

National Guidelines for the Prevention of Nosocomial Invasive Aspergillosis During Construction/Renovation Activities DEVELOPED BY A SUB-COMMITTEE OF THE SCIENTIFIC ADVISORY COMMITTEE OF THE NATIONAL DISEASE SURVEILLANCE CENTRE

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Scientific Advisory Committee Aspergillus Sub-committee Members

Dr. Lynda Fenelon (Chair) Consultant Microbiologist, St. Vincent's Hospital, Dublin.

Dr. Olive Murphy Consultant Microbiologist, Bon Secours Hospital, Cork.

Prof. Shaun McCann¹ Consultant Haematologist, St James's Hospital, Dublin.

Dr. Eibhlín Connolly Deputy Chief Medical Officer, Department of Health and Children.

Mr. Eoin O'Moráin Architect, Scott Tallon Walker Architects, Dublin. Representing Royal Institute of Architects of Ireland.

Mr. Anthony Hogan Engineer, JV Tierney & Co., Dublin. Representing Institution of Engineers of Ireland.

Mr Frank Jackman² Chief Architectural Adviser, Department of Health and Children.

Mr. Des Fitzgerald Architectural Adviser, Department of Health and Children.

Mr. Wilf Higgins Engineering Adviser, Department of Health and Children.

Ms. Helen Murphy³ Infection Control Nurse, Our Lady's Hospital for Sick Children, Dublin. Representing the Infection Control Nurse's Association.

Ms. Siobhan Prout Infection Control Nurse, St Vincent's Hospital, Dublin. Representing Infection Control Nurse's Association.

Dr Niamh O'Sullivan Consultant Microbiologist, Our Lady's Hospital for Sick Children, Dublin. Joined Committee in January 2002.

Dr. Paul Browne Consultant Haematologist, St James's Hospital, Dublin.

Dr. Margaret Fitzgerald (Secretary) Surveillance Scientist, National Disease Surveillance Centre.

- 1. Prof. Shaun McCann took sabbatical in January 2002 and was replaced on committee by Dr. Paul Browne.
- 2. Mr. Frank Jackman retired form DoHC in September 2000 and was replaced on committee by Mr. Des Fitzgerald and Mr. Wilf Higgins.
- 3. Ms. Helen Murphy retired from committee in May 2000 and was replaced by Ms. Siobhan Prout.

This document has been prepared with particular reference to the following:

- Construction-related Nosocomial Infections for Patients in Health Care Facilities: Decreasing the Risk of Aspergillus, Legionella and Other Infections. Canada Communicable Disease Report 2001, **27**(S2); 1-55 (http://www.hc-sc.gc.ca).
- Centers for Disease Control and Prevention Healthcare Infection Control Practices Advisory Committee (HICPAC). Draft Guideline for Environmental Infection Control in Healthcare Facilities, 2001.
- Newcastle-upon-Tyne City Health Trust Estates Department Operational Policy for *Aspergillus* Management EOP53 (Version 1 updated 2nd February 2000)
- Aspergillus website ~ www.aspergillus.man.ac.uk

These guidelines are mainly consensus based, with evidence used where available. A consultation document containing draft guidelines was circulated in April 2001 to interested parties and was also posted on the NDSC website for general consultation. The final document was prepared following the consultation process and the Sub-Committee would like to thank all those who participated in this process.

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Nosocomial outbreaks of invasive aspergillosis have become a wellrecognised complication of construction, demolition or renovation activities in or near hospital wards accommodating immunocompromised patients. Nosocomial aspergillosis is a cause of severe illness and mortality in these patients.

The purpose of this document is to act as guidance for healthcare staff to ensure that construction/renovation activities in hospital providing for atrisk patients are undertaken in a safe and appropriate manner to reduce the risk of infection in these patients. The document outlines the risk factors contributing to nosocomial invasive aspergillosis and identifies the at-risk patients. Recommendations are made as to the measures that can be undertaken to reduce these health risks.

Where construction/renovation projects are planned in hospitals providing for at-risk patients, a multi-disciplinary team comprising of hospital administrators, technical services staff, designers, infection control staff and relevant clinicians should be established to develop and monitor the implementation of risk management and infection control policies. Clear lines of communication among all personnel involved must be established at the planning phase. The protection of vulnerable patients will depend on the acceptance and effectiveness of implementing infection control measures which will require a high level of commitment, understanding and co-operation from all personnel involved in the construction/renovation project.

Dr Lynda Fenelon Chairperson Aspergillus Sub-committee It is recognised that outbreaks of nosocomial invasive aspergillosis may occur in association with construction/renovation activities. Because of the high mortality rate associated with invasive aspergillosis in immune suppressed patients, the committee recommends that measures be implemented in hospitals to control this risk where construction/renovation activities are planned. The following are the recommendations of the committee:

Organisational duties and responsibilities

That hospital managers ensure that hospitals have an infection control committee with responsibility for drawing up a hospital policy for the prevention of invasive aspergillosis.

That when major construction work is planned, hospital managers ensure that a multidisciplinary team comprising hospital administrators, infection control staff, technical services staff, designers and relevant clinicians in high risk areas is established, and that policies and procedures are put in place to minimise the risk of invasive aspergillosis that clearly outline the responsibilities of all personnel involved.

Classification of at-risk patients

That patients are risk assessed and divided into categories according to the degree of risk of invasive aspergillosis.

Preventive measures to control invasive aspergillosis

That a number of measures be undertaken to protect at-risk patients from exposure to *Aspergillus* spores. These measures may be divided into construction and ventilation measures, infection control measures and chemoprophylaxis.

Construction and ventilation measures should consist of

- Measures to reduce dust from construction areas.
- Measures to physically protect at-risk patients.

Infection Control measures should include

- The education of health care workers, project managers, contractors, design teams, health and safety supervisors, cleaning supervisors, patients and relatives of the patients on the risk of invasive aspergillosis and the steps that should be taken to reduce this risk.
- Cleaning procedures directed at reducing dust in clinical areas.
- The control of pedestrian, supply and construction-related traffic.

A Construction Permit should be used to ensure that the construction, ventilation and infection control measures are appropriately instituted. A sample Construction Permit is provided in Appendix 1.

Chemoprophylaxis

- That antifungal chemoprophylaxis is considered in at-risk patients in line with current guidelines and hospital policy. Chemoprophylaxis may also be considered in at-risk groups in the presence of construction work if these patients cannot be protected by environmental measures.
- That each centre evaluates its at-risk population and determines if chemoprophylaxis is likely to be of benefit.

Diagnostic strategies for invasive aspergillosis

- That all effort be made to ensure an early diagnosis of invasive aspergillosis.
- That a multidisciplinary approach combining clinical, radiological and microbiological criteria be used to predict the probability of invasive disease.
- That newer technologies, which aid the early diagnosis of infection, continue to be evaluated and developed.
- That a National Mycology Reference service be developed to improve the management of aspergillosis and other fungal infections.

1. Introduction

1.1 Background

Certain types of construction activities can result in increased incidence of invasive aspergillosis among immunosuppressed patients. Because of the high mortality rate associated with invasive aspergillosis in these patients, it is essential to minimise these risks. While construction activities are taking place it is necessary that immunosuppressed patients be protected over that period. As there is no real consensus worldwide as to how this should be done, there is a real need to develop Irish National Guidelines to control invasive aspergillosis during hospital construction/renovation activities. Therefore, with the agreement of the Department of Health and Children, the Scientific Advisory Committee (SAC) of the National Disease Surveillance Centre (NDSC) established a multidisciplinary sub-committee of SAC to develop these guidelines.

1.2 Membership of the Sub-Committee

This multidisciplinary sub-committee comprises of representatives from Microbiology, Infection Control, Haematology, Department of Health and Children, Engineering, Architecture and the National Disease Surveillance Centre.

1.3 Terms of Reference of the Sub-Committee

The sub-committee was requested to address the following:

- 1. To identify (a) at-risk patients and (b) risk factors which contribute to invasive aspergillosis in hospitals during construction/renovation activities.
- 2. To identify measures to reduce the incidence of invasive aspergillosis.
- 3. To develop national guidelines for the prevention of invasive aspergillosis during construction/renovation activities in hospitals.
- 4. To identify the requirements in relation to the use of reference facilities.

