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Aspergillus endocarditis after open heart surgery: an epidemiological investigation

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Summary: The occurrence of aspergillus endocarditis in four patients after open heart surgery, within a period of 10 months, in a centre where no case had been encountered in the previous 7 years, led us to investigate the possible source and factors contributing to this 'outbreak'. The ventilation system, air conditioning plant, air and inanimate sources in the operating theatre were investigated. With the exception of the operating room which was fitted with laminar air flow, it was possible to isolate *Aspergillus* spp. from all rooms in the operating suite. Air conditioner cooling coils and pigeon droppings on the ledges outside the suite were found to harbour aspergillus spores in large amounts. The ubiquitous presence of *Aspergillus* spp. in the operating suite indicated that the existing ventilation system was ineffective in eliminating aspergillus spores from the operating environment. The use of a newly introduced broad spectrum antibiotic protocol seemed to be a major contributory factor according to incidental evidence (although no case control studies were done). Improvements in the ventilation system and the restriction of newly introduced antibiotics was recommended. No further case of fungal endocarditis was observed up to the time of reporting (6 months after the last case).

Keywords: *Aspergillus*; open heart surgery; endocarditis

Introduction

Endocarditis due to opportunistic fungi is rare, almost always fatal, and forms one of the serious complications of open heart surgery (McLeod & Remington, 1977). As there is no effective treatment for this condition, prevention assumes paramount importance. The occurrence of four cases of fungal endocarditis within a short period of 10 months led us to investigate possible sources and contributory factors in an attempt to prevent the occurrence of further cases.

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Epidemiological investigation

Report of cases

Within a 10-month-period (Nov 87–Aug 88) four patients who had undergone open heart surgery involving implantation of a valve prosthesis succumbed to fungal endocarditis in the late postoperative period. Details of these patients are given in Table I. *Aspergillus* spp. was the fungus implicated in all four cases based on histopathological evidence, i.e. the affected tissues showed plenty of septate, hyaline fungal hyphae with dichotomous branching.

Three cases were diagnosed on postmortem examination; in one case it was possible to isolate *Aspergillus fumigatus* from the arterial blood antemortem. The infected cases had the following in common: operation in cardiovascular operating theatre B (see Figure 1); open heart surgery with cardiopulmonary bypass; implantation of intracardiac prosthesis (synthetic cardiac valve of dacron and titanium, 3 cases and dacron patch, 1 case); duration of operation for over 5 h; development of bacterial infection in the immediate postoperative period, and therapy with multiple broad spectrum antibiotics.

Operative procedures and environment

Methods of asepsis during operations, sterilization techniques and preoperative preparation of patients were reviewed in detail and found to be satisfactory according to the hospital disinfection policy. Disposables were used as far as possible including catheters and components of the pump oxygenator used for cardiopulmonary bypass. No major changes in procedures or policy were found to have occurred in the preceding 10 months.

Operating theatre ventilation

The ventilation system and plan of the operating suite is diagrammatically represented in Figure 1. The air conditioning plant delivered 100% fresh filtered air into the theatre suite via ducts situated at ceiling level. The inlet was situated on the 1st floor (same floor as the theatre). Ledges adjacent to the air inlet outside the theatre were inhabited by pigeons. Two exhaust fans in the scrubbing area extracted the air; the number of air changes were about 4–5 h^{-1}. The filters were situated in the air conditioning plant room (Figure 1). They were ordinary air filters made up of several layers of wire mesh; the microbiological specifications of these were not available. One of the operating rooms (theatre A) was fitted with a horizontal laminar air flow system (Gelman) with high efficiency particulate air (HEPA) filters giving a filtering efficiency of 99·9% down to a particle size of 0·3 microns; air speed was 0·45 m s^{-1} with 720 air changes h^{-1}. This room also had two window type air conditioners which were switched on to ease the discomfort while the laminar air flow system was working. These window air conditioning units were in the vicinity of pigeon inhabited areas. The external

Table I. *Details of patients who developed fungal endocarditis after open heart surgery*

Serial number	Age/sex	Operation*	Post-operative antibiotics**	Onset of symptoms of endocarditis	Fungal culture	Outcome	Positive site on histopathology***
1.	23/F	VSD repair, correction of IS	Cz, Ge, Mx, Ct, Cl	2 m	Negative	Fatal	Pulmonary valve (PM)
2.	30/M	MVR	Cz, Ge, Ct, Pe, Mx, Nf	2·5 m	Negative	Fatal	Prosthetic valve (PM)
3.	19/M	MVR	Cz, Ge, Ct	2·2 m	Negative	Fatal	Prosthetic valve (PM)
4.	47/M	AVR	Cz, Ge, Ct, Cx, Nf, AmB	3·5 m	Positive: blood, embolus	Fatal	Embolus (AM)

