2012 will be withdrawn

Appendix F: Commissioning and Validation of Ventilation Equipment and Systems

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/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.

The contract documents should provide for the following, *inter alia*, to be completed prior to substantial completion:

- The completion by the Contractor of all tests and commissioning reports required to verify the proper functioning of the works, services, equipment and systems.
- The carrying out of witnessed validation tests in the presence of the Hospital/Estates representatives.
- The training of hospital staff in the operation of new equipment and systems.
- The preparation of all as-built drawings, operation and maintenance manuals, test certificates and warranties for the specified systems to be issued at handover and for inclusion in the project Safety File.
- Advice to the Employer regarding the maintenance at optimum efficiency of the service systems and need for entering into maintenance contracts for the various systems installed.

The ventilation systems are to be commissioned in accordance with HTM03-01 (85, 86) requirements. The AHU will be commissioned in accordance with HTM-03-01 (85, 86) and the European standard EN 1886:2007 and EN 13053:2006+A1:2011 (124, 125). Validation shall be provided by a competent independent third party.

Manufacturers' test certificates must be provided for all filters; fine filter grades to comply with the European standard EN 799:2012, ISO 16890, while HEPA filters to comply with EN 1822:2009. Filters should be inspected or tested *in situ*. Fine filter grades to EN 799:2012, ISO 16890 should be visually inspected to ensure that they are free from tears or other damage at time of installation. They should be a good fit in their housing with no obvious gaps that could allow bypass. HEPA filters should be checked with a particle counter using the method set out in EN 1822:2009 for *in situ* aerosol testing.

Isolation rooms should be tested for air permeability as detailed in HBN04-01 Supplement 1, 2013 Appendix II (82). Test pressures should be 50 Pa. Testing should be undertaken following initial commissioning and thereafter retested at least annually to ensure conformity.

Appendix G: General Air Filter Selection Guidelines

The careful selection and application of air filters in ventilation systems and air handling unit (AHU) applications has never been more important for the reasons outlined below. The main issues that decide selection are:

1. The filter efficiency as this will determine the indoor air quality with respect to particulates.
2. The energy efficiency of the filter as energy will be the major cost element during the life cycle of the filter.

These two issues are linked. Below is a list of points, which should also be carefully considered.

- a. Have the air filters been selected in line with the recommendations of EN 13779:2007? This standard advises minimum secondary filter efficiency of filters.
- b. Have the filters been tested to air filter test standard EN 779:2012, ISO 16890 for particulate efficiency? The 2012 standard is important, because it highlights the drop in performance with some filter types. When the electrostatic charge in the media is discharged over the first few days of use, the performance of some filter types drops off significantly. Ask to see performance data and an EN 779:2012, ISO 16890 test certificate. This will show both un-discharged and discharged filter efficiency.
- c. Check to see if the performance data for the filters you are considering have been independently tested. Is the filter range Eurovent accredited and therefore can be specified with confidence? Reliable data are important especially when making long-term life cycle costing analysis and assessing infection control risks.
- d. Always select air filters that are used within their rated performance but have the lowest pressure drop that can be achieved within the design constraints of the project. The working pressure drop dictates the energy consumption of the filter. Always allow adequate length on filter sections where possible in an AHU as this enables the best filter arrangement for optimum filter efficiency and energy efficiency. Specify a minimum media area for each filter. This is required to optimise filter and energy efficiency. The European standard EN 13053 (rating and performance for units, components and sections of AHUs) states "if a single stage filter system is used, a minimum of filter class F7 shall be fitted."
- e. Front withdrawal filter mounting frames in the AHU will limit air bypass. EN 1886:2007 (124) states that "air bypass around the filter cells will decrease the effective efficiency of the filter, especially a high efficiency one".
- f. Always use air filter life cycle costing (LCC) where possible because it will enable filter costs to be minimised throughout the life cycle of an AHU or air system over what could be a 20 year period. Compare the LCC results with the Eurovent filter energy ratings.
- g. In terms of energy ratings, filters should be specified as having a minimum energy rating of "B" according to Eurovent 4/11 (Energy efficiency classification of air filters for general ventilation purposes).

