Aspergillosis in immunocompromised paediatric patients: associations with building hygiene, design, and indoor air

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Abstract

Background – Nosocomial aspergillosis is a well known complication of immunosuppression in cancer patients and those undergoing transplantation and has usually been associated with major building construction or demolition. An observational study is reported of the hospital environment associated with an outbreak of aspergillosis in a paediatric oncology ward.

Methods – All cases of aspergillosis were identified from the hospital records and categorised as definite or probable according to the extent of supportive clinical and laboratory findings. All relevant aspects of building ventilation, air filtration, and aerosol generation considered relevant were examined and air samples for fungi were taken in triplicate at 25 sites using a slit sampler with appropriate culture media.

Results – Six cases of aspergillosis were identified over one year out of the 148 patients who attended the unit – the only part of the hospital where cases were found. Examination of the building services and function suggested that the cause or source was isolated to this paediatric oncology/haematology ward and may have been attributed to a defective disposal conduit door as well as the dispersal of a contaminated aerosol from the ward vacuum cleaner which had the highest measured concentrations of *Aspergillus fumigatus* in or around the building (65 colony forming units (cfu)/m³ compared with 0–6 cfu/m³ elsewhere). No further cases were identified in the two years after these hygiene arrangements were changed.

Conclusions – The investigation of this outbreak of nosocomial aspergillosis identified several possible sources of fungally contaminated aerosol which could have been implicated as the cause. Their modification was followed by a reduction in the incidence of further cases. Each should be incorporated as an issue of importance in hospital building design and hygiene.

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Key words: aspergillosis, immunosuppression, building-related disease.

Respiratory illness associated with the genus *Aspergillus* has three main diagnostic categories

which only rarely overlap, and each type usually requires some form of deficiency in pulmonary defence or structure¹: (1) colonisation of a cavity within the lung can produce a fungal ball (aspergilloma); (2) a hypersensitivity-related, predominantly airway disorder (allergic bronchopulmonary aspergillosis) which can complicate other lung diseases such as asthma and cystic fibrosis; and (3) invasive aspergillosis which occurs as a result of environmental exposure to *Aspergillus* in patients who have more severe impairment of immunity which tends to develop during hospital residence. Nosocomial aspergillosis has been reported following surgical procedures,^{2,3} large organ transplantation,^{4–6} bone marrow transplantation,^{7,8} or in association with leukaemias.⁹

The major problem is that, once fungal infection is present in these immunosuppressed patients, invasive aspergillosis is very difficult and expensive to treat. Hitherto, the principal manoeuvres have been to prevent or minimise exposure by filtering air for isolated patients.^{9,10} Although outbreaks of invasive aspergillosis have been associated with the environmental disruption of construction around a hospital site,^{11–14} the precise source of the fungus is often difficult to trace with certainty. Furthermore, hospital buildings are subjected to continuous and sometimes haphazard alteration which may not be consistently followed by a measurable change in airborne fungal counts or aspergillosis.¹⁵ While the hypothesis of nearby construction as the cause of an outbreak may be attractive, the other aspects of buildings and indoor air quality which may be relevant should not be overlooked,¹⁶ although very few of these factors have been characterised with specific regard to immunosuppressed patients.

We report the environmental investigation of a paediatric haematology and oncology ward which recorded a rise in the number of infections caused by *A. fumigatus* and other species of *Aspergillus*.

Methods

Staff within a haematology/oncology unit increasingly suspected that the incidence of aspergillosis had risen over a period of months within their department where only one case had occurred over the previous five years. In response, an outbreak committee was assembled with the aim, firstly, to confirm that an outbreak of aspergillosis had occurred and, secondly, to investigate the possible causes.

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Table 1 Probable and definite cases of aspergillosis

Age	Diagnosis	Tissue	Organism
11 years	ALL	BAL	<i>A fumigatus</i>
4 years	ALL	Pericardial fluid, cardiac vegetation	<i>A fumigatus</i>
10 years	Neuroblastoma (post BMT)	BAL	<i>A fumigatus</i>
6 years	Neuroblastoma	Blood culture	<i>A flavus</i>
9 months	AML	Necroscopic lung	<i>A terreus</i> (1 colony) <i>Aspergillus</i> sp
10 years	ALL (post BMT)	Blood culture	histology <i>A niger</i>

ALL=acute lymphatic leukaemia; BAL=bronchoalveolar lavage fluid; BMT=bone marrow transplant; AML=acute myeloid leukaemia.

The committee gathered representatives from all staffing groups within the building who had any possible connection with air quality and the clinical management of the patients. In addition, a group of individuals from outwith the hospital, who had previous experience of building-related disease and associated outbreaks of respiratory disease, were invited to join the investigation.

PATIENTS

Any cases of aspergillosis during 1993 in this paediatric hospital were identified through the microbiological records and details were verified by consulting the hospital case notes. Only those cases with isolates from tissue or body fluids were considered to have either definite or probable aspergillosis. Definite aspergillosis was diagnosed if tissue histopathological examination showed septate acute branching hyphae or if, in the absence of histological evidence, a positive culture was obtained by an invasive procedure. Probable aspergillosis was diagnosed if, in the context of neutropenia, a patient developed chest radiological abnormalities or other clinical findings compatible with aspergillosis.

BUILDING SURVEY

After consulting the building engineers, all floors of the structure (modern multistorey concrete building completed in the early 1970s) were assessed by two of the investigators (KA and GM) to identify all sources of air intake and the dispersal routes of air throughout the hospital. The haematology ward was visited and walked through on several days at different times to judge whether particular activities or functions of the ward seemed relevant. All recent building records were discussed with the building services managers and engineers. External ventilation contractors were consulted regarding the overall function of the building ventilation.

FUNGAL ISOLATION

Air samples were taken in triplicate from 25 sites throughout the hospital, at the intakes, inside, and exhausts of each of the mechanical ventilation units and in each ward. In the suspect ward 15 sites were sampled, including the ceiling void, soft toys (encouraged to release aerosol by firm handling), and the exhausts of the ward vacuum cleaners. The air sampler

used (SAS, Cherwell Laboratories, Oxford, UK) was hand held for ease of access and incorporated appropriate culture media (Czappek-Dox and Rose Bengal). Settle plates of similar media were distributed through the suspect ward and several other sites in the hospital. Swabs were taken from surfaces throughout the hospital and the suspect ward.

AIR DUST SAMPLING

Airborne dust concentrations were calculated from a change in dry filter weight (Whatman 47 mm glass fibre A; Whatman Ltd, Maidstone, Kent, UK) before and after air was drawn through an open face filter at 100 l/min for a period of 10 minutes (L100 pump; Rotheroe and Mitchell Ltd, Middlesex, UK). The filters were weighed on a balance sensitive to 1 µg (Sartorius R 200 D; Sartorius Ltd, Epsom, Surrey, UK).

FUNGAL IDENTIFICATION

All fungal isolates were identified by standard culture and morphological appearance.¹⁷

OUTCOME

After the investigation, factors were identified which were considered relevant to the outbreak and the case incidence was reviewed one year later.

STATISTICAL ANALYSIS

The Mann-Whitney U test was used to assess the significance of the measured values when appropriate.

Results

During 1993 148 patients with paediatric neoplasms (predominantly leukaemia) attended the unit and were admitted intermittently for periods of treatment (chemotherapy, radiotherapy, and bone marrow transplantation). From April to December 1993 six cases of invasive aspergillosis associated with *A fumigatus* or other species of *Aspergillus* were identified whereas only one case of aspergillosis had occurred in the previous five years. The details of the cases where *Aspergillus* infection was present or probable are shown in table 1. All cases were treated with liposomal amphotericin and broad spectrum antibiotics and this regimen became standard as treatment of pyrexias within the ward before bacteriological confirmation of the cause.

The ward where the cases were identified (haematology/oncology) occupied part of the seventh floor of a tower of wards with mainly mechanical ventilation from air handlers on the floor above and a lesser amount of natural ventilation through the stairwell from the ground floor entrance and the service ducts. A summary of the building characteristics is

Table 2 Principal features and enclosures of the building which directed the method of investigation and influenced sites for air sampling

Eight storey stack: two columns, central lift/stairwell
Several intercommunicating corridors to adjoining buildings
Ventilation:
Natural – windows, stairwells, basement vents
Mechanical – 8th floor air handler units dedicated to each column
Communication space
Electrical ducts
Water pipes
Pneumatic specimen/result transport ducts
Suspended ceiling spaces (insulation material)
Clinical waste disposal
Haematology/Oncology ward
HEPA units
Day treatment area
Drug preparation cabinet
Soft toys
Hygiene equipment (vacuum cleaner)

Table 3 Isolation of fungi from the building

Site within building	Fungi detected
Indoor/outdoor air	<i>A. fumigatus</i> (0–6 cfu/m ³)
Mechanical ventilation	<i>A. fumigatus</i> (0–6 cfu/m ³)
HEPA filters	Swab culture (<i>A. fumigatus</i>)
Ceiling insulation	<i>A. fumigatus</i> , <i>A. niger</i> , <i>A. terreus</i> , <i>Paecilomyces</i> spp, <i>Penicillium</i> spp
Waste disposal duct	Swab culture (<i>A. fumigatus</i> , <i>A. niger</i> , <i>A. flavus</i> , <i>A. terreus</i>)
Disposal door frame	Swab culture (<i>A. fumigatus</i>)
Pneumatic transport outlet	Swab culture (mixed <i>Aspergillus</i> spp)

cfu = colony forming units.

shown in table 2. A notable feature of the building was the specimen transport system which operated by pneumatic principles from a compressor in the basement of the hospital. This would effectively push columns of basement air around as determined by a ward or laboratory despatch, thereby emitting the distal column of air beyond the despatch at several end points, one of which was the haematology/oncology ward.

Building work and redecoration had been carried out during May/June in a ward nearby served by a different ventilation supply. Two of the cases preceded this work and the others seemed evenly spaced over the six months, suggesting continued exposure rather than an illness which developed in response to a single episode. Similarly immunosuppressed patients were treated in another ward area (renal transplant) on a different level in the same column of the building but no suspected cases were identified in that ward. Likewise, no patients were identified in the intensive care unit which was in a different area of the hospital. These observations when taken together suggested that the source of the infection should be sought within the confines of the haematology/oncology area.

The initial results of the aeromycology studies (table 3) showed a generally low level of *A. fumigatus* in the air sampled throughout the building (0–6 colony forming units/m³) with similar measurements in outdoor air.

The suspended ceiling of the haematology ward consisted of tiles which had been removed and replaced many times over the years to allow service access. No airborne *A. fumigatus* was

Table 4 Results of air sampling taken close to the ward vacuum cleaner before and during use and subjective measure (agreement of four observers) of air quality

	Before use	During use
Airborne particulates (mg/m ³)	<0.01	0.10
Airborne <i>A. fumigatus</i> (cfu/m ³)	24	62
Air quality	Fresh	Fusty

cfu = colony forming units

isolated in the airspace cavity overlying the suspended ceiling by air sampling but the organism was identified from the insulating material enclosed by the tiles. *A. fumigatus* was recovered from the intake filters of the two high efficiency particulate air (HEPA) filtration units in the ward, but the air in the high dependency room served by the filters was sterile (one room while unoccupied). Numerous soft toys were present in most areas of the ward but no fungal source was found when several were sampled.

The ward disposal unit for bags of clinical waste was sited in the central part of the ward and led by a vertical conduit directly to the basement. A draught of cool air was detected even when the door was firmly closed because of an ill-fitting rubber gasket, and plumes of fine dust were deposited close to these draughts around the door frame from which a mixed *Aspergillus* population was cultured (table 3).

Airflow studies throughout the building columns performed by the external contractor revealed that the handling of the air ventilation was balanced slightly in favour of exhaust, which implied that some of the air within the building was drawn in away from the main air handling units (possibly through doors, windows, and communication ducts, including the disposal conduit).

The ward vacuum cleaner (dry vacuum cleaner incorporating a large particle filter), which had only been used in the haematology ward, was taken from the ward so that room air could be sampled for particles and fungi before and during operation of the machine. Both samplers were positioned 0.5 metres above and lateral to the exhaust of the machine (table 4). The airborne concentration of *A. fumigatus* was significantly different from the other measurements taken in the hospital ($p < 0.002$). The level of airborne particulates was initially at the lower limit of the detectable range for the air sampler and increased after the vacuum cleaner was switched on. The vacuum cleaner was dismantled and a contact plate containing fungal culture medium on the exhaust filter produced an overgrowth of *A. fumigatus*. Vacuum cleaners from four other wards in the hospital close to the outbreak ward were also sampled but none produced particulates or fungi in a higher quantity than the background level measured within the hospital.

No further cases of aspergillosis have been identified in the ward over a period of 18 months since the disposal door was sealed and the vacuum cleaner was replaced by a machine of higher efficiency. Air samples have been taken at regular intervals over one year at 10 sites within the hospital and at specific points

outside the building and no significant change in the concentration of *Aspergillus* spp has been found. A decision was also taken to introduce prophylaxis with itraconazole to all patients undergoing bone marrow transplantation but it should be noted that not all of the patients who developed aspergillosis in the outbreak were bone marrow transplant patients. Nasal swabs have been taken routinely from all patients since the outbreak and only one case of colonisation with *Aspergillus* spp has been found.

Discussion

Invasive fungal disease as a complication of immunosuppression has been an increasingly difficult issue in transplantation and oncology over the past 20 years as the number of cases with fungal complications follows the increasing number of patients.^{18,19} This is mainly a reflection of the more rapid advances in transplantation procedures than in the rate of development of effective antifungal therapy. Air filtration was considered to be the only possible solution, although antifungal prophylaxis has recently been used more often.^{19,20} Despite early suggestions that HEPA filter systems effectively reduced spore counts,¹⁰ and a supportive case control study which detected 14 cases of aspergillosis out of 74 without HEPA and none in 39 patients with HEPA,⁸ reports of cases and outbreaks of nosocomial aspergillosis continue.^{11,12,21–23} Moreover, improper operation or poor maintenance of sophisticated ventilation systems can lead to outbreaks of aspergillosis on units fitted with HEPA facilities.²⁴

The environmental control of nosocomial aspergillosis is a complex subject given that even HEPA units are not completely effective for preventing disease. The possibility that a patient is inhaling fungi outside areas with HEPA filter systems implies isolation failure and, in these subjects, fungal exposure would be more precisely studied using a personal air sampling device but there is no fungal sampler currently available which can be used in this way. There are also severe limitations on the duration of the sampling time of fungal samplers so transient peaks of fungi in aerosols might be better detected by gravity plates. Gravity plates may also be an imperfect compromise because of varying airflows determined by the activity of the occupants and external influences on the indoor microclimate – for example, solar heat gain or nocturnal heat loss.

The finding of peak spore counts in March and June in the recent study by Goodley *et al* in London¹⁵ was unexpected as previous work^{25–27} had suggested that *Aspergillus* levels were higher in autumn and winter. A seasonal incidence of invasive aspergillosis has never been reported, although there is evidence to support an increase in the incidence of allergic bronchopulmonary aspergillosis in winter.²⁸ *Aspergillus* species are found widely as contaminants – for example, in potting compost, nuts, soiled linen, pharmacy solutions, pigeon excreta²⁹ – so reasonable avoidance measures are appropriate if minimal exposure is the only

necessary component to induce the development of invasive aspergillosis in transplantation patients.

We had initially expected that the air handling units, ceiling design, or recent building work would have been the most likely source of the fungal infection and, although our results do not entirely exclude a transient peak from inside or outside air, the combination of the disposal duct, the negatively balanced air handling system, and the entrapped dust within the ward cleaning machine seem to have produced a suitably contaminated aerosol which would be dispersed over a long enough time to explain the incidence pattern which was observed. We are unaware of any previous reports to incriminate this type of cleaning machinery as a cause of infection in immunosuppressed patients, although the theoretical dissemination of *Aspergillus* by vacuum cleaning has previously been discussed.³⁰

An outbreak of aspergillosis was recently attributed to carpet contamination following a building fire close to a hospital after which the carpeting was cleaned with a “bonnet buffing” machine.²² Wet cleaning was instituted instead and the outbreak of cases ceased. Another important feature of this report was that building construction nearby could have led the investigators to attribute the cases to that cause had they not investigated the environment within the hospital more thoroughly. The wider issue is whether an aerosol of this type could be associated with the development of lung disease in normal or less susceptible subjects with pre-existing lung disease such as asthma. Whether or not this aspect is also important in patients with asthma or immunocompromised patients outwith hospital remains to be addressed.

The specific relevance of building construction near a transplant unit to the development of a fungal infection does not seem clearcut in view of the results presented here. Hospitals are buildings of continuous change and adaptation, so construction may extend to various sites throughout the year. Our general feeling is that the wide range of individuals responsible for controlling the components of indoor air quality are unaware of the potentially catastrophic complications of a failure in the system where even the least likely and unsuspected connecting fragment in a long list of interrelated factors might be incriminated. Our building survey (table 2) presents each component of the site which required assessment. This approach to buildings uses the analogy of standard clinical evaluation to clarify what might seem initially to be an almost impossible task. Each section of the building could have contributed in some way to the development of aspergillosis and was gradually excluded by simple investigation. At an early stage we considered that the specimen transport system might be guilty since air was transported around from various parts of the hospital, thus facilitating communication between the laboratory services and the wards. This had been installed with general agreement but the question of an influence on air quality was never fully

appreciated. We would suggest that such systems should only be installed in hospitals after careful consideration of the source of the air to drive the specimen transport as well as careful positioning of the exit points. Likewise, planned disposal of clinical waste must be carefully balanced so that materials are not allowed to accumulate needlessly and are transported away regularly from particularly sensitive patients. Unfortunately the disposal duct system within this modern building was not appropriate for the special nature of the unit and the communication door to the duct was sealed. We speculate that the dust from this disposal system was collected by the vacuum cleaner which then acted as a disseminator well beyond the disposal duct area. Since failure of the disposal system was likely to be the initial event resulting in contamination of the vacuum cleaner, the outbreak of aspergillosis might have been more accurately described as having an architectural cause with the vacuum cleaner acting effectively as a biological trap. During the investigation we also found fungal spores in swab samples from the HEPA filters in the drug preparation cabinet and in the filters which served the rooms of the neutropenic patients. This indicated that the filters were operating correctly and also offered a relatively uncomplicated (but unquantifiable) method of confirming whether fungal spores were circulating in the air of the ward.

The overall management of immunosuppressed patients relies on close medical observation but also necessitates a precision of awareness in non-medical staff above that which is acceptable for the patient whose immune system is functioning more normally. This awareness is not too difficult to provoke after a major event, but we would suggest that any medical unit which handles immunosuppressed patients must have a code of practice on air quality which clearly states the responsibility of each of the supporting services. For instance, if any building works take place nearby, the implications for air quality within the hospital should be carefully assessed. The building engineers in this paediatric hospital currently stipulate that any works within the hospital conform to the highest dust avoidance standards and use the directives issued for the removal of asbestos from buildings. The area of work must be sealed and appropriate external air extraction installed. Likewise, the general fabric of the building should be closely examined by a responsible engineer so that no component is overlooked – a checklist similar to the standard required for the surveillance of aircraft structure would be advisable. Given the occasionally short term employment of ancillary and cleaning staff within hospitals, education at this level is difficult but should be a clear responsibility of the employer whether the staff are based within the hospital or subcontracted. All cleaning machinery should be cleaned regularly and should conform to a high standard of particle removal. Bacterial and fungal contamination of filters in the cleaners should be considered inevitable and these

should be cleaned regularly and monitored by the infection control staff within the hospital.

Our practical results suggest that the deterioration in air quality resulting from a contaminated vacuum cleaner can be suspected by simple observation as the air becomes musty. Little was gained by showing that dust levels and fungal counts also rose when the machine was operating, although this was necessary to confirm our suspicions. Indeed, the plume of dust and fungus dispersal could have been wider and the rate of emission of noxious exhaust need not remain constant. We have presented results for these contaminants which were limited by the method of aerosol monitoring, but such is the difficulty of sampling aerosols consistently and rapidly in field work. We might assume that the vacuum cleaner was operating for periods well in excess of the sampling time and, in the enclosed space of a ward or single room, might produce concentrations considerably higher than those which we recorded, leading to a more severe and persistent exposure for the patient; this might be repeated several times during a day depending on the circumstances of the ward. The rate of change in the concentration of the fungal aerosol would be a function both of the output of the vacuum cleaner and the rate of air change in the hospital ward, so that fungal levels would increase steadily until the cleaner was turned off. Given the nature of the patients on the ward, we did not test this hypothesis.

The precise circumstance required to produce an outbreak of aspergillosis in susceptible patients is obscure because the environmental mycology of most outbreaks of nosocomial aspergillosis is poorly defined.⁷ There is a natural and understandable tendency for those who are in direct contact with the affected patients to react immediately so that an environment might change before more experienced investigators are contacted. The development of molecular biology techniques that are more directly applicable to identifying *Aspergillus* species may eventually help to resolve some of these difficulties.^{21 23} In the meantime, the identification of a source of airborne infection in a modern building with a complex ventilation system requires a rigorous examination along a planned route – a process similar to clinical problem solving when there are a number of abnormal findings which are possibly interrelated in origin and the aetiology is not immediately obvious.

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