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REVIEW

Nosocomial aspergillosis in outbreak settings

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KEYWORDS
Aspergillus outbreaks; Aspergillus; Environmental air sampling/culturing; Immunocompromised hosts; Outbreak investigations

Summary Nosocomial aspergillosis represents a serious threat for severely immunocompromised patients and numerous outbreaks of invasive aspergillosis have been described. This systematic review summarizes characteristics and mortality rates of infected patients, distribution of *Aspergillus* spp. in clinical specimens, concentrations of aspergillus spores in volumetric air samples, and outbreak sources. A web-based register of nosocomial epidemics (outbreak database), PubMed and reference lists of relevant articles were searched systematically for descriptions of aspergillus outbreaks in hospital settings. Fifty-three studies with a total of 458 patients were included. In 356 patients, the lower respiratory tract was the primary site of aspergillus infection. Species identified most often were *Aspergillus fumigatus* (154 patients) and *Aspergillus flavus* (101 patients). Haematological malignancies were the predominant underlying diseases (299 individuals). The overall fatality rate in these 299 patients (57.6%) was significantly greater than that in patients without severe immunodeficiency (39.4% of 38 individuals). Construction or demolition work was often (49.1%) considered to be the probable or possible source of the outbreak. Even concentrations of *Aspergillus* spp. below 1 colony-forming unit/m^3 were sufficient to cause infection in high-risk patients. Virtually all outbreaks of nosocomial aspergillosis are attributed to airborne sources, usually construction. Even small concentrations of spores have been associated with outbreaks, mainly due to *A. fumigatus* or *A. flavus*. Patients at risk should not be exposed to aspergilli.

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Introduction

Aspergillus spores are ubiquitous in their distribution, and inhalation of spores is believed to be the usual route of transmission. In most healthy individuals, spores are removed by functional innate defence mechanisms such as monocyte-derived and resident macrophages.[1] Unfortunately, in severely immunocompromised hosts, such as patients suffering from haematological malignancies[2–6] or solid organ transplant patients,[7–11] invasive aspergillosis (IA) may represent a serious complication in the course of disease. The incidence of IA is increased in these high-risk patients[12] with an overall case-fatality rate of one-half to two-thirds.[13] IA is difficult to treat and multi-variate analysis has revealed it to be an independent risk factor for mortality in critically ill patients.[14]

To prevent hospital-acquired aspergillus infections, high-risk patients are usually placed in protective isolation rooms in which positive air pressure is maintained compared with surrounding areas.[15] These special rooms are provided with high-efficiency particulate air (HEPA) filters and an air flow of at least 12 air changes/h because HEPA filtration significantly reduces the concentration of fungal spores[16] and the incidence of IA.[17] In addition, horizontal laminar air flow (LAF) is provided in some facilities which drives contaminants out through the ducts.[18] However, additional protection due to LAF remains a matter of debate and the use of LAF is not explicitly recommended by the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA) or the American Society of Blood and Marrow Transplantation (ASBMT) for the care of haematopoietic stem cell transplant recipients.[15,19] Despite such guidelines for the care of highly susceptible patients and maximum protective efforts, nosocomial outbreaks of IA do occur.[19,20] This systematic review was carried out to summarize the data from all nosocomial aspergillus outbreak reports published to date.

Methods

Collection of data

The outbreak database (www.outbreak-database.com), a web-based register of nosocomial epidemics, was searched for outbreaks due to any type of *Aspergillus* spp.[21] Furthermore, a PubMed search (1 January 1966—15 August 2005) was performed to identify additional aspergillus outbreaks by using the term 'outbreak' in combination with 'aspergillus' or 'aspergillosis'. References were subsequently screened for additional descriptions of aspergillus epidemics in hospital settings.

Extraction of data

The following data were obtained: (1) number of patients involved in the outbreak; (2) number of patients that died due to aspergillus infection; (3) underlying diseases of affected patients; (4) primary site of mycosis; (5) distribution of *Aspergillus* spp. in clinical specimens; (6) concentration of airborne mould spores in diverse hospital areas; (7) genotyping of fungal isolates to confirm an epidemiological relationship; (8) source of the outbreak.