To summarise, ventilation system secondary filters should be selected to EN 13779:2007 guidelines. Air filters should be tested in accordance with EN 779:2012, ISO 16890 with a type test certificate available to give both the discharged and initial efficiency for the filters. The air filter manufacturer should be independently accredited by Eurovent to guarantee published data is accurate. Air filters should be manufactured under approved quality system EN 9001:2000. Request filter test certificate EN 779:2012, ISO 16890 that shows any loss in particulate efficiency is not significant in terms of its long-term performance.

EN 1822 classification of HEPA and ULPA filters:

The European Committee for Standardisation (CEN) has launched EN 1822 for classification and testing of HEPA and ultra low penetration air (ULPA) filters based on filter efficiency at the most penetrating particle size (MPPS). Testing per EN 1822 is normally done with an aerosol probe which can be moved over the entire surface of the filter. This moving of the aerosol probe, or scanning, results in the measurement of many local collection efficiencies. These local efficiencies can be used to calculate the overall efficiency of the filter or the "leak rate" of a specific area of the filter. The overall efficiency calculation is often termed the integral value, while the leak rate is often termed the local value. When it comes to filtration, we should note that the factory test EN 1822 cannot be performed on site as the test equipment and method differs. When testing on site not only is the filter considered, but so is the housing that accommodates it. The EN 1822 standard, rates the efficiency/leak rate at the MPPS however, this cannot be determined on site. So the efficiency of these filters is tested for the ratio of the particle count downstream of the filter to the particle count upstream. Various type aerosols (smoke) are used to perform this test and the known mean particle size has been established for these products. In most cases where filters are tested an efficiency of 0.01% is considered a pass. For the discrete particle counter (DPC) test the filter face is sampled at several points to establish

the smallest non-penetrating particle size. This will directly relate to the grade of filter under test. The filter face, its seal and housing, are then scanned and if a significant number of particles at or above this size are detected there is deemed to be a leak at or near the test position. Should the HEPA filter fail this test it must be replaced. Should the filter mounting seal or housing fail this test, it may be repaired and the test repeated. It's important that the complete filter installation is tested to EN 1822, DIN 1946 and EN 14644 method of testing for the determination of filter installation leaks. The following table shows the various classifications of high-efficiency filters per EN 1822.

Table A2. Classification of EPA, HEPA and ULPA filters as per EN 1822

Filter class	Integral value		Local value	
	Collection efficiency %	Penetration %	Collection efficiency %	Penetration %
E10	85	15	-	-
E11	95	5	-	-
E12	99.5	0.5	-	-
H13	99.95	0.05	99.75	0.25
H14	99.995	0.005	99.975	0.025
U15	99.9995	0.0005	99.9975	0.0025
U16	99.99995	0.00005	99.99975	0.00025
U17	99.999995	0.000005	99.9999	0.0001

The filter class descriptions are:

EPA 10 - EPA 12: Efficiency Particulate Air Filters

HEPA 13 - HEPA 14: High Efficiency Particulate Air Filters

ULPA 15 - UPLA 17: Ultra Low Penetration Air Filters

Aspergillus spore filter recommendations

These recommendations are given under two categories:

1. **Aspergillus and other fungi (spore size 2.5-3.5 µm):** Based on the particle size of the *Aspergillus* spore of 2.5-3.5 µm where an F7 primary filter and an F9 secondary filter are installed in compliance with EN 779:2012 this is adequate for the protection of at-risk patients classified in Group 2 (see Chapter 2, Section 2.2). The filters must be installed, commissioned and independently validated to prevent entry of this spore size into the ventilation system. Under the EN 779:2012 the F9 will have a minimum life efficiency (MLE) of 70%, so in order to reduce the risk to patients the MLE value should be quoted at 85-86% at 0.4 µm for an F9 filter and 55% for an F7 filter. The *Aspergillus* spore size in the range of 2.5-3.5 µm is removed by this F7/F9 filter arrangement with minimum life efficiencies of 55% and 86%, respectively. However, it is important to take into consideration that the air will take the route of least resistance; all frames should be secure and let no air by-pass. This risk is greater with bag filter frames as the quality of the seal would not be as efficient as that provided with a HEPA installation. An F7 filter (EN 779:2012) must be installed upstream of the F9 secondary filter. A risk assessment should be implemented before deciding on the final filter selection and arrangement to determine if an F7/F9 filter arrangement is adequate without the need for HEPA filtration. If an F7/F9 filter arrangement is chosen for the Group 2 at-risk patients this could mean that no significant alterations are required to some existing AHUs if the risk assessment deemed that filter selections with an MLE of 86% for an F9 filter at 0.4 µm and F7 pre-filter with an MLE of 55% is acceptable. This arrangement with the correct MLE, properly installed, will satisfy the requirement to capture particles in the range 2.5-3.5 µm. This filter arrangement will satisfy the majority of Group 2 applications where the *Aspergillus* spore size to be removed is in the range of 2.5-3.5 µm and subject to an infection control risk assessment to determine if HEPA filters need to be installed.
2. **For fungi with a particle size of 2.5 µm and lower:** To guarantee 100% efficiency it is necessary to install an H13 HEPA filter where required for patients in Groups 3 and 4 (see Chapter 2, Section 2.2). Where HEPA filters need to be installed always use filters with a large surface area. This will reduce the running cost and prolong their lifetime.

General Recommendation

Avoid using filters that will lose their efficiency after a short time in service. Use filters that maintain their efficiency over their lifetime. A minimum MLE% of 55% at 0.4 μm for an F7 and 86% for an F9 will also protect the AHU equipment, ductwork, patients and staff by delivering a good level of indoor air quality. Use filters with large surface area; this will reduce energy costs and prolong the life of the filters.

Summary and Conclusions

The purpose of this section is to address what filtration level is required to filter the *Aspergillus* spore size of 2.5-3.5 μm . However, it must be remembered that an F9 filter, according to the standard (EN 779:2012), is only required to have a lower minimum efficiency of 70%. To reduce the risk to patients and reduce the need for HEPA filters for Group 2 patients, it should be stated that the MLE value should be 85-86%. If lower grade F9 filters are installed it will be necessary to upgrade to an E10 filter (EN 1822) for the purpose of filtering *Aspergillus* to prevent the risk associated with an F9 being supplied with the lower efficiency. There will be additional cost implications both in purchase terms but also more energy costs for lower risk applications. There is always the risk that a lower grade F9 filter with a reduced MLE may be installed, hence, it is safer to specify the MLE at 86% for an F9 and 55% for an F7 and install the same filter specifications for all applications to avoid ambiguity and guarantee certainty in the quality of the primary air supply.

For high and very high-risk patients (Groups 3-4), a higher grade of filter configuration F7/F9/H13 is recommended to provide an MLE of 100%. See HBN04-01 Supplement 1, 2005 (79) for the test method to be applied to provide the necessary assurance regarding air leakage into or out of at-risk locations. The rooms must be pressure tested to both +50 Pa and -50 Pa whereby the average leakage must be below 1 l/s/m³ of the room volume (79). All filtration systems including frames must be maintained and checked periodically as required by the standards. This is the only way in which assurance can be provided on the quality of air delivered. Filter systems should be monitored via BEMS systems in accordance with HTM03 requirements. The big advantage of specifying a HEPA filter installation is that high efficiency air filters can also capture ultrafine particles 2.5 μm diameter and below. They provide a greater degree of protection in capturing particles smaller than the *Aspergillus* spore size of 2.5-3.5 μm . Therefore, for Group 3 and 4 at-risk patients an F7/F9/H13 filter sequence configuration is recommended (Table A3).

It is critical that the ventilation system design incorporates an integrated approach and is installed in accordance with current standards such as HTM03; otherwise it will be impossible at commissioning/handover stage to accept the system as complying with HTM03. For lower risk Group 2 patients and construction/renovation activities A and C which are minor works, an F7/F9 filter arrangement with MLE of 55% and 86% at 0.4 μm installed and maintained to current standards is a reasonable approach for existing and new systems subject to infection control risk assessment. This risk assessment will determine if additional HEPA H13 filter is required to provide a higher MLE to capture particles below 2.5 μm . For all specialist healthcare ventilation systems it is essential and critical that the systems are commissioned and validated by an independent competent engineer who neither designed nor installed the system. No matter what technical engineering solution is proposed it must be applied in tandem with a stringent user operational protocol. An F7/F9/H13 filter configuration is recommended for all Group 3 and 4 patients and construction work type B and D. An F7/F9 filter combination with MLE of 55% and 86% is recommended as the minimum for all Group 2 patients and construction work type A and C. An infection control risk assessment will determine if HEPA filtration is required for Group 2 application in addition to the F7 pre-filter and F9 secondary filter noted above.