2. Construction-Associated Nosocomial Invasive Aspergillosis

2. A Literature Review

Construction-related indoor fungal aerosol pollution can create unhealthy conditions for susceptible individuals. The source of such aerosols can originate from outdoor or indoor activity, which causes the disturbance of settled spores or the disruption of a locus of growth. The release of indoor spore aerosols may be caused by activities ranging from construction to cleaning. Outdoor sources of indoor fungal aerosols depend on proximity to such activities as construction or lawn mowing and the status of building penetrations by aerosolised mould and/or weather conditions. The source of such an aerosol problem must be recognised and eliminated to protect the health and safety of the building occupants. Airborne fungi that infect hospital patients are generally in the genus *Aspergillus*.

Aspergillus species are ubiquitous fungi that commonly occur in soil, water, organically enriched debris and decaying vegetation.¹ Many species of *Aspergillus* have been recognised in nature but only a few have been associated with human disease, namely *A. fumigatus, A. flavus, A. niger, A terreus* and *A. nidulans*.¹ *Aspergillus* spp. are responsible for a wide spectrum of human illnesses ranging from colonisation of the bronchial tree to rapidly invasive and disseminated diseases.² Invasive aspergillosis is primarily an infection of severely immunocompromised patients i.e. patients with haematological malignancies and bone marrow and organ transplants³⁻⁶ and is difficult to diagnose and treat.⁷ Mortality is still high despite new therapies, thus making prevention a high priority in the management of all at-risk patients.⁸⁻¹²

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. *Aspergillus* spores are superbly adapted to airborne dissemination.¹³ 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 (2.5–3.5 µm) permits them to reach the pulmonary alveolar spaces, where they may germinate to form hyphae.¹⁴ 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.¹⁵

Cases of aspergillosis may increase dramatically especially in immunocompromised patients during hospital construction/renovation activities. Hospital outbreaks of aspergillosis have been reported, for example, in transplantation units,¹⁶⁻¹⁸ haematology and oncology units,^{5,8,19} intensive care units, ²⁰⁻²¹ renal unit¹¹ and medical wards where immunosuppressed patients were nursed.²²⁻²³ Summaries of the documented reports on construction-related aspergillosis outbreaks are outlined in Table 1.

The majority of the outbreaks reported were 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 health care 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. Aspergillosis outbreaks have also been associated with improper operation and poor maintenance of sophisticated air ventilation systems. Furthermore, any dust generating activities such as maintaining the ventilation system, cleaning, vacuuming and dry mopping can render *Aspergillus* spp. airborne (see Table 1 for details).

Etiologic Agent	Underlying Medical Condition	Source of Etiologic Agent	Number of patients infected	Number of deaths	Reference Number
A. niger A. flavus A. fumigatus	Diagnosis not provided Hospital admits patients with cancer	Aspergillus spore settled on wet fireproofing material when installed during construction. Spores dispersed when the dry fireproofing material was disturbed above false ceiling during renovation and maintenance.	œ	n	8
A. fumigatus (3)	Renal transplant	Renovation activity in floor above caused dust to be dispersed from false ceilings in the renal transplant ward.	က	-	16
A. fumigatus A. flavus	Haematologic malignancy (2) Advanced age (1) Renal transplant (7)	Window air conditioners in the renal transplant unit heavily contaminated with <i>Aspergillus</i> spp. Unit was in close proximity to adjacent road construction.	10	10	17
A. flavus (32)	Old cavity TB, Diabetes Idiopathic thrombocytopenic purpura Leukaemia, Lung cancer Chronic obstructive airways disease Bacterial pneumonia	Construction activity adjacent to hospital and defective ventilation system and air filtration system.	۵	Ŧ	24
A. flavus (3) A. fumigatus (2) A. niger (1)	Leukaemia	Repair of false ceiling due to water leak in storeroom housing intravenous supplies. Adhesive tape and arm boards were contaminated.	ΰ	N	25
Aspergillus	Neonatal ward (premature infants)	Major source of mould was dust above the false ceiling.	5	2	26

* 32 patients had Aspergillus isolated from a respiratory specimen, however, only 6 patients regarded as infected, the remainder were colonised

Etiologic Agent	Underlying Medical Condition	Source of Etiologic Agent	Number of patients infected	Number of deaths	Reference Number
A. flavus (4) A. fumigatus (1) A. niger (1) Other Aspergillus spp.	Immunosuppressed patients	Not provided. Patients were either located on the same floor or the floor below the construction area.	÷	÷	2
A. fumigatus (18)	Leukaemia (22)	Spores freed into the atmosphere as a result of demolition of ducts and false ceilings, the removal of fibrous thermal insulating materials and work on roller-blind castings.	22	8	4
Aspergillus (3) Zygomycetes (2)	Burkitt's lymphoma (1) Leukaemia (4)	Exposure to construction activity, windows could be opened in unit patients were in.	Q	Q	27
A. fumigatus (6)	Bone Marrow Transplant	Heavy spore contamination resulted from construction of an adjacent BMT unit.	G	ω	18
A. fumigatus (6)	Immunocompromised	Cluster of cases was due to a common source outbreak related to construction activity in a central radiology suite serving the hospital.	ω	N	28
Aspergillus	Immunosuppressive therapy for vasculitis	Construction work and demolition of hospital buildings adjacent to the medical unit the patients were housed. Contributing factors: no special ventilation system and windows could not be completely closed.	n	σ	53
A. fumigatus (3)	Heart transplant (3)	Connecting bridge between the old and new unit allowed dust to circulate from the construction site. In addition, one air vent was not properly closed.	R	5	29

Table 1 continued

Etiologic Agent	Underlying Medical Condition	Source of Etiologic Agent	Number of patients infected	Number of deaths	Reference Number
Aspergillus	Patients in haematology unit	Large-scale excavation work while hospital was being rebuilt. The isolation rooms that housed the patients overlooked the building site.	a	ى	30
A. fumigatus	Patients in intensive therapy unit	Spores in fibrous insulation material above perforated metal ceiling dispersed during minor building in adjacent offices and stores area.	Ű	Ю	20
A. terreus (4)	Bone Marrow Transplant (2) Leukaemia (1) Disseminated choriocarcinoma (1) Diagnosis not available (2)	Renovations taking place two floors below intensive care unit (ICU). Air pressure in ICU negative to hallway and nearby elevator shaft.	G	4	21
A. flavus (5) A. fumigatus (6)	Patients in Bone Marrow Transplant/ leukaemic unit	Fire in an old building close to the hospital, and repeated window opening by a patient shortly afterwards suggest that fungal spores dispersed during the fire were the source. The hall carpet then became contaminated and was an ongoing source of infection until cleaning regime was altered.	ξ	Ω	ñ
A. fumigatus (2) A. flavus (1) Unknown (2)	Oncology	Significant increase of mould in air in patient rooms and corridors after construction started. Leaks around windows suspected as the major source, as amount mould in the air decreased following sealing these leaks.	Q	Not provided	19
Aspergillus	Patients in burns, dialysis and oncology units	Air intake vents in units where the patients were housed had not been covered during demolition work.	υ	Not available	32

Table 1 continued

Etiologic Agent	Underlying Medical Condition	Source of Etiologic Agent	patients infected	Number of deaths	Number
A. fumigatus (3)	Oncology	Remodelling of adjacent radiology department. Dust barriers had not been installed.	m	-	33
A. fumigatus A. niger A. terreus	Burn (2) Trauma (1) Perforated viscus (1)	Aspergillus spores dispersed as a result of renovations in inventory control department. Settled on supply boxes, packages inside became contaminated. Patients then infected when packages opened during dressing changes.	4	Not available	34
Aspergillus	Leukaemia (34) Bone Marrow Transplant (2)	Hospital construction may have been related to the outbreak.	36	17	ω
A. flavus (6) A. fumigatus (1) M. rhizopus (1)	Leukaemia Cancer	Directly related to increased spore counts from soil excavation that occurred during hospital construction.	ω	ß	٥
A. fumigatus (1)	Chronic obstructive airways disease (2)	Exposure to high concentrations of airborne <i>Aspergillus</i> spp. following air filter change in ICU	8	Ν	10 **
A. fumigatus (3)	Renal disease (3)	Hospital renovation on a unit near the renal unit where the patients were housed.	σ	Ν	5
A. fumigatus (4) Aspergillus spp. (3)	Rheumatology (5) Not stated (2)	Extensive renovation throughout the hospital. Construction areas were neither sealed off from patient areas nor under negative pressure relative to patient-care areas.	2	4	12

Table 1 continued

3.1 Introduction

Host immunity plays a major role in determining who may be at risk of developing invasive aspergillosis. When a patient with normal immunity is exposed to *Aspergillus* spp., macrophages kill the conidia while neutrophils are a defence against the mycelia. When the host is immunocompromised, an increased likelihood of invasion of tissue by *Aspergillus* spp. can occur. The major risk factor for invasive aspergillosis is prolonged and severe neutropenia, both disease- and therapy-induced. The duration of neutropenia is an independent risk factor for the development of invasive fungal infections. The incidence of invasive aspergillosis in at-risk groups is shown in Table 2. Bone-marrow transplant recipients are the population at highest risk. However, 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 and steroid therapy.