* AVR, Aortic valve replacement; IS, infundibular stenosis; MVR, mitral valve replacement; VSD, ventricular septal defect.
** AmB, Amphotericin B; Cl, chloramphenicol; Ct, cefotaxime; Cx, cloxacillin; Cz, cefazolin; Ge, gentamicin; Mx, metrogyl; Nf, norfloxacin; Pe, penicillin.
*** Histopathological picture showing uniform septate dichotomously branching hyphae with acute angle of branching, suggestive of *Aspergillus*. AM, Antemortem; PM, postmortem.

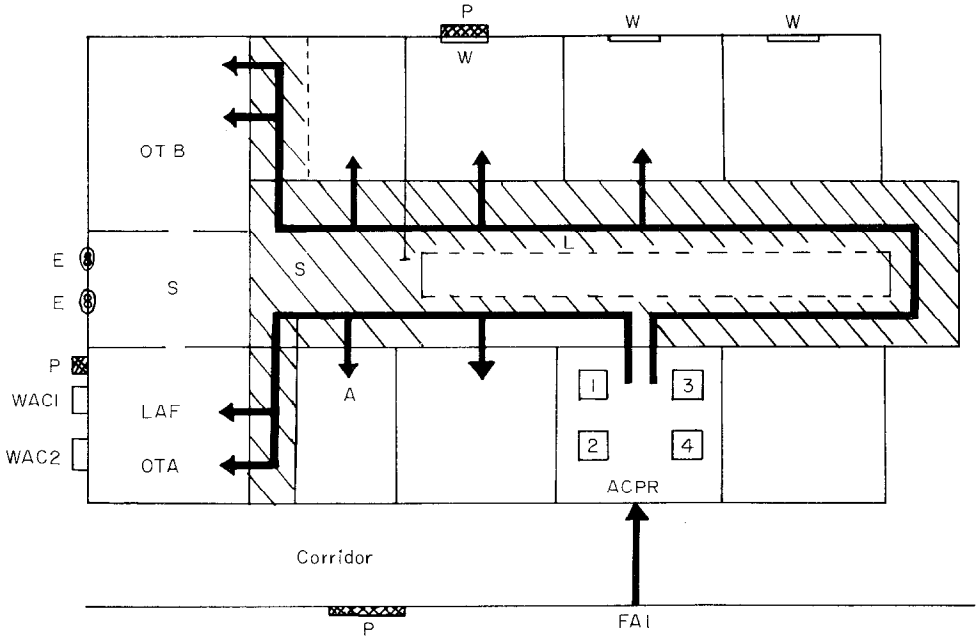

Figure 1. Plan of operating suite and ventilation. OTA, Theatre A; OTB, theatre B; LAF, laminar air flow; WAC, window air conditioner; ACPR, air conditioning plant room; FAI, fresh air inlet; 1,2,3,4, filters; P, pigeon roosting areas; W, window; E, exhaust fan; A, anaesthesia room; L, lobby; S, scrubbing room.

temperature during the period November to August ranged from 10 to 22°C during the winter months and 35 to 44°C during the summer. Relative humidity ranged from 60 to 100%.

Antibiotic prescribing practice

Major changes in antibiotic usage had occurred in the preceding year. After March 1987, the prophylactic regimen for patients undergoing open heart surgery was changed from a 7-day ampicillin and gentamicin regimen starting the day before surgery, to cefazolin and gentamicin for 48 h, and the dosage schedule was changed to include a loading dose to cover the period of operation. Cefazolin had recently been introduced in the country; in vitro tests showed that the majority of hospital pathogenic bacteria were susceptible to it as compared with ampicillin. If the patient developed an infective complication, antibiotics were continued. It was the practice to give multiple antibiotics for prolonged periods in case the patient developed fever, respiratory, wound or urinary tract infection. Antibiotics were often prescribed on the presumptive evidence of infection. Combinations of two to four of the following antibiotics were administered: ampicillin, cephalexin, gentamicin, amikacin, tobramycin, cloxacillin, carbenicillin and

metronidazole. After December 1987, the third generation cephalosporin, cefotaxime, and the quinolone norfloxacin were introduced in the country and began to be used enthusiastically for the treatment of infections. Their use was favoured over the others as they were found to be highly effective against the prevailing pathogens when compared with existing antibiotics.