Table A3. *Aspergillus* engineering and filter risk assessment table/matrix

Population Risk Group*	Construction Renovation Activity	Ventilation	Supply Filter Sequence Bag/Bag/HEPA	Positive Pressure Pascals	Air Change Rate (ACH)	Ventilation and overall System Standards compliance
4	D	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
	C	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
	B	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
	A	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
3	D	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
	C	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
	B	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
	A	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
2	D	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
	B	S/E	F7/F9/H13	10 Pa	10-12	HTM03, HTMs, HBNs
	C	S	F7/F9**	10 Pa	10-12	HTM03, HTMs, HBNs
	A	S	F7/F9**	10 Pa	10-12	HTM03, HTMs, HBNs

*As outlined in Section 2.2 of this document

S = Supply Air; E = Extract Air

** An infection control risk assessment will determine if HEPA filtration is required for Group 2 application in addition to the F7 pre-filter and F9 secondary filter arrangement as specified above.

Filter bypass leakage shall meet the EN 1886 requirements for at least F9 class filter with a maximum filter bypass leakage rate of 0.5% for both first (F7) and second stage (F9) filters. For each filter section provided within the air handling unit, the filter bypass leakage shall be tested separately. For bag filters as per EN 13053:2006+A1:2011 (125) the filter area should be at least 10 m² per 1 m² equipment cross-section. The seals used shall be of a closed cell type shall not absorb any moisture and shall not form a nutrient substrate for micro-organisms. A permanent tight fit shall be guaranteed for the seal (e.g. operation from the dusty air side).

Appendix H: ISO 16890 - Air filters for General Ventilation

The ISO 16890 standard was published towards the end of 2016 and consists of four parts, under the general title "Air filters for general ventilation". This new standard will co-exist with EN 779:2012 until mid-2018. After this period, ISO 16890 will become the one global international standard for testing and classification of air filters and will create a significant harmonisation for the filtration industry.

The new ISO 16890 standard filter efficiencies will be determined based on particulate matter size classes PM_{10} , $PM_{2.5}$ and PM_{10} . With the introduction of the new ISO 16890 standard, actual operating conditions will be more effectively taken into account. Instead of considering only the particle size $0.4 \mu m$, as previously with EN 779:2012, a broad range between $0.3 \mu m$ and $10 \mu m$ will be used to determine separation efficiencies for particulate matter fractions PM_{10} , $PM_{2.5}$ and PM_{10} . For example, PM_{10} means all particulate matter with size range of $0.3 \mu m - 10 \mu m$.

A prerequisite for each group is that a filter captures at least 50% of the appropriate particle size range. If a filter, for example, captures more than 50% of PM_{10} particles, it will be grouped as an ISO ePM_{10} filter. The respective efficiency is then reported, rounded in 5% increments. Therefore, air filters will now be rated, for example, as ISO ePM_{10} 80%. In other words, the filter separates 80% of PM_{10} particles. As a result, classes in the strict sense of the previous EN 779:2012 or ASHRAE 52.2 will no longer exist. Alongside fine dust filters, the new ISO standard also evaluates coarse dust filters as ISO coarse i.e. filters that capture less than 50% PM_{10} . Note, ISO 16890 (all parts) refers to particulate air filter elements for general ventilation having an ePM_{10} efficiency less than or equal to 99% and a PM_{10} efficiency greater than 20% when tested as per the procedures defined within parts 1-4 of the ISO 16890 standard. In the context of healthcare applications and aspergillus spore size the focus needs to be on ePM_{10} classification of filter.