Evaluation of data

Outbreak data were evaluated by both authors independently. Patients were grouped depending upon underlying diseases into the following classes: (1) haematology and bone marrow transplantation; (2) solid organ transplantation; (3) other immunodeficiency; (4) no known severe immunodeficiency. If a relevant immunodeficiency could not be excluded but definite classification of underlying disease was not possible either, patients were grouped as 'other immunodeficiency'. Mortality was calculated for all groups and then compared. Statistically significant differences in mortality rates in diverse patient groups were determined using Chi-squared test (Epi-Info software, Version 3.3.2). Outbreak sources were considered 'probable' if stated so by the authors of the outbreak. Sources were considered 'possible' if there were circumstances that may have been the source of the outbreak but no exact link could be made with infection.

Results

A total of 53 outbreaks and 458 affected patients were included in this review. Comprising a total of 299 individuals (65.3%), haematological malignancies were the predominant underlying disease. In all but one outbreak, air was the route of fungal spore transmission and the major site of primary infection (356 patients) was the lower respiratory tract.[22] Surgical site infections and superficial skin infections were observed far less frequently (24 patients each). Interpatient spread was only described on one occasion.[23] Species identified most often from clinical samples were *Aspergillus fumigatus* (154 patients) and *Aspergillus flavus* (101 patients). Species differentiation was not

Table I Characteristics of patients and causative *Aspergillus* spp. in nosocomial outbreaks