Table 2. Incidence of invasive aspergillosis in at-risk groups

Host group	Incidence of invasive aspergillosis
Allogeneic bone marrow transplantation	5-10%35-36
Autologous bone marrow transplantation	0-5%35-36
Peripheral blood stem-cell transplantation	5 %*36
Cytotoxic-therapy-induced granulocytopenia	Up to 70%37
Kidney transplantation	0-3%38
Liver transplantation	1-15% ³⁹⁻⁴¹
Heart/Lung transplantation	0-20%42-43
Heart transplantation	0-25%44

* Preliminary data as this is a new therapy

3.2 Classification of at-risk patients

At-risk patients may be categorised as follows:

Group 1 ~ No evidence of risk

- 1. Staff members, Service Providers and Contractors
- 2. All patients not listed in Groups 2 4 below

Group 2 ~ Increased risk

- 1. Patients on prolonged courses of high dose steroids particularly those hospitalised for prolonged periods
- 2. Severely immunosuppressed AIDS patients
- 3. Patients undergoing mechanical ventilation
- 4. Patients having chemotherapy who are not neutropenic**
- 5. Dialysis patients

Group 3 ~ High risk

- 1. Neutropenia for less than 14 days following chemotherapy
- 2. Adult acute lymphoblastic leukaemia (ALL) on high dose steroid therapy
- 3. Solid organ transplantation
- 4. Chronic Granulomatous Disease of Childhood (CGDC)
- 5. Neonates in intensive care units (ICU)

Group 4 ~ Very high risk

- 1. Allogeneic bone marrow transplantation
 - a. during the neutropenic period
 - b. with graft versus host disease
- 2. Autologous bone marrow transplantation, i.e. during the neutropenic period
- 3. Peripheral stem cell transplantation, i.e. during the neutropenic period
- 4. Non-myeloablative transplantation
- 5. Children with severe combined immuno-deficiency syndrome (SCIDS)
- 6. Prolonged neutropenia for greater than 14 days following chemotherapy or immunosuppressive therapy
- 7. Aplastic anaemia patients

4.1 Introduction

The key to eliminating *Aspergillus* infection is first to minimise the dust generated during construction activity and second, to prevent dust infiltration into adjacent patient care areas. Studies have demonstrated the effectiveness of preventive measures when implemented in health care facilities ^{2,8,45-47} as well as in commercial and residential buildings.⁴⁷

In a study by Loo *et al.* (1996)⁸ the following environmental control measures were used: (i) portable high-efficiency particulate air (HEPA)-filter air purifier units were installed in rooms housing neutropenic patients; (ii) application of copper-8 quinolinolate formulation to walls, doors, frames, baseboards, exterior surfaces of radiators, vents in the rooms and above the false ceilings of the adjacent hallway to decontaminate the area; (iii) windows were sealed; (iv) existing perforated ceiling tiles were replaced with easy-to-clean, non-perforated, vinyl-faced aluminium tiles; (v) horizontal dust-accumulating blinds were replaced with vinyl opaque, roller shades; (vi) the ventilation system was meticulously maintained; (vii) patient rooms were cleaned regularly and (viii) patients were moved to another area of the hospital during the implementation of these measures. In this particular study the authors concluded the environmental control strategy implemented played an important role in controlling the outbreak of construction-associated invasive aspergillosis.⁸

Other measures that have been used include the erection of airtight plastic and dry wall barriers around the construction sites, the use of negative-pressure ventilation in the construction area,² covering of all air intake and exhaust vents in the construction zone with plastic to prevent the introduction of contaminated air into the hospital heating, ventilation and air conditioning systems, capping the open ends of any existing ventilation ducts in the construction zone, redirection of construction traffic away from patient areas, regular removal of the construction debris from the site in sealed containers or at least covered by a damp cloth, the use of sticky mats and damp cleaning.⁴⁶

The environmental control 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 the risk assessment. The categories of construction/renovation activities and the recommended preventive measures for these activities are outlined in a Sample Construction Permit provided in Appendix 1.

Preventive measures can be considered under the following headings: (i) construction and ventilation measures; (ii) infection control measures and (iii) chemoprophylaxis.

4.2 Construction and Ventilation Measures

A number of measures may be implemented by hospital construction designers and maintenance personnel to protect at-risk patients during building activities on hospital sites. The measures identified in the available literature on the subject vary from basic minimal precautions and good housekeeping to major mechanical services intervention involving dedicated HEPA filtered installation systems to protect the areas in which the at-risk patients are housed.

These measures may be divided into:

- Measures to reduce dust emission from construction area
- Measures to physically protect at-risk patients

4.2.1 Measures to reduce dust emission from construction area

 The construction area should be sealed fully during the construction period. A dust barrier should be created from the floor to the slab (true ceiling) and edges sealed. For short-term minor projects this may be plastic sheeting, however for more longterm projects this should be a solid sealed barrier. It may be necessary to create a lobby (anteroom) if the barrier is the entrance/egress for construction workers.

- 2. All windows, doors, vents, plumbing penetrations, electrical outlets and any other sources of potential air leak should be sealed in the construction zone.
- 3. Air pressure in the construction zone should be negative compared with adjacent areas. An extract fan may be used for this purpose. Air from the construction zone should be exhausted directly to the outside and this is the most appropriate option. If this is not possible then the air should be filtered through HEPA filters (that have been properly fitted and strictly monitored) before being re-circulated to the hospital.
- 4. Dust reduction techniques should be used for cutting and hole boring.
- 5. Debris should be removed from the construction area at the end of each working day. Debris should be removed in covered containers preferably through window openings. A chute may be necessary if the construction is above ground floor level. In addition, normal good housekeeping procedures should prevail during the operation in particular, holding skips and other containers should be kept moistened and/or covered. The construction area should be vacuumed on a daily basis or more frequently if required, to maintain an environment as free from dust as possible.
- 6. A mat with a sticky surface or moist carpet should be placed inside the exit from the construction zone to trap dust. This should be vacuumed/changed daily or more frequently when visibly soiled.
- 7. Construction workers should wear protective clothing, which should be removed before leaving the construction zone.

The measures implemented to reduce dust emission from the construction area will vary depending on the construction/renovation activity. The measures required for the various types of construction activity are outlined in the Sample Construction Permit (Appendix 1).