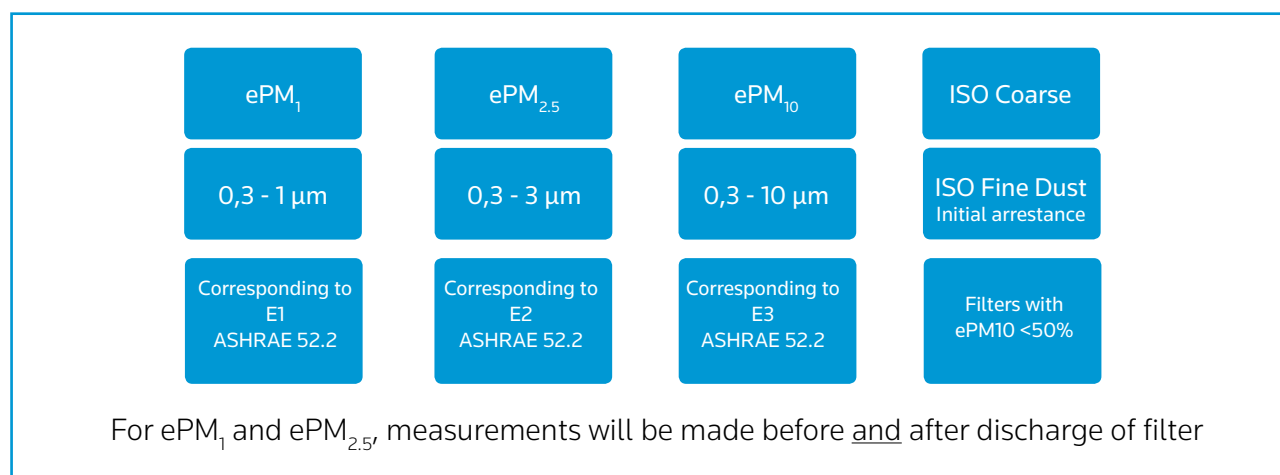


Figure A4. ISO 16890 filter classification

Efficiency values are measured and correlated into four efficiency ranges.

Note: For ePM_{10} and $ePM_{2.5}$, measurements are made before and after discharge of filter, the reported efficiency is an average between the new and discharged efficiency, both need to be 50% or greater.

Table A4. ISO 16890 classification table

PM ₁ classification	PM _{2.5} classification	PM ₁₀ classification	Coarse
ePM ₁ [95%] ePM ₁ [90%] ePM ₁ [85%] ePM ₁ [80%] ePM ₁ [75%] ePM ₁ [70%] ePM ₁ [65%] ePM ₁ [60%] ePM ₁ [55%] ePM ₁ [50%]	ePM _{2.5} [95%] ePM _{2.5} [90%] ePM _{2.5} [85%] ePM _{2.5} [80%] ePM _{2.5} [75%] ePM _{2.5} [70%] ePM _{2.5} [65%] ePM _{2.5} [60%] ePM _{2.5} [55%] ePM _{2.5} [50%]	ePM ₁₀ [95%] ePM ₁₀ [90%] ePM ₁₀ [85%] ePM ₁₀ [80%] ePM ₁₀ [75%] ePM ₁₀ [70%] ePM ₁₀ [65%] ePM ₁₀ [60%] ePM ₁₀ [55%] ePM ₁₀ [50%]	Arrestance reported in 5% increments starting at 5%
Requirement: ≥50% initial efficiency ≥50% discharged efficiency	Requirement: ≥50% initial efficiency ≥50% discharged efficiency	Requirement: ≥50% initial efficiency No discharge requirement	No discharge requirement

Table A5. Filter classification based on EN 779:2012 and ISO 16890

EN 779:2012 Filter classification	ISO 16890 Typical efficiencies against PM ₁	ISO 16890 Classification
F7	50-75%	ISO ePM ₁ (50%) to ISO ePM ₁ (75%)
F9	85%-95%	ISO ePM ₁ (85%) to ISO ePM ₁ (95%)
H13	99.95% at MPPS*	Not applicable†

*MPPS, most penetrating particle size

†ISO 16890 standard deals with bag and panel filters for now, but not HEPA filters, the latter covered by EN 1882