Author (year, country)	Patient group (*N* patients)	Patients (*N* fatal)	Primary site of infection (*N*)	Clinical *Aspergillus* spp. isolates (*N*)
Gage *et al.* (1970, USA)[53,54]	T-SURG (4)	4 (3)	Endocarditis (4)	*fumigatus* (3); *glaucus* (1)
Burton *et al.* (1972, USA)[55]	RTX (4)	4 (0)	LRTI (4)	*fumigatus* (4)
Rose (1972, USA)[39]	HEMA (?); others (?)	Total: 23 (total: 12)	LRTI (23)	*fumigatus* (≥12)
Aisner *et al.* (1976, USA)[40]	HEMA (8)	8 (≥3)	LRTI (7); sinusitis (1)	Unknown (8)
Kyriakides *et al.* (1976, USA)[56]	RTX (3)	3 (1)	LRTI (3)	*fumigatus* (3)
Arnow *et al.* (1978, USA)[57]	RTX (3)	3 (1)	LRTI (2)	*fumigatus* (3)
Mahoney *et al.* (1979, USA)[58]	HEMA (5)	5 (3)	Sinusitis (3); LRTI (2)	*fumigatus* (1); unknown (4)
Lentino *et al.* (1982, USA)[49]	RTX (7); HEMA (3)	Total: 10 (total: 4)	LRTI (10)	Unknown (10)
Sarubbi *et al.* (1982, USA)[59]	HEMA (?); others (?)	Total: 22 (total: 1)	LRTI (1)	*flavus* (22)
Gustafson *et al.* (1983, USA)[60]	RTX (9)	9 (7)	LRTI (8); epidural abscess (1)	*fumigatus* (3); unknown (6)
Gerson *et al.* (1984, USA)[61–63]	HEMA (15)	15 (?)	LRTI (15)	Unknown (15)
Grossman *et al.* (1985, USA)[64]	HEMA (6)	6 (0)	Skin infection (6)	*flavus* (3); *fumigatus* (2); *niger* (1)
Krasinski *et al.* (1985, USA)[65]	Neonates (1)	1 (1)	Skin infection (1)	Unknown (1)
Rotstein *et al.* (1985, USA)[66,67]	HEMA (10)	10 (10)	LRTI (9); sinusitis (1)	*fumigatus* (7); *flavus* (3)
Opal *et al.* (1986, USA)[68]	HEMA (7); steroids (3); ONCO (1)	7 (7) 3 (3) 1 (1)	LRTI (11)	*flavus* (4); *fumigatus* (1); *niger* (1); unknown (5)
Allo *et al.* (1987, USA)[69]	HEMA (9)	9 (2)	Skin infection (9)	*flavus* (8); unknown (1)
Perraud *et al.* (1987, France)[70,71]	HEMA (22)	22 (18)	LRTI (22)	*fumigatus* (22)
Ruutu (1987, Finland) [72,73]	HEMA (8)	8 (8)	LRTI (8)	*fumigatus* (8)
Sherertz *et al.* (1987, USA)[3]	HEMA (14)	14 (13)	LRTI (14)	*fumigatus* (?); *flavus* (?)
Weems *et al.* (1987, USA)[74]	HEMA (3)	3 (3)	LRTI (3)	Unknown (3)
Harvey *et al.* (1988, UK)[75]	ICU patients low risk (2); high risk (2)	2 (2) 2 (2)	Endocarditis (3)	*fumigatus* (≥3)
Barnes and Rogers (1989, UK)[18]	HEMA (6)	6 (6)	LRTI (6)	Unknown (6)
Hara *et al.* (1989, USA)[76]	HEMA (1); steroids (1)	1 (1) 1 (1)	LRTI (1); sinusitis (1)	*terreus* (2); *fumigatus* (1)
Hopkins *et al.* (1989, USA)[77]	RTX (3); HEMA (2); ONCO (1)	3 (1) 2 (0) 1 (1)	LRTI (6)	*fumigatus* (6)
Mehta *et al.* (1990, India)[78]	T-SURG (4)	4 (4)	Endocarditis (4)	*fumigatus* (1); unknown (3)
Weber *et al.* (1990, USA)[79]	HEMA (18)	18 (18)	LRTI (17)	*fumigatus* (1); unknown (3)
Arnow *et al.* (1991, USA)[44]	HEMA (12); LiTX (3)	12 (?) 3 (?)	LRTI (15)	*flavus* (9); *fumigatus* (6)
Humphreys *et al.* (1991, UK)[48]	ICU patients low risk (3); steroids (3)	3 (0) 3 (2)	LRTI (≥4)	*fumigatus* (6); *flavus* (1)
Loosveld *et al.* (1992, The Netherlands)[80]	HEMA (5); ONCO (1)	5 (3) 1 (0)	LRTI (6)	*fumigatus* (6)
Pla *et al.* (1992, Spain)[81]	LiTX (2)	2 (2)	SSI (2)	*fumigatus* (2)

Table I (*Continued*)

