MAJOR ARTICLE

Outbreak of Invasive *Aspergillus* Infection in Surgical Patients, Associated with a Contaminated Air-Handling System

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An outbreak of *Aspergillus* infection at a tertiary care hospital was identified among inpatients who had amputation wounds, peritonitis, allograft nephritis, or mediastinitis. During a 2-year period, 6 patients were identified, all of whom had *Aspergillus* species recovered from samples from normally sterile sites. All cases clustered in the operating theater during a single 12-day period. To assess operating theater air quality, particle counts were measured as surrogate markers for *Aspergillus* conidia. A substantial increase in the proportion of airborne particles ⩾3 μm in size (range, 3-fold to 1000-fold) was observed in many operating rooms. A confined space video camera identified moisture and contamination of insulating material in ductwork and variable airflow volume units downstream of final filters. No additional invasive *Aspergillus* wound infections were identified after the operating theater air-handling systems were remediated, suggesting that this unusual outbreak was due to the deterioration of insulating material in variable airflow volume units.

Aspergillus species are ubiquitous thermotolerant molds that produce numerous conidia 2–4 μm in diameter. The small size of these fungal spores allows ready dispersion on air currents and deposition into human alveoli. However, despite routine inhalation of these spores, *Aspergillus* species remain an uncommon cause of disease. These fungi are only occasionally associated with colonizing syndromes (e.g., aspergilloma, allergic bronchopulmonary aspergillosis, or chronic sinusitis) and rarely cause invasive infection. Individuals at particular risk for invasive disease include those with protein-calorie malnutrition, patients receiving chemotherapy for malignancy, recipients of bone marrow or solid-organ transplants, and persons with congenital or acquired immune disorders [1–5]. Predisposing host factors include defects in alveolar macrophages, which kill conidia, and neutrophils, which kill hyphae [6, 7]. Although immunocompromised patients are predisposed to invasive infections, these infections are distinctly uncommon in immunocompetent persons [8–12], accounting for <10% of all cases in a recent large series [2].

Aspergillus fumigatus and *Aspergillus flavus* account for the majority of disease-producing species [2]. Establishing a diagnosis of invasive infection due to *Aspergillus* can be difficult. Convincing evidence includes growth of *Aspergillus* species from a sample from a normally sterile site or histopathological evidence of typical fungal elements invading tissue with acute-angle branching, septated, nonpigmented hyphae that are 2–4 μm in width [13].

Aspergillus species are infrequent causes of nosocomial infection. Pulmonary disease in immunocompromised patients is the most common presentation. Wound infections occur much less frequently but have been reported after cardiac and abdominal surgery [14–21]. Hospital-associated outbreaks usually occur dur-

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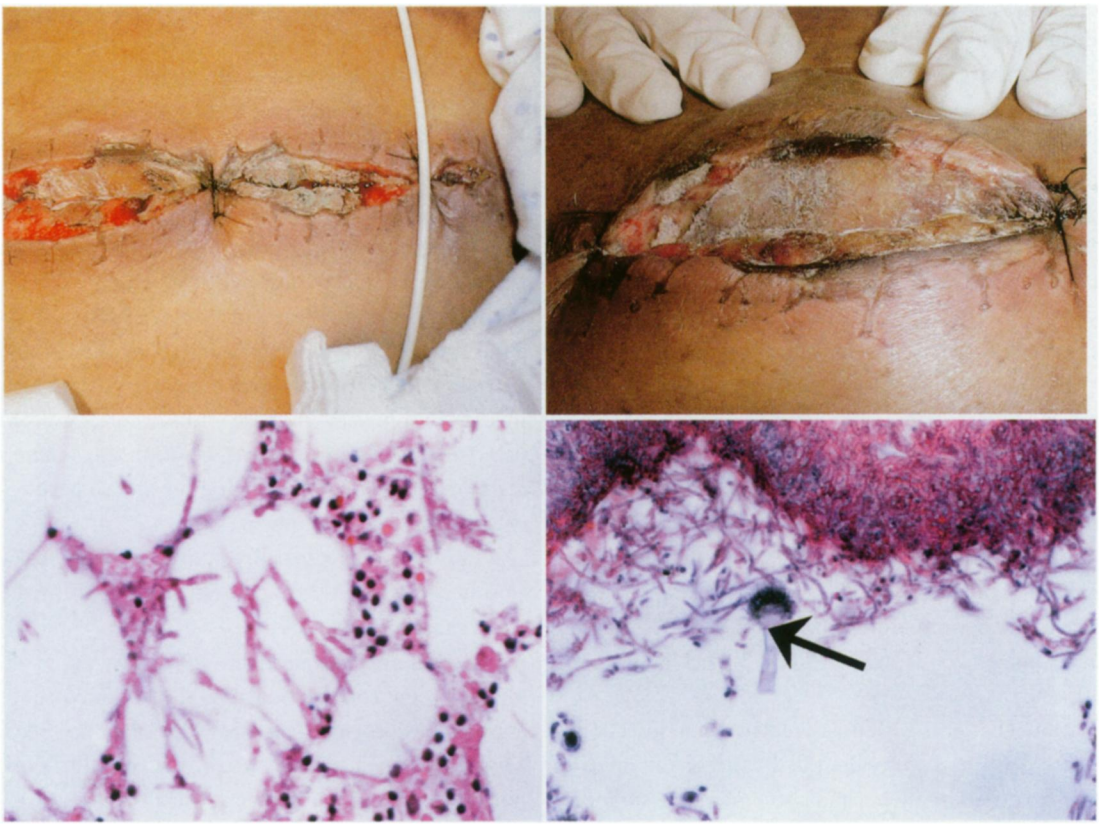

Figure 1. *Top,* Mold and necrotic tissue in the midline abdominal wound from the index case that grew *Aspergillus fumigatus. Bottom,* Examination of the biopsy specimen demonstrates hyphae invading the blood vessel wall and surrounding tissue. Flowering conidia are visible within the blood vessel *(arrow).*

ing periods of construction or renovation [22–30], when increased environmental contamination with *Aspergillus* species can occur [31–34]. Although air contamination is often implicated, direct contamination of air-handling systems is unusual [22, 34–37]. Alternatively, hospital water systems have been implicated recently as a source of nosocomial aspergillosis [38]. Herein, we describe an outbreak of invasive *Aspergillus* infection in postsurgical patients that was ultimately traced to a contaminated air-handling system in an operating theater.

INDEX CASE

A 52-year-old obese woman was admitted to a tertiary care hospital on 24 October 2000 with a humeral fracture after a motor vehicle accident. On the following morning, she became hypotensive, and, during surgery, she had a liver laceration repaired. There was no evidence of intra-abdominal infection. The next day, she returned to the