Table A6. ISO 16890 filter groups

Group designation	Requirement			Class reporting value
	ePM ₁ , min	ePM _{2.5} , min	ePM ₁₀ , min	
ISO Coarse	–	–	<50%	Initial grav. arrestance
ISO ePM ₁₀	–	–	≥50%	ePM ₁₀
ISO ePM _{2.5}	–	≥50%	–	ePM _{2.5}
ISO ePM ₁	≥50%	–	–	ePM ₁

Appendix I: Checklist of Action Points in the Event of a Suspected Cluster of Cases of Nosocomial Aspergillosis

- IPCTs must be vigilant at all times for an increase in the number of cases of IA. Clinical teams should also be informed to report cases of suspected/proven IA to the IPCT, especially during periods of renovation/construction work.
- The IPCT should undertake a preliminary investigation of the circumstances when an unexpected increase in number of suspected/proven cases is reported. The following should be assessed during this preliminary review:
 - The number of cases and the strength of evidence of each case
 - The time period when the cases occurred
 - What are the host risk factors for IA?
 - What is the ventilation system provided to the ward/clinical area?
 - Is there nearby renovation/construction work?
 - Are there any other patients in that ward/clinical area with *Aspergillus* spp. growing from respiratory samples?
 - Are any records available from monitoring of air quality through *Aspergillus* CFUs or particle counts, including corresponding counts from the area outside the ward/clinical area? If so, these should be reviewed for evidence of ingress of *Aspergillus* spp.
 - Air sampling of the clinical area should be considered at this stage.
 - The ward/clinical area should be inspected for: evidence of dust, damage to infrastructure, e.g. to ceiling tiles, open windows; maintenance records of air ventilation systems that provide air supply to the ward/clinical area.
- The results of the preliminary investigation should inform the IPCT whether or not a formal hospital investigation should be undertaken.
- If a formal hospital investigation is required, this will likely involve convening a multidisciplinary meeting comprising the IPCT with representatives of the clinical team(s) involved, the Microbiology Department, Estates Department, and Senior Management, and may quickly transform into the Outbreak Control Team (OCT) in accordance with local policy.
- The Public Health Department should be notified at this stage that a possible outbreak of nosocomial aspergillosis is under investigation.
- If not already completed, air sampling for *Aspergillus* spp. CFUs should be undertaken both within the affected ward and outside the ward to identify if there has been ingress of *Aspergillus* spp.
- Further consideration should be given to the need for:
 - Antifungal prophylaxis for, at the least, high-risk (Group 3) and very high-risk (Group 4) patients.
 - The employment of portable HEPA filtration units, pending further investigation of the ventilation system and possible sources of *Aspergillus*.
 - Transfer of patients from the affected ward/clinical area may need to be considered if an ongoing source of *Aspergillus* is identified.

Appendix J: Information Leaflet on Aspergillosis during Construction Activities

General Information

The purpose of this leaflet is to inform patients, relatives, healthcare workers and those involved in the activities of construction of the risk of aspergillosis during construction work. This leaflet should be considered as introductory information only.

Aspergilli are tiny fungi that cannot be seen by the eye but commonly occur in soil, water and decaying vegetation. They can also live in old buildings or in areas such as ventilation shafts. Many types of *Aspergillus* are found in nature but only a few species cause human diseases.

Aspergillus may be released into the air during construction/renovation/demolition activities. *Aspergillus* can be transported great distances by normal conditions such as air currents and wind. Small pieces of dirt or dust in the air are the main ways that *Aspergillus* travels and causes infection in hospitals. Hospital activities that generate dust such as maintaining the ventilation system, cleaning, vacuuming and dry dusting can also allow *Aspergillus* to travel through the air.

Patients who are undergoing high dose chemotherapy for leukaemia and related illnesses or who are having bone marrow, stem cell or other transplants, or who are having other forms of therapy which may suppress their immune system may be at risk of developing infection with this fungus in the lungs or other parts of the body. Healthy adults and children are not at increased risk of infection during construction work.