Culture methods

Environmental Sampling. This was performed during August and September 1988. Air in the various rooms of the operation theatre was sampled by a settle plate method instead of by volumetric air sampling as we lacked an air sampler. Petri dishes of chloramphenicol Sabouraud's agar with Emmon's modification (Sab) were exposed for 1 h at table level during operation. The air currents from the air conditioners and ducts were sampled by exposing Sab agar plates for 10 min directly in the blast. The plates were incubated for 5 d and the number of colonies of aspergilli (as recognized by colonial character and microscopic examination) were enumerated. The colony forming units per cubic foot of air per minute (cfu ft^{-3} min^{-1}) were calculated by the formula:
Number of colonies/(area of the plate in ft^2 × duration of exposure in min).

Air conditioner cooling coils, floors, sinks, operation table, respirators and other inanimate objects were sampled by rubbing a saline moistened swab over an area 4 × 4 in and then inoculated in Sabouraud's broth which was subcultured on Sab agar when turbidity appeared. Inoculated media were incubated at 37°C for 5 d and examined for fungi. Aspergilli were identified by colonial morphology, microscopic examination and slide culture. For pigeon roosting areas and droppings suspensions were made in 5 ml saline, serial dilutions of which were plated on Sab agar.

Tests of disinfectants. The disinfectants used were iodophor 5% (Betadine), Savlon 5%, glutaraldehyde 2% (Cidex). These were tested by the capacity test for fungicidal activity against spore suspensions of *Aspergillus* spp. (Czezkowicz, 1983).

Pump blood was tested before and after bypass by collecting a sample in Castenada's biphasic medium (brain heart infusion broth and agar) which was periodically examined for growth till 15 days.

Results

Table II presents the results of culture of theatre air, the ventilation system and inanimate surfaces for *Aspergillus* spp. The aspergillus count for air is expressed as the mean cfu ft^{-3} min^{-1} whereas aspergillus contamination of surfaces was estimated as the number of times the surface was positive for aspergillus out of the number of times the surfaces was sampled. All rooms of the operation suite except theatre A, which was fitted with laminar flow, showed the presence of aspergilli in the air. The currents of air emitted

Table II. *Distribution of* Aspergillus spp. *in theatre environment (figures rounded to nearest whole number)*

Environmental site	Number of samples	Aspergillus cfu ft^{-3} min^{-1}	Number of samples positive for Aspergillus
Air			
Theatre A (table level)	10	0	
Theatre B (table level)	10	3	
Scrubbing room	8	5	
Anaesthesia room	5	3	
Lobby	5	6	
Ventilation system			
Air conditioner current (1)	5	5	
Air conditioner current (2)	5	8	
Ventilator opening (1)	5	1	
Ventilator opening (2)	5	4	
Surfaces			
Walls	7		2
Floor	7		1
Operating table	4		0
Sink	4		2
Air conditioners			
Cooling coils (1)	5		3
Cooling coils (2)	5		5
Anaesthesia equipment	3		1
Theatre light	2		0
I.V. stand	4		0
Refrigerator	3		2

directly from the ventilatory ports and the air conditioners was contaminated with spores of *Aspergillus* spp.

The cooling coils of the air conditioners grew *Aspergillus* spp., particularly air conditioner 2 which was positive on all sampling occasions. Culture of pigeon droppings on the ledges in the vicinity of air conditioners and the air inlet of the ventilation system showed numerous colonies of *Aspergillus* spp. Pump blood was sampled in five instances before and after bypass; no aspergilli were isolated. All disinfectants tested passed the capacity test.

Discussion

Previous investigations in the wake of fungal endocarditis following cardiac surgery have implicated the ventilation system of the operating theatre. In one investigation, pigeon excreta and moss in the immediate vicinity of the ventilator intake port were found to harbour large numbers of aspergillus spores (Gage *et al.*, 1970), whereas in another study, an overhead ventilator directly above the pump oxygenator was implicated (Hall, 1974).