4.2.2 Measures to physically protect at-risk patients

- Patients who are at risk should be moved to an area away from the construction zone if the air quality cannot be guaranteed during construction. At-risk patients (Groups 2-4) should wear protective masks if it is necessary to transport them through a construction area. These masks should be capable of filtering *Aspergillus* spores such as particulate-filter respirators (PFR 95) which give a >95% filtration efficacy of 0.3 µm particle size and are used in association with the National Institute for Occupational Safety and Health (NIOSH) regulations.
- 2. All windows, doors (apart from essential access points) and vents should be sealed in areas of the hospital containing patients who are most susceptible (Groups 2-4), if the construction or demolition work is considered likely to result in *Aspergillus*contaminated air entering these areas. If the area is not served by a ventilation system, these precautionary measures may result in unacceptable environmental conditions within the area involved. Any fresh air introduced into this area must be HEPA filtered. If the area is connected to a central ventilation system, it is important that prior to construction works, the ventilation should be thoroughly checked and if it is to remain functional, it should be fitted with HEPA filters if air from the construction zone may be drawn into the system.
- 3. For very high-risk patients (Group 4), it is recommended that an environment that is fully HEPA filtered and at positive pressure is provided. This involves the installation of dedicated remote air handling systems, which are ducted through supply systems to the at-risk area. The intake air handling unit is fitted with a combination of coarse bag and panel filters and finally a HEPA filtered section which is the only filter capable of trapping the 2.5 to 3.5 µm size of the *Aspergillus*

spore. Typically, these dedicated ventilation/filter units should provide an air exchange rate of >12 air changes per hour within the at risk area and a pressure differential for positive pressure areas of >2.5 pascals (ideal pressure differential of >8 Pa).⁴⁸

4. A mat with a sticky surface should be placed at the entrance to the patient care area. This should be changed or vacuumed daily or when visibly soiled.

4.3 Infection Control Measures

Communication and education are two vital elements to the successful implementation of proactive infection control measures in the reduction and the attempt to eliminate the risk of nosocomial invasive aspergillosis in immunocompromised patients. Effective communication between all relevant parties; architects, engineers, technical services, sub-contractors, infection control, medical and nursing staff is of vital importance during all stages of construction work to implement effective infection control preventive measures. The hospital should designate education co-ordinators for each of the relevant parties.

4.3.1 Education

Health care workers should be educated on:

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

Project managers, contractors, design teams and health & safety supervisors should be educated 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.

Supervisors of cleaning staff/ contract cleaners should be educated 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.

At-risk patients (Groups 2-4) and the relatives of these patients should be informed of:

• The risks of nosocomial aspergillosis infection.

An information leaflet on aspergillosis should be provided (Appendix 2). The purpose of this leaflet is to inform patients, relatives of patients, health care 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.

4.3.2 Dust containment

The objectives of dust containment measures are:

- To minimise the dust generated during the work activity
- To prevent dust infiltration into adjacent patient care areas.

The categorisation of the construction activity in conjunction with its geographical location will determine the controls required to achieve these objectives. The use of a construction permit will assist in achieving compliance with the requirements (Appendix 1).

4.3.3 Cleaning

In addition to minimising dust through measures outlined in the construction permit increasing the existing cleaning regimes to prevent dust accumulation on surfaces, ceilings and air duct grilles will be necessary. As the quantity of dust generated will vary depending on the type of building activity, the increased cleaning regimes need to be adjusted accordingly to minimise dust accumulation. Damp dusting not dry cleaning is recommended. Air filtration systems must be regularly checked. Where vacuum cleaners are used, in areas where high-risk and very high-risk patients are cared for and in adjacent areas, these should be equipped with HEPA filters and appropriately maintained to minimise dust dispersal. Filters in the air filtration systems and the vacuum cleaners need to be changed regularly and a record/log should be kept of these changes.

4.3.4 Traffic

Pedestrian: Pedestrian traffic from the construction area should be directed away from patient areas, with workmen having a separate entrance to the construction site as outlined in the construction permit. When possible, patients and visitors should avoid entering the hospital adjacent to major construction/demolition sites, where debris or dust is being removed from the works area.

Supplies: Alternative routes, which avoid the construction site, through which inanimate items are transported throughout the hospital, may need to be identified during construction. Clean or sterile supplies or equipment should be transported to storage areas by a route that minimises contamination risks from the construction site.

In some critical areas and in some instances where it may not be possible to alter traffic patterns consideration will have to be given to scheduling construction to off-hour periods and weekends. Some areas may need to be relocated or closed temporarily.

4.4. Chemoprophylaxis and the Prevention of Invasive Aspergillosis

Data supporting the widespread use of antifungal chemoprophylaxis for the prevention of invasive aspergillosis are lacking. Some workers have found that antifungal chemoprophylaxis reduces fungal morbidity and mortality in high-risk groups but studies have been hampered by the low incidence of invasive aspergillosis and the use of small study groups making statistical analysis difficult. There is a well-recognised need for further studies in a variety of patient populations.

To date only two antifungal agents with activity against *Aspergillus* are licensed in this country, amphotericin B and itraconazole. However, newer agents will probably be available in the near future. Amphotericin B, in a variety of formulations, has been the gold standard in terms of the therapy of invasive disease. More recently the availability of a liquid and intravenous preparation of itraconazole has helped to overcome some of the bioavailability problems associated with the capsule formulation of this drug. In terms of chemoprophylaxis both of these agents, amphotericin B (in a variety of forms i.e. capsules, paste and various systemic preparations) and itraconazole have been used.

The use of non-absorbable and topical (intranasal and nebulised) amphotericin B for the prevention of invasive aspergillosis has been shown to be of some benefit however recent data have challenged their use. The use of low doses of parenteral amphotericin B has also failed to demonstrate an

adequate response and the toxic effects preclude the use of the conventional formulation at higher concentrations. A controlled trial of the lipid formulation however suggests that this approach may be useful,⁴⁹ but further work is required.

The problem with absorption of itraconazole in certain high-risk groups and the lack of an intravenous preparation has now been largely overcome with the advent of itraconazole-cyclodextrin. A number of studies have shown some benefit in those patients given prophylaxis however these again failed to reach statistical significance because of the low incidence of disease. A further issue with itraconazole is its potential for drug interactions and possible potentiation of toxicity of certain anti-cancer agents.

Who should receive antifungal prophylaxis based on current evidence?

Despite the lack of evidence, antifungal chemoprophylaxis has been recommended by some authors in patients expected to be neutropenic (ANC, $0.1-0.5 \times 10^9$ /l) for at least two weeks or profoundly neutropenic (ANC, $< 0.1 \times 10^9$ /l) for more than one week. The British Society for Antimicrobial Chemotherapy (BSAC) also made recommendation in 1993 for neutropenic and transplant patients nursed without HEPA filters where there is a high institutional rate of invasive aspergillosis or where building works are being undertaken.⁵⁰ Some authors have found a benefit to secondary prophylaxis in patients with a history of invasive aspergillosis and undergoing further treatments.⁵¹⁻⁵³ The use of chemoprophylaxis in the management of liver transplant recipients is again controversial although some centres use low dose amphotericin B.

Needless to say given the lack of evidence for the use of prophylaxis in high-risk patients, no data exist for its use in the lower risk groups. Bearing this in mind chemoprophylaxis may be considered in at-risk groups in the presence of construction work if these patients cannot be protected by environmental measures. Each centre should evaluate its at-risk population and determine if prophylaxis is likely to be of benefit.

4.5 Protective Measures for At-Risk Patients

Patients deemed to be at risk of systemic mould infection should be stratified on the basis of their underlying disease, its treatment and the area in the hospital in which they are being treated in relation to the proposed building programme.

4.5.1 Environmental measures

Very high-risk patients (Group 4)

Patients at very high risk (Group 4) should receive maximum protection irrespective of the type/size of the building programme. All very high-risk patients should be nursed in HEPA filtered positive pressure rooms during the neutropenic period. If they are subsequently transferred to a ward the windows should be sealed and suitable air quality provided (See Section 4.2.2, Point 2).

High-risk patients (Group 3)

Patients at high risk (Group 3) should receive protection if the area of treatment is juxtaposed or near the hospital construction area or if it is otherwise likely that *Aspergillus*-contaminated air may enter the area. High-risk patients should be nursed in a ward with sealed windows and suitable air quality (See Section 4.2.2, Point 2).

Increased-risk patients (Group 2)

Patients at increased risk (Group 2) are usually dispersed throughout the hospital and therefore physical protection may be impractical. Consideration should be given to moving patients away from the construction area.

4.5.2 Chemoprophylaxis

Antifungal chemoprophylaxis should be considered in at-risk patients in line with current guidelines and hospital policy.

4.6 Diagnosis and Surveillance

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 review of relevant clinical cases at ward level and review of relevant microbiological/histological specimens at laboratory level.

4.6.1 Diagnostic Strategies for Invasive Aspergillosis

Despite many advances in diagnostic microbiology, the diagnosis of invasive aspergillosis continues to present difficulties and challenges. Such difficulties hamper the ability to diagnose this disease in the early stages thus contributing to the high mortality associated with this infection. In addition this disease is uncommon and affects varied patient populations and many clinicians may have limited experience in the diagnosis and management of invasive aspergillosis.

There is no single diagnostic test that is applicable to all patients groups and the sensitivity and specificity of the available tests vary. The current gold standard involves the performance of invasive procedures, which are often contraindicated. A number of alternative methods are under development, however until the ability to diagnose this infection improves, a high index of suspicion in patients at risk of invasive disease is essential.

Currently a combination of clinical, radiological and microbiological criteria can be used to predict the probability of invasive disease. Such an approach however lacks both sensitivity and specificity. Post mortem examinations may be useful, when possible and acceptable to the relatives of the deceased, to detect infections undiagnosed in life. In the future it is likely that newer technologies will aid the early diagnosis of infection and initiation of appropriate therapy. It is important that diagnostic strategies continue to be developed and that expertise is readily available to assist clinicians in the management of these patients. It is recommended that a National Mycology Reference service be developed to address these issues (see Section 6).

Criteria that may be used to aid in the diagnosis of invasive aspergillosis

1. Clinical criteria: Invasive aspergillosis may manifest differently in different patient groups. It is important to insure that clinicians with at-risk patients under their care are aware of the additional risk that occurs during construction/renovation activities, that a high index of suspicion is maintained and clinical expertise in the area of diagnosis and management is readily available. Once a clinical suspicion exists appropriate investigations can be performed.

2. Radiological criteria: Radiological examination remains an essential part of the diagnostic strategy and hospitals managing these patients must ensure that appropriate facilities are available. The routine CXR is insensitive and patients with clinical features compatible with infection and in an at-risk group should have high resolution CT or MR imaging as soon as practicable after suspecting the diagnosis. The presence of lesions suggestive of invasive aspergillosis should trigger appropriate investigations and consideration of the need for immediate empirical antifungal therapy.

3. Microbiological techniques: The most appropriate diagnostic approach depends on the site of the infection.

Demonstration of tissue disease: The gold standard is the demonstration of fungal hyphae and the isolation of *Aspergillus* spp. from tissue specimens. As already outlined biopsy is often contraindicated in patients at risk and suspected of having invasive disease and is rarely performed.

Microscopy and Culture: This examination can be performed on a variety of specimens including biopsies, fluid aspirates, broncho-alveolar fluid, tracheal aspirates or sputum. Culture alone is insensitive, however, the combination of microscopy and culture will increase the diagnostic yield by 15-20%. Isolation of *Aspergillus* spp. from non-sterile sites e.g. upper respiratory tract may reflect colonisation and results should be interpreted in a clinical and radiological context. The use of specific fungal media has also been found to improve sensitivity.

Serology: Fluid, blood and aspirates can be examined for the presence of antibodies and antigen.

Antigen Detection

The detection of antigen remains a useful test in the diagnosis of invasive aspergillosis. *Aspergillus* spp. release antigens during growth *in vivo* and *in vitro*. A number of methods including latex agglutination, radioimmunoassay and enzyme immunoassay have been developed with varying sensitivity and specificity. A commercially available latex agglutination kit for the detection of galactomannan has been shown to have poor sensitivity and variable specificity, ~ 30% and 53-100%, respectively.⁵⁴⁻⁵⁷ The sensitivity of the test improves with the examination of serial samples and broncho-alveolar fluid. More recently a sandwich enzyme-linked immunosorbent assay (ELISA) for the detection of *Aspergillus* galactomannan, with improved sensitivity and good specificity (56-93% and 80-99%), has been developed.⁵⁶⁻⁶¹ The ELISA test is a more sensitive assay, detecting 0.5-1.0 ng/ml compared with 15 ng/ml for the latex test.⁵⁹ Galactomannan was detected at an earlier stage of infection by the ELISA assay, often before clinical and radiological signs of infection became apparent and in animal models the concentration of galactomannan in the serum was shown to correspond with the tissue burden. Again the examination of serial samples improved the sensitivity of the ELISA test. The major drawback is a false positivity rate of 10%.

Antibody Detection

Recent data suggest that antibody detection in transplant recipients may be of use in identifying those at risk of invasive aspergillosis and in those with chronic invasive aspergillosis.

Molecular techniques: The detection of *Aspergillus* spp. DNA in blood and other specimens has not been developed as yet to a clinically useful level. Such technology however will probably become an important part of the diagnostic workup in the future. The availability of reference laboratory facilities will be an important part of this development.

4.6.2 Environmental sampling for Aspergillus spp.

It is well recognised that air sampling for *Aspergillus* spp. is difficult and not always useful. Generally it is not recommended that sampling be performed routinely even if construction/renovation activities are taking place. However, there are occasions when sampling may be useful (Table 3).

If a decision is made to undertake air sampling, it is important that that the operator has a clear objective in mind, the limitations of the procedure are understood and a suitable method is used. It is particularly important that users understand that a sample will only reflect what is happening at one point in time and hence multiple samples at different sites and times will be required to give an accurate picture.

A recent review by Morris *et al.* (2000)⁶² summarises the factors that influence air sampling and examines the suitability of different air samplers. Examples as to when air sampling can be usefully applied and a simple procedure that has been used in previous outbreaks are outlined in this review. This recommended method is outlined in Appendix 3 and has been reproduced by permission of the senior author, Dr. Malcolm Richardson.

Tal	ble 3 Occasions when sampling for Aspergillus spores may be useful ⁶²
•	To monitor levels of contamination prior to occupancy of special controlled environments e.g. to determine efficiency of HEPA filters in laminar flow facilities
•	To identify potential sources of nosocomial aspergillosis when a case has been identified
•	To predict environmental spore contamination from outside sources
•	To identify defects/breakdown in hospital ventilation/filtration systems
•	To correlate outbreaks of invasive aspergillosis with hospital construction or demolition work
•	To monitor efficiency of procedures to contain hospital building wards where at-risk patients are managed

5.1 Introduction

A proactive approach is required to minimise the occurrence of nosocomial invasive aspergillosis. The categories of patients who are at risk of invasive aspergillosis are outlined in Section 3.2. Each hospital, which provides service to high-risk patients, should have procedures and policies in place to ensure that all relevant personnel are aware of the risks of invasive aspergillosis in these patients and the preventive measures required to minimise that risk; and should develop and adopt risk management and infection control policies in this regard that are regularly monitored for compliance and effectiveness.

5.2 Hospital Managers

The hospital Chief Executive Officer/Manager has overall responsibility for the health and safety of patients, staff and visitors. Hospital managers should ensure policies and procedures are put in place that clearly outline the responsibilities of all personnel involved in the prevention of invasive aspergillosis, either on a routine basis or in the course of minor or major maintenance and construction works. In general the hospital manager may devolve responsibility for the development of policies and procedures to the hospital ICC, but ultimate responsibility lies with the hospital manager to ensure that these policies and procedures are implemented.

5.3 Liaison and Communication

Communication and awareness of the risk factors associated with the development of invasive aspergillosis is the key to reducing the risk to patients. The hospital ICC should ensure that a policy is in place outlining the necessary action for the prevention of invasive aspergillosis, both on a routine basis and in the course of minor or major maintenance or construction/renovation activities. The ICC should follow current knowledge of best practice in the control of *Aspergillus* and ensure that all policies are kept up-to-date. In the event that major construction/renovation activities are planned in hospitals providing for at-risk patients, a multidisciplinary team comprising hospital administrators, technical services staff, designers, infection control staff and relevant clinicians in high-risk areas should be established. This team should have the responsibility for drawing up a specific policy for the planned activities and should have overall responsibility for monitoring its implementation.

5.4 Technical Services Staff

Technical services staff should be aware of the risks posed by construction activity to at-risk patients (Groups 2-4) and should consult with the infection control team in advance of all minor or major construction or renovation activities. Technical services staff should monitor implementation of preventive practices and maintain records relating to fixed plant precautions and maintenance of *Aspergillus* protection systems. The use of a Construction Permit (Appendix 1) is recommended to control such activities.

5.5 Infection Control Team

It is crucial that infection control personnel are consulted and play a major role in planning construction or renovation activities. Technical services staff should ensure details of all works and maintenance activities are communicated to the infection control team who in turn should liaise with medical and nursing staff. Although the construction activity may be considered minor, infection control personnel should be notified and a risk assessment should be carried out.

5.6 Medical and Nursing Staff

Medical and nursing staff should be aware of patient populations at risk, potential hazards that construction/renovation projects pose to patients, and the preventive measures required. The infection control team should collaborate with medical and nursing staff to identify patients at risk, and to monitor the effectiveness of preventive measures taken throughout the project.

5.7 Preparation of Briefs

When planning major hospital construction works, the preventive measures required should be identified in advance during the initial risk assessment and should be included in the tender documents to ensure all necessary precautionary measures are taken. This should also be incorporated into the contract documents. A mechanism should be established whom has the authority to stop the construction project if there is a significant breach in the preventive measures. Notes on Preparation of Requirements are outlined in Appendix 4.

5.8 Construction/Renovation Activities in Close Proximity to the Hospital

It should be noted that similar risks are present in the context of large-scale construction/renovation activities external to but proximal to the hospital. Hospital managers should ensure that they are aware of such activities (e.g. by liasing with the planning authorities to receive notification of planning decisions in the locality) and institute precautionary measures to protect at-risk patients where appropriate, based on the findings of the risk-assessment.

6. National Reference Laboratory Facilities

It is recommended that a National Mycology Reference Laboratory be established to provide a laboratory reference service to the population of Ireland. Samples referred should be accepted from laboratories throughout Ireland. A service agreement between the Department of Health and Children and the "provider" of the reference laboratory service for fungi should be drawn up. The provider would be expected to comply with the relevant quality standards, audits and performance targets.

A national reference facility should be capable of providing the following services:

- 1. Identification of fungal isolates
- 2. Molecular typing of fungi
- 3. Molecular and serological diagnosis of fungal infections
- 4. Therapeutic drug monitoring
- 5. Development of new techniques
- 6. Provision of advice on:
 - Diagnosis and treatment of fungal infections
 - Control and prevention of infection
- 7. Provision of epidemiological information to the National Disease Surveillance Centre
- 8. Training of medical/technical staff

Appendix 1: Sample Construction Permit

CONSTRUCTION PERMIT				
Permit No:	Permit Expiration Date:	Project Start Date:		
Location of Construction:	E	stimated Duration:		
Contractor:	Contact Person:	Tel:		
CEO Approval:				
Name	Signed:	Tel:		
Hospital Technical Services Manager Approval:				
Name:	Signed:	Tel:		
Infection Control Personnel Approval:				
Name:	Signed:	Tel:		

Construction/Renovation Activity	Population Risk Groups
 Type A - Minor Internal Containable Activities 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 visual inspection (limited to 1 tile per 5m²), 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. Activities that require access to conduit spaces, cutting of walls or ceilings where dust migration can be controlled for installation or repair of minor electrical work, ventilation components, telephone wires or computer cables. It also includes minor plumbing. 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 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 include digging trial pits and minor foundations, trenching, landscaping and minor construction and demolition work. Type D - Major External Non-Containable Activities include digging trial pits and minor foundations, trenching, landscaping and minor construction and demolition work. 	 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 Severely immunosuppressed AIDS patients Patients undergoing mechanical ventilation Non-neutropenic patients on chemotherapy Dialysis patients Group 3 - High Risk Neutropenic patients (<14 days) following chemotherapy Adult acute lymphoblastic leukaemia (ALL) on high dose steroid therapy Solid organ transplantation patients Patients in neo-natal intensive care units (ICUs) Chronic Granulomatous Disease of Childhood Laboratories (prevent contamination of microbiological specimens and thereby avoid pseudo-diagnosis) Group 4 - Very High Risk Allogeneic bone marrow transplantation patients During the neutropenic period With graft versus host disease Autologous bone marrow transplantation patients, i.e. during neutropenic period Peripheral stem cell transplantation patients Children with severe combined immunodeficiency syndrome (SCIDS) Patients with prolonged neutropenia (>14 days) following chemotherapy or immunosuppressive therapy

Recommendations For Infectio	n Control Preventive Measures
Class I	Class II cont'd
Class I Preventive Measures are recommended for Minor Internal Containable Construction Activities (Type A)	Infection Control • As for Class I
 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 Control Personnel Approval to be given 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 area. If it is not possible to move e.g. ICU patients an impermeable dust barrier should be erected around the construction area Minimise patients exposure to the construction /renovation area 	 Patient Risk Reduction Move all patients from the construction area If possible move at-risk patients (Groups 2-4) who are adjacent or near to the construction area Ensure that patients do not go near construction area All windows, doors, air intake and exhaust vents should be sealed in areas of the hospital containing patients who are classified as high-risk, if the construction or demolition work is considered likely to result in <i>Aspergillus</i>-contaminated air entering these areas Very high-risk patients (Group 4) should be treated in HEPA-filtered, positive pressure rooms 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 area 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)
Minimise dust and increase cleaning in patient area	Dust Control
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	 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 Debris Removal and Cleaning
 Dust Control Erect an impermeable dust barrier 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 Area Seal windows Maintain negative pressure within construction zone by using a portable extract fan Ensure air is exhausted directly to the outside and away from intake vents or filtered through a HEPA filter before being re-circulated Ensure 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 	 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 Control Approval to be given 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 If possible move at-risk patients (Groups 2-4) who are adjacent or near to the construction area Ensure that patients do not go near construction area All windows, doors, air intake and exhaust vents should be sealed in areas of the hospital containing patients who are classified as high risk, if the construction or demolition work is considered likely to result in <i>Aspergillus</i>-contaminated air entering these areas Very high-risk patients (Group 4) should be treated in HEPA-filtered, positive pressure rooms Traffic Control See Class II measures

Appendix 2: Information Leaflet on Aspergillosis during Construction Activities

General Information

The purpose of this leaflet is to inform patients, relatives, health care 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 cause human diseases.

Aspergillus may be released into the air during construction/renovation activities ranging from demolition and renovation, to construction. *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

During building work every effort will be made to prevent the spread of *Aspergillus*. The medical team who is treating you will be in close communication with builders and the Microbiology/Infection Control Department 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 3: A recommended method for the sampling of Aspergillus species spores in air

Taken from "Sampling of *Aspergillus* spores in air" a review by Morris *et al.*, *J Hosp Infect*, 2000; 44(81) 81-92; reproduced by kind permission of author Dr. Malcolm Richardson.⁶²

This sampling method to isolate and enumerate *Aspergillus spp*. spores in air should be conducted as follows:

Materials and equipment:

Sampling Instrument:	Surface Air Systems microbiological air sampler.
Manufacturer:	Pool Bioanalyse Italian (PBI), Milan, Italy
U.K. Supplier:	Cherwell Laboratories, Churchill Rd., Bicester, Oxon,
Collection Rate:	180 l/min
Medium:	Czapek Dox Agar (Oxoid)

Method

Sampling Procedure (general)

The air sample is aspirated through the instrument at a nominal rate of 180 litres per minute for a preselected period of between 20 seconds and 6 minutes giving a volume range between 60 litres and 1080 litres. The airflow is directed towards the agar surface of a 50 mm diameter contact plate that contains 12.5 ml of agar so that particles whose aerodynamic diameter causes them to leave the air stream are deposited on the agar surface. The plate is then removed for incubation.

Sampling location

Sampling location is dependent on circumstances but should accord broadly with the breathing zone of potentially affected personnel. The choice of sampling height is 1.2 metres for room hygiene, with other samples taken for exploratory purposes near suspected or potential sources of contamination. Multiple samples are preferable to a single sample, as they will highlight temporal and spatial variation in spore levels within any environment.

Selection of sampling time

Selection of an appropriate sampling period is vital to the success of the sampling operation. If the sampling time selected is long in a heavily contaminated environment then the colonies, once cultivated, can only be expressed as exceeding a particular number. Where confluent growth occurs the colonies may even be uncountable. A chart is supplied with the instrument to assist in selection of the sampling time, which on the basis of an assumption regarding the level of contamination in the environment permits the number of sampling units (periods of 20) to be estimated. In practice, whilst some knowledge of the levels of contamination may build up over time, certainly initially the selection of the sampling period must largely be done by trial and error.