For the Patient

Should you be undergoing treatment in hospital which suppresses your immunity to infection you may become susceptible to developing infection with a fungus found in the environment called *Aspergillus*. Everyone breathes it into their airways and it normally doesn't do any harm. However, this fungus can be a major cause of illness if you become exposed to high numbers of *Aspergillus* in the air while your immunity is suppressed. This immunosuppression can be caused by an underlying blood cancer like leukaemia, by chemotherapy, or other immunosuppressive drugs e.g. drugs like corticosteroids, by stem cell or solid organ transplantation, or because of an underlying chronic lung condition. During building work every effort will be made to prevent the spread of *Aspergillus*. The medical team who are treating you will be in close communication with builders and the Microbiology/Infection Prevention and Control Team to make sure that the risk of spreading *Aspergillus* is kept to a minimum and will tell you if you need to take any special precautions.

Appendix K: Frequently Asked Questions (FAQs)

What is *Aspergillus* and why is it a hazard for certain hospitalised patients?

Aspergillus is an environmental mould fungus that survives in soil and dust. Disturbance of these during hospital building, renovation or demolition work can generate airborne spores of the fungus which if inhaled by susceptible patients can lead to an often fatal lung infection called invasive aspergillosis.

Which patients are at risk of developing invasive aspergillosis?

Severely immunocompromised patients such as those undergoing treatment for leukaemia, transplant recipients or those receiving long-term immunosuppressive therapies, e.g. steroids, are at risk of developing invasive aspergillosis. Patients in intensive care, particularly those with underlying chronic lung conditions e.g. Chronic Obstructive Pulmonary Disease (COPD) have more recently been identified as being at increased risk. On the basis of the known incidence of invasive aspergillosis in these patient populations an at-risk classification can be devised which guides the preventive measures needed for their protection during hospital building work.

What preventive measures are effective to prevent nosocomial aspergillosis?

A risk assessment will help to devise a combination of measures that may include environmental dust control and cleaning, prevention of ingress of airborne spores from outside clinical areas, protective environments for highest risk patients, and antifungal drug prophylaxis.

What type(s) of protective environment are used to prevent nosocomial aspergillosis?

HEPA-filtered positive pressure isolation rooms are the only type of protective environment for which there is a scientific evidence base. Recently, neutral pressure isolation rooms have been introduced which may provide some protection to at-risk patients but they have not been shown to reliably prevent ingress of fungal spores from outside the patient's isolation room.

Which antifungal drugs are effective for prophylaxis against *Aspergillus* infection, and which patients should be prescribed them?

Published international guidelines show that the evidence for effective prevention of *Aspergillus* infection is limited to patients with haematological malignancies and those undergoing haematopoietic stem cell transplantation. The triazole Posaconazole has the strongest grade of recommendation in these groups.

Is there concern about triazole antifungal drug resistance in *Aspergillus*?

Resistance to the triazoles in the main pathogenic species *Aspergillus fumigatus* has been reported in an increasing number of countries. To date, the prevalence of drug resistance is variable and unpredictable. Ideally all clinical isolates of *A. fumigatus* from at-risk patients should be tested *in vitro* for susceptibility to triazoles. Other *Aspergillus* species are less commonly identified as pathogens in this setting but have less predictable susceptibility to triazoles.

Should clinical areas with at-risk patients be monitored by environmental air sampling?

Routine air sampling is not recommended; however, where major works are to be undertaken it may be useful to establish baseline levels of *Aspergillus* in the air and continue to monitor during construction work in order to detect increased counts which will prompt additional preventive measures.

Is aspergillosis difficult to diagnose?

Yes, because clinical symptoms and signs are not specific to invasive aspergillosis and a definitive diagnosis by e.g. lung tissue biopsy is often not feasible. A combination of clinical, radiological, and laboratory criteria help to identify patients with probable invasive aspergillosis. These measures should be employed as part of monitoring at-risk patients during any construction activities.

Do all patients who develop evidence of invasive aspergillosis acquire it from the hospital environment?

No, some patients may be admitted to hospital with *Aspergillus* infection that is not clinically manifested but only when they receive intensive immunosuppression do they develop clinical signs and symptoms.

What measures should be taken before a hospital project associated with potential release of airborne *Aspergillus* spores is started?

All interested parties must be informed in advance of the scope and activity of the planned project. The Hospital Infection Prevention and Control Team will advise on which clinical areas with at-risk patients may become affected and what appropriate preventive measures are required. Tender documents must comply with national and local guidelines on prevention of nosocomial aspergillosis. A permit to work will be required for each phase of the project.