In the present investigation, the temperature and humidity were conducive to the growth of *Aspergillus* spp. in the environment. Studies on airborne fungi have revealed that pigeon droppings (Gage *et al.*, 1970), plant debris, decaying leaves (Mullins, Harvey & Seaton, 1976), and adjacent reconstruction and renovation work (Lentino *et al.*, 1982, Opal *et al.*, 1986) can increase the level of airborne aspergillus spores. These factors exist around most hospital environments at some time. To provide safe conditions for cardiac surgery, a spore-free environment within the theatre would be necessary. Here, aspergilli were found in all areas of the theatre suite except in the room fitted with laminar air flow. All four cases who developed fungal endocarditis were operated upon in the room without laminar air flow. As the size of airborne fungal particles ranges from 2·5–10 μm (Noble & Clayton, 1963), the external air would need to be passed through filters with pore size small enough to exclude particles of 2·5 μm. Besides contaminated external air introduced through ventilating ducts, the source of infective organisms may be the patient and personnel within the theatre suite (Walter, 1969). Ventilatory systems should therefore be able to provide an adequate number of air changes to prevent the accumulation of spores generated within the theatre. The minimum number of air changes recommended for operation theatres is $30\,h^{-1}$ and ideally $60\,h^{-1}$ (Walter, 1969). In our situation, air was filtered through ordinary wire mesh filters and the number of air changes was $4–5\,h^{-1}$. As aspergilli were found in all areas of the theatre suite except in the room fitted with the laminar air flow (although the air conditioners fitted in the windows of this room harboured the fungus), this unit proved effective in providing a spore free environment. In an environment contaminated with aspergilli, the most likely time of implantation of infection would be the period of operation where the endocardium is exposed for long periods to the theatre air. Moreover, the use of a suction device during intracardiac suction procedures, is liable to increase the chances of contamination of the circulation with airborne organisms. The frequent involvement of the intracardiac prosthesis as observed by us and others (McLeod & Remington, 1977) is probably due to the avascularity of the prosthesis and lack of local immune defences. Spores implanted here would have a better chance to germinate. Extracorporeal circulation, the essential feature of these operations, can further compromise local and systemic immunity (Kittle & Reed, 1961; Geraci, Dale & McGoon, 1963, Goodman *et al.*, 1968). The late appearance of symptoms of infection can be attributed to the natural course of the disease. Previous reports of fungal endocarditis also demonstrate that patients have been well enough to return home and have been reasonably well for about two months after surgery (Gage *et al.*, 1970; Hall, 1974). The fatal outcome of this condition is the rule and only 5% of cases of aspergillus endocarditis have been reported to survive (McLeod & Remington, 1977). All our cases were fatal including the case that was given an antifungal agent.

The present investigation indicates that the ventilation system was ineffective in eliminating fungal spores from the environment; however, it had been in use for the previous 7 years during which no case of postoperative fungal endocarditis had been encountered. The cluster of cases in the preceding 10 months made it reasonable to look for relevant factors during this period which had not prevailed earlier. Detailed enquiry to discover any change in procedure or policy regarding disinfection and aseptic practices in the theatre and related areas was negative. However, the 10-month-period during which the cases occurred corresponded to a period of major changes in antibiotic usage. Three highly effective broad spectrum antibiotics were introduced and used enthusiastically. Besides receiving the antibacterial combination of cefazolin and gentamicin as prophylaxis, all four cases were given multiple antibiotics for prolonged periods—including cefotaxime and norfloxacin—due to the development of septic complications in the immediate postoperative period. This was the standard practice for all cases developing infection in the period corresponding to the 'outbreak'. Only one of the four who developed fungal endocarditis received antifungal therapy as antemortem diagnosis was not possible in the others; this did not change the course of the disease. Antibiotics are known to contribute to opportunistic fungal infections either by direct action on cellular fungicidal mechanisms (Cooper *et al.*, 1961) or by suppressing the normal bacterial flora (Goodman *et al.*, 1968; Freeman, 1980).

Based on these investigations, efforts were made to improve the ventilation system, theatre discipline and aseptic procedures and to revise antibiotic prescription practices. The recommendations made to improve the ventilation system were: (a) weekly scrub of filters and refrigeration coils; (b) replacement of the present filters by a series of prefilters and HEPA filters of 99·9% efficiency down to 0·3 μm; (c) increasing the number of air changes to $30\ h^{-1}$. In the meantime all open heart operations were to be done under laminar air flow. The newly introduced broad spectrum antibiotics were to be restricted to severe infections with sensitive organisms, and where other antibiotics were not likely to be effective. Up to the time of reporting (6 months after the last case) there have been no further occurrences of fungal endocarditis.

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