Sampling steps

- 1. Unscrew the top cover plate avoiding contact with the inner or outer surfaces of the drilled area. The cover plate should be cleaned after each use.
- 2. Insert a contact plate with Czapek Dox agar (Oxoid Basingstoke UK) with the lid still in place, remove the contact plate lid and replace the instrument cover plate.
- 3. Set the digital selector on the instrument to zero units.
- 4. Switch on the battery pack.
- 5. Turn the timer to the desired setting.
- 6. Press the instrument start button.
- 7. Following completion of the sampling the instrument will switch off. The cover plate can then be

removed and the exposed contact plate agar surface immediately covered by replacing the contact plate lid.

8. The contact plate should then be removed for incubation.

Laboratory procedure

- 1. On receipt of the contact plates, these are placed in a pre-heated incubator to 28°C for 48 hrs to permit germination and colony formation.
- 2. The plates are then microscopically examined at 100X magnification to enumerate colonies growing on the plate.
- 3. Identification of fungal colonies is based on colony characteristics and micro-morphological characteristics ascertained through microscopic examination at 400X magnification.
- 4. Specimens for examination should be prepared using a wet needle mount using lactophenol with cotton blue stain (0.75%).
- 5. A colour key is available for the specific identification of different *Aspergillus* spp. grown on Czapek Dox agar or broth.

N.B. Czapek Dox is recognised as a suitable medium for isolation and culturing of *Aspergillus* spp., whilst permitting growth of the majority of airborne fungal species. This permits general levels of fungal contamination to be simultaneously appraised as an indicator of building hygiene.

Enumerating the colony forming units

There is a possibility that any colony that grows on the contact plate derives from more than one colony-forming unit passing through a single hole in the cover plate. This possibility increases with the number of colonies on the plate and for higher counts a correction factor is applied according to the following formula:

$Pr = N(1/N+1/(N-1) + 1/(N-2) + \dots + 1/(N-r+1))$

Where

Pr is the probable statistical total N is the number of holes in the sampling head r is the number of colonies counted

Tables have been prepared by the manufacturer, which can be read off to give a value for P once r has been established.

The number of colony forming units calculated from the above formula is normally expressed as CFU/m³. This is calculated using the formula:

X = <u>Adjusted colony count on plate x 1000</u> Volume of air drawn into sampler (litres)

The interpretation of air sampling data and recommendations for intervention are given in Table 4.

Table 4. Interpretation of air sampling data and recommendations

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 sampling has to be performed.

No strict numerical guidelines are available, 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):
 - Total fungal count: 10³ to 10⁵ CFU/m³,
 - Aspergillus: 0.2-3.5 conidia/m³
- HEPA filtered air (>95% efficiency and >10 air changes per hour): < 0.1 CFU/m³
- No air filtration: 5.0 conidia/m³
- Construction/defective ventilation: 2.3-5.9 conidia/m³

If total fungal count exceeds 1.0 CFU/m³ on several occasions the air systems or procedural practice in patent areas requires intensive evaluation.

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

- 1. The infection control and technical officer, as designated by the CEO, in consultation with medical and nursing staff, as necessary, should prepare a set of requirements for protection against invasive aspergillosis either for
 - (a) Inclusion in planning brief for a single building project to be responded to by the design team when appointed.

or

- (b) For direct attention by the health facilities own technical staff for a single project or for application on an ongoing basis.
- 2. Where a project team sits for a particular project, it should consider the protection briefing material and approve of its content before its inclusion in the overall brief.
- 3. Where planning brief requirements for protection against invasive aspergillosis are documented, they should include
 - (a) Details of existing accommodation for immuno-compromised patients including location, physical condition, layout, services & occupancy.
 - (b) Within the context of overall project a description of proposed work to existing accommodation for such patients and/or proximity to other external works, occupancy changes (if any) etc.
 - (c) The required standards of air cleanliness, air pressures, ventilation, ingress of outside air allowable (e.g. need for lobbies), finishes etc. to be met.
- 4. The design team or designated technical officer should be required to submit proposed solution(s) to the project team or CEO, as appropriate, for their examination and consideration with the assistance of infection control.
- 5. The levels of requirements/standards of protection to be met should relate to the degree of patient risk involved taking cognisance of the type and illness of patients, type of work, proximity to work etc.

- 1. Tilton RC and McGinnis MR. Opportunistic fungi. In: *Clinical and Pathogenic Microbiology*. B. J. Howard, ed. St Louis, MO: C.V. Mosby Co.; 1987: p. 609-623.
- 2. Opal SM, Asp AA, Cannady Jr PB, Morse PL, Burton LJ, Hammer II PG. Efficacy of infection control measures during a nosocomial outbreak of disseminated aspergillosis associated with hospital construction. *J Infect Dis* 1986; **153**: 634-637.
- 3. Rotstein C, Cummings M, Tidings J, *et al*. An outbreak of invasive aspergillosis among allogeneic bone marrow transplants: a case-control study. *Infect Control* 1985; **6**: 347-355.
- 4. 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.
- 5. Anderson K, Morris G, Kennedy H, *et al.* Aspergillosis in immunocompromised paediatric patients: associations with building hygiene, design, and indoor air. *Thorax* 1996; **51**: 256-261.
- 6. 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.
- 7. Rhame FS. Nosocomial aspergillosis: how much protection for which patients? *Infect Control Hosp Epidemiol* 1989; **10**: 296-298.
- 8. Loo VG, Bertrand C, Dixon C, et al. Control of construction-associated nosocomial aspergillosis in an antiquated hematology unit. *Infect Control Hosp Epidemiol* 1996; 17: 360-364.
- 9. Lueg EA, Ballagh RH, Forte V. Analysis of the recent cluster of invasive fungal sinusitis at the Toronto Hospital for Sick Children. *J Otolaryngol* 1996; **25**: 366-370.
- 10. Pittet D, Huguenin T, Dharan S, *et al*. Unusual cause of lethal pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; **154**: 541-544.
- 11. Sessa A, Meroni M, Battini G, et al. Nosocomial outbreak of Aspergillus fumigatus infection among patients in a renal unit? Nephrol Dial Transplant 1996; **11**: 1322-1324.
- 12. Garrett DO, Jochimsen E, Jarvis W. Invasive *Aspergillus* spp. infections in rheumatology patients. *J Rheumatol* 1999; **26**: 146-149.
- 13. Rhame FS. Prevention of nosocomial aspergillosis. J Hosp Infect 1991; 18 (Suppl. A): 466-472.
- 14. Walsh TJ and Dixon DM. Nosocomial aspergillosis: environmental microbiology, hospital epidemiology, diagnosis and treatment. *Eur J Epidemiol* 1989; **5**: 131-142.
- 15. 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.
- 16. Arnow PM, Andersen RL, Mainous PD, Smith EJ. Pulmonary aspergillosis during hospital renovation. *Am Rev Respir Dis* 1978; **118**: 49-53.
- 17. 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.

- 18. Barnes RA, Rogers TR. Control of an outbreak of nosocomial aspergillosis by laminar air-flow isolation. *J Hosp Infect* 1989; 14: 899-894.
- 19. 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.
- 20. 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.
- 21. 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 (letter).
- 22. 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.
- 23. 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.
- Sarubbi FA, Kopf HB, Wilson MB, McGinnis MR, Rutala WA. Increased recovery of Aspergillus flavus from respiratory specimens during hospital construction. Am Rev Respir Dis 1982; 125: 33-38.
- 25. Grossman ME, Fithian EC, Behrens C, Bissinger J, Fracaro M, Neu HC. Primary cutaneous aspergillosis in six leukemic children. *Am Acad Dermatol* 1985; **12**: 313-318.
- 26. Krasinski K, Holzman RS, Hanna B, Greco MA, Graff M, Bhogal M. Nosocomial fungal infection during hospital renovation. *Infect Control* 1985; **6:** 278-282.
- Weems Jr JJ, Davis BJ, Tablan OC, Kaufman L, Martone WJ. Construction activity: an independent risk factor for invasive aspergillosis and zygomycosis in patients with hematologic malignancy. *Infect Control* 1987; 8: 71-75.
- 28. Hopkins CC, Weber DJ, Rubin RH. Invasive *Aspergillus* infection: possible non-ward common source within hospital environment. *J Hosp Infect* 1989; **13**; 19-25.
- 29. Hospital Infection Control. APIC coverage: dust from construction site carries pathogen into unit. *Hosp Infect Control* 1990; **17**: 73.
- 30. Shields ML, Joyner MV, Lee R. Invasive aspergillosis in immunosuppressed patients. *BMJ* 1990; 301: 1046-1047 (letter).
- 31. Gerson, SL, Parker P, Jacobs MR, Creger R, Lazarus HM. Aspergillosis due to carpet contamination. *Infect Control Hosp Epidemiol* 1994; 15: 221-222 (letter).
- 32. American Health Consultants. Aspergillosis: a deadly dust may be in the wind during renovations. *Hosp Infect Control* 1995; **22**: 125-131.
- Berg R. Nosocomial aspergillosis during hospital remodel. In: Infections and nursing practice prevention and control. Soule BM, Larson EL, Preston GA, eds. St.Louis: Mosby; 1995: p. 271-274.
- 34. Bryce EA, Walker M, Scharf S, et al. An outbreak of cutaneous aspergillosis in a tertiary-care hospital. *Infect Control Hosp Epidemiol* 1996; **17**: 170-172.
- 35. McWhinney PHM, Kibbler CC, Hamon MD, *et al.* Progress in the diagnosis and management of aspergillosis in bone marrow transplantation: 13 years' experience. *Clin Infect Dis* 1993; **17**: 397-404.

- Iwen PC, Reed EC, Armitage JO, *et al.* Nosocomial invasive aspergillosis in lymphoma patients treated with bone marrow or peripheral stem cell transplants. *Infect Control Hosp Epidemiol* 1993; 14: 131-139.
- 37. Schwartz RS, Mackintosh FR, Schrier SL, Greenberg PL. Multivariate analysis of factors associated with invasive fungal disease during remission induction therapy for acute myelogenous leukaemia. *Cancer* 1984; **53**:411-419.
- 38. Toree-Cisneros J, Lopez OL, Kusne S, et al. CNS aspergillosis in organ transplantation: a clinicopathological study. J Neurol Neurosurg Psychiatry 1993; 56: 188-193.
- 39. Collins LA, Samore MH, Roberts MS, *et al.* Risk factors for invasive fungal infections complicating orthotopic liver transplantation. *J Infect Dis* 1994; **170**: 644-652.
- 40. Wajszczuk CP, Dummer JS, Ho M, *et al.* Fungal infections in liver transplant recipients. *Transplantation* 1985; **40**: 347-353.
- 41. Kusne S, Dummer JS, Singh N, *et al.* Infections after liver transplantation. An analysis of 101 consecutive cases. *Medicine* (Baltimore) 1988; **67**: 132-143.
- 42. Guillemain R, Lavarde V, Amrain C, Chevalier P, Guinvarc'h A, Glotz D. Invasive aspergillosis after transplantation. *Transplant Proc* 1995; **27**: 1307-1309.
- 43. Kramer MR, Marshal SE, Starnes VA, Gamberg P, Amitai Z, Theodore J. Infectious complications in heart-lung transplantation. Analysis of 200 episodes. *Arch Intern Med*, 1993; **153**: 2010-2016.
- 44. Hofflin JM, Potasman I, Baldwin JC, Oyer PE, Stinson EB, Remington JS. Infectious complications in heart transplant recipients receiving cyclosporin and corticosteroids. *Ann Intern Med* 1987; **106**: 209-216.
- 45. Streifel AJ, Lauer, JL, Vesley D, Juni B, Rhame FS. *Apergillus fumigatus* and other thermotolerant fungi generated by hospital building demolition. *Appl Environ Microbiol* 1983; 45: 375-378.
- 46. Overberger PA, Waowsky RM, Schaper MM. Evaluation of airborne particulates and fungi during hospital renovation. *Am Ind Hyg Assoc J* 1995; **56**: 706-712.
- Rautiala S, Reponen T, Nevalainen A, Husman T, Kalliokoski P. Control of exposure to airborne viable microorganisms during remediation of moldy buildings: report of three cases. *Am Ind Hyg Assoc J* 1998; **59**: 455-460.
- 48. Centres for Disease Control and Prevention (CDC), Healthcare Infection Control Practices Advisory Committee (HICPAC) (2001) Draft guideline for environmental infection control in healthcare facilities (http://www.cdc.gov/ncidod/hip/enviro/guide.htm).
- 49. Tollemar J, Ringden O, Andersson S, *et al.* Prophylactic use of liposomal amphotericin B (AmBisome) against fungal infections: a randomised trial in bone marrow transplant recipients. *Transplant Proceed* 1993; 25: 1495-1497.
- 50. Working Party of the British Society for Antimicrobial Chemotherapy. Chemoprophylaxis for candidosis and aspergillosis in neutropenia and transplantation: a review and recommendations. *J Antimicrob Chemother* 1993; **32**: 6-21.
- 51. Robertson MJ, Larson RA. Recurrent fungal pneumonias in patients with acute nonlymphocytic leukaemia undergoing multiple courses of intensive chemotherapy. *Am J Med* 1988; 84: 233-239.
- 52. Martino R, Lopez R, Sureda A, Brunet S, Domingo-Albos A. Risk of reactivation of a recent invasive fungal infection in patients with haematological malignancies undergoing further

intensive chemo-radiotherapy. A single-centre experience and review of the literature. *Haematologica* 1997; 82: 297-304.

- 53. Offner F, Cordonnier C, Ljungman P, *et al.* Impact of previous aspergillosis on the outcome of bone marrow translantation. *Clin Infect Dis* 1998; **26**: 1098-1103.
- 54. Ansorg R, Heintschel von Heinegg E, Rath PM. *Aspergillus* antigenuria compared to antigenemia in bone marrow transplant recipients. *Eur J Clin Microbiol Infect Dis* 1994; **13**: 582-589.
- 55. Manso E, Montillo M, De Sio G, D'Amico S, Discepoli G, Leoni P. Value of antigen and antibody detection in the serological diagnosis of invasive aspergillosis in patients with haematological malignancies. *Eur J Clin Microbiol Infect Dis* 1994; **9**: 756-760.
- 56. Verweij PE, Stynen D, Rijs AJMM, de PAUW BE, Hoogkamp-Korstanje JAA, Meis JFGM. Sandwich enzyme-linked immunosorbent assay compared with Pastorex latex agglutination test for diagnosing invasive aspergillosis in immunocompromised patients. *J Clin Microbiol* 1995; **33**: 1912-1914.
- 57. Machetti M, Feasi M, Mordini N, *et al.* Comparison of an enzyme immunoassay and a latex agglutination system for the diagnosis of invasive aspergillosis in bone marrow transplant recipients. *Bone Marrow Transplant* 1998; **21**: 917-921.
- 58. Sulahian A, Tabouret M, Ribaud P, *et al.* Comparison of an enzyme immunoassay and latex agglutination test for detection of galactomannan in the diagnosis of invasive aspergillosis. *Eur J Clin Microbiol Infect Dis* 1996; **15**: 139-145.
- 59. Maertens J, Verhaegen J, Demuynck H, *et al.* Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for haematological patients at risk of invasive aspergillosis. *J Clin Microbiol* 1999; **37**: 3223-3228.
- 60. Fortun, J, Martin-Davila P, Alvarez ME, *et al.* Aspergillus antigenemia sandwich-enzyme immunoassay test as a serodiagnostic method for invasive aspergillosis in liver transplant recipients. *Transplantation* 2001; **71**: 145-149.
- 61. Sulahian A, Boutboul F, Ribaud P, Leblanc T, Lacroix C, Derouin F. Value of antigen detection using enzyme immunoassay in the diagnosis and prediction of invasive aspergillosis in two adult and pediatric haematology units during a 4-year prospective study. *Cancer* 2001; **91**: 311-318.
- 62. Morris G, Kokki MH, Anderson K, Richardson M. Sampling of Aspergillosis spores in air. *J Hosp Infect* 2000; 44: 81-92.

Notes

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