Author (year, country)	Patient group (*N* patients)	Patients (*N* fatal)	Primary site of infection (*N*)	Clinical *Aspergillus* spp. isolates (*N*)
Richet *et al*. (1992, USA)[50]	T-SURG (6)	6 (0)	SSI (6)	*fumigatus* (6)
Flynn *et al*. (1993, USA)[82]	HEMA (3); ONCO (1)	3 (3) 1 (1)	LRTI (4)	*terreus* (4)
Tritz and Woods (1993, USA)[4]	HEMA (4)	4 (4)	LRTI (4)	*terreus* (4); *fumigatus* (1)
Buffington *et al*. (1994, USA)[24]	HEMA (7)	7 (6)	LRTI (7)	*fumigatus* (3); *flavus* (2); unknown (2)
Iwen *et al*. (1994, USA)[83]	HEMA (5)	5 (5)	LRTI (5)	*fumigatus* (2); *flavus* (1)
Tang *et al*. (1994, UK)[25]	RTX (2)	2 (1)	LRTI (2)	*fumigatus* (2)
Bryce *et al*. (1996, Canada)[41]	Surgery (?); burn unit (?)	Total: 4 (?)	Skin infections (4)	Unknown (4)
Leenders *et al*. (1996, The Netherlands)[26,84]	HEMA (5)	5 (?)	LRTI (2); sinusitis (1); eye infection (1); mastoiditis (1)	*fumigatus* (3); *flavus* (2)
Loo *et al*. (1996, Canada)[85]	HEMA (36)	36 (17)	LRTI (34); sinusitis (2)	*flavus* (10); *fumigatus* (6); *niger* (1)
Singer *et al*. (1998, Germany)[22]	Neonates (4)	4 (3)	Skin infection (4)	*fumigatus* (3); *flavus* (1)
Tabbara and al Jabarti (1998, Saudi Arabia)[86]	Cataract surgery (5)	5 (?)	Eye infection (5)	*fumigatus* (5)
Gaspar *et al*. (1999, Spain)[87]	HEMA (11)	11 (1)	LRTI (11)	Unknown (5)
Mellado *et al*. (2000, Spain)[27]	Steroids (8); other lung disease (2)	Total: 10 (total: 6)	LRTI (10)	*fumigatus* (10)
Thio *et al*. (2000, USA)[28]	HEMA (21)	21 (6)	LRTI (21)	*flavus* (≥5); unknown (16)
Burwen *et al*. (2001, USA)[29]	HEMA (6)	6 (?)	LRTI (6)	*flavus* (6)
Lai (2001, USA)[88]	HEMA (3)	3 (2)	LRTI (3)	*flavus* (2); unknown (1)
Oren *et al*. (2001, Israel)[89]	HEMA (31)	31 (0)	LRTI (31)	Unknown (≥15)
Hahn *et al*. (2002, USA)[90]	HEMA (10)	10 (8)	LRTI (10)	*flavus* (≥7); *niger* (≥2)
Pegues *et al*. (2002, USA)[23]	LiTX (3)	3 (≥2)	SSI (2); LRTI (1)	*fumigatus* (3); *flavus* (1); *oryzae* (1)
Lutz *et al*. (2003, USA)[30]	Surgery (3); RTX (1); T-SURG (2)	3 (1) 1 (0) 2 (1)	SSI (6)	*fumigatus* (4); *flavus* (2)
Myoken *et al*. (2003, Japan)[31]	HEMA (3)	3 (?)	Stomatitis (3)	*flavus* (3)
Panackal *et al*. (2003, USA)[32]	RTX (4)	4 (4)	LRTI (3)	*fumigatus* (4)
Heinemann *et al*. (2004, Belgium)[33,91,92]	T-SURG (9)	9 (2)	SSI (9)	*flavus* (9)

?, exact number unknown; T-SURG, thoracic surgery; RTX, renal transplantation; HEMA, haematology and bone marrow transplantation; ONCO, non-haematologic malignancy; ICU, intensive care unit; LiTX, liver transplantation; LRTI, lower respiratory tract infection; SSI, surgical site infection.

performed in 108 clinical isolates. Genotyping of clinical and environmental isolates was performed in 11 studies[23–33] and revealed similar or identical band patterns of at least some isolates in all but four of those investigations.[27,29,30,32] Detailed data concerning patients' characteristics and causative *Aspergillus* spp. in each outbreak are summarized in Table I.

Table II shows mortality rates in various groups of patients. In 49 patients, the distribution of

Table II Number of patients with different underlying diseases and associated mortality

Underlying disease	No. of patients	Mortality (%)
Haematologic malignancy	299	57.6
Solid organ transplantation		55.9
Renal transplantation	36	
Liver transplantation	8	
Other immunocompromised patients		52.3
High-dose steroid therapy	15	
Neonates	5	
Other malignancy	4	
Chronic lung disease	2	
ICU patients ('high risk')	2	
No exact classification possible	49	
Patients without severe immunodeficiency		39.4
Thoracic surgery	25	
Cataract surgery	5	
ICU patients ('low risk')	5	
Other surgical patients	3	
Total	458	55.0

ICU, intensive care unit.

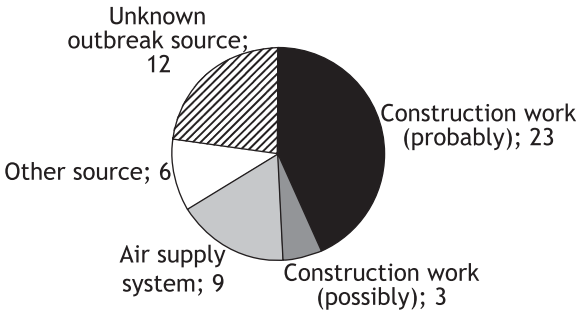

Figure 1 Distribution of sources of nosocomial aspergillus outbreaks.

underlying diseases was not described in detail but all of those diseases did show a relevant immunodeficiency. Therefore, these patients were grouped as described in the Methods section. Mortality was greatest (57.6%) among patients suffering from haematological malignancies. The mortality in this group was significantly higher compared with the mortality of patients without any known immunodeficiency (39.4%; $P < 0.05$).

In 24 outbreaks, volumetric air samples in the hospital and outdoors were taken during the environmental investigation (Table III). The concentration of airborne fungi in patient care areas

Table III Concentration of airborne aspergillus spores (colony-forming units/m^3)

Study	Site of renovation	Operating theatres	Wards, stairs, elevators	Rooms (no HEPA)	Rooms (HEPA)	Outdoor samples
Arnow *et al.*[57]	>235.0		>235.0			
Lentino *et al.*[49]		0.0	0.0	0.0		
Rotstein *et al.*[66]			0.0–5.0	0.0–5.0		3.0
Opal *et al.*[68]	5.9		1.7		<0.1	0.1
Allo *et al.*[69]		0.0–400.0				
Perraud *et al.*[70,71]				6.0		
Sherertz *et al.*[3]			0.2	<0.1	<0.1	1.0
Harvey *et al.*[75]		0.0	0.0	0.0		0.0
Barnes and Rogers[18]			133.0			12.0
Arnow *et al.*[44]			1.1–>90			
Humphreys[48]			0.0			
Richet *et al.*[50]		0.0	0.0			
Flynn *et al.*[82]			>71.0			
Buffington *et al.*[24]	Took volumetric air samples but did not describe exact results of environmental investigation					
Leenders *et al.*[26,84]			0.0–<0.1		0.0–<0.1	0.9–1.3
Loo *et al.*[85]			6.8			
Singer *et al.*[22]				0.0		
Gaspar *et al.*[87]	48.0		5.0–35.0			
Thio *et al.*[28]			0.8–18.0			
Lai[88]			0.0–5.9		0.0	
Oren *et al.*[89]	15.0		15.0		0.2	
Hahn *et al.*[90]			<4.0–>150.0			
Pegues *et al.*[23]			1.1–106.8			
Heinemann *et al.*[33,91,92]			<5.0–115.0			

HEPA, high-efficiency particulate air.

during outbreak investigations ranged from 0 to more than 100 spores/m^3.

As shown in Figure 1, construction work or renovation activities within the hospital or in surrounding areas were most commonly (49.1%) considered to be the probable or possible source of the nosocomial aspergillus outbreak, followed by a contaminated or defective air supply system (17%). In 12 of the 53 outbreaks, the source remained unknown or was not described.

Discussion

Today, construction in or around hospitals is a never-ending phenomenon. This review suggests that construction, renovation, demolition and excavation activities are the main causes of nosocomial aspergillus outbreaks. This is plausible because renovation and demolition work have been shown to increase the amount of airborne fungal spores dramatically,[34] and in consequence increase the risk for aspergillus infection in susceptible patients.[35] Routes of aspergillus transmission in nosocomial outbreaks other than airborne spores are rarely described.[22] Although aspergilli have also been detected in water supply systems, there is no evidence that nosocomial outbreaks derive from the plumbing system.[36,37]

No *Aspergillus* spp. may be disregarded with respect to severity of infection. Instead, any *Aspergillus* spp. in air samples from special care areas should raise concern of invasive infection, although certain *Aspergillus* spp. are more commonly involved in nosocomial outbreaks than others. This may, in part, be explained by an increased pathogenicity of this species, but it may also reflect the natural distribution of aspergilli in the environment.[38]

Environmental investigations are usually initiated in order to assess the quality of air and to identify potential sources of the epidemic. In many studies, the burden of fungal spores in air has been evaluated by gravity sedimentation methods alone (e.g. open Petri dish method).[39–41] However, this method is not volumetric, cannot be calibrated, and hence provides qualitative rather than quantitative results. In preference, air samples should be drawn by impacting particles from an air stream on to agar surfaces after centrifugal acceleration (e.g. Anderson sampler). This technique is more sensitive, allows determination of aspergillus spores in a standardized volume, and is recommended for calculation of the actual density of fungal contamination.[3,42] To date, the minimal airborne concentration of aspergillus spores necessary to cause infection in patients with significant immunodeficiency remains unknown.[43] Even concentrations of airborne aspergillus spores below 1 colony-forming unit (cfu)/m^3 have been shown to be sufficient to cause outbreaks in immunocompromised patients.[3,44] In contrast, the rate of nosocomial IA did not increase in other studies when a median spore count of 0 cfu/m^3 was maintained or high-efficiency filtration face masks were used for neutropenic patients outside patient rooms during the construction period.[45,46]

In accordance with guidelines published by the Healthcare Infection Control Practices Advisory Committee of the CDC, the Association for Professionals in Infection Control and Epidemiology, the IDSA and the ASBMT,[19,20,47] the authors' recommend application of the following measures for nosocomial IA prevention:

(1) avoid non-emergent admissions during heavy construction periods;
(2) if possible, locate high-risk patients as far as possible from areas of demolition or construction;
(3) seal off patient care areas with adequate and impermeable barriers, and keep doors and windows closed;
(4) verify that HEPA air filtration is sufficient and proper air exchange rates are maintained. Check possible plugging or leakage of air filters. Ensure that air pressure relationships are adequate compared with adjunct rooms. Aim for positive pressure in patient rooms and for negative pressure in in-house construction areas;
(5) provide treatment in the patient's room if possible. Transport via an alternate route, schedule transportation during periods with minimal construction activity, minimize waiting times outside, and use appropriate face masks for susceptible patients if it is necessary for them to leave their rooms and pass through potentially contaminated areas;
(6) wet-clean wards thoroughly without raising dust;
(7) surveillance of infections in patients that are at increased risk for IA should be performed.

There are limitations in this approach to determine the minimal infectious dose of aspergillus spores by outbreak analysis. First, environmental investigation starts some time after an increased incidence of nosocomial aspergillosis is recognized, but the concentration of environmental airborne fungal spores varies constantly, e.g. due to climate changes or phases of spores' dissemination from construction work.[48] As such, a single peak of increased spore concentrations at the time of

infection may not be detected. Spores may have settled down in the meantime, and can be detected by environmental swabs while volumetric air samples remain free of fungi.[49,50] Second, after an outbreak has occurred, air sampling should be conducted using large volumes (>1000 L) to increase the likelihood of detecting a low level of spores;[28] however, that was not the case in many outbreak reports. Third, standardized criteria for definite, probable or possible IA were not used in all the studies included in this review. In 2002, international definitions for IA in immunocompromised patients were proposed, but data of earlier outbreak investigations may be influenced by different criteria for IA determination.[51] Finally, despite wide diversity within each species of aspergillus,[52] genotyping was seldom performed to ascertain a common source of infection.[23–33] Even if indistinguishable strains are found, it is also noteworthy that nosocomial aspergillosis is one of the few settings where nosocomial outbreaks can, and probably usually, occur due to a variety of unrelated strains. Thus, findings of similar strains in the nosocomial outbreak setting may also represent inadequate sensitivity of typing methods.

Prospective approaches where the actual airborne fungal concentration is determined in small time intervals in patient care areas during hospital construction periods could be helpful to identify an increase of airborne mould concentrations at an early stage before cases of nosocomial aspergillosis are observed. Detection of airborne aspergilli in high-risk patient care areas should always draw attention to the potential risk of a serious infection. Based on the data available at present, it is concluded that airborne mould spores at any concentration may represent a threat for severely immunocompromised patients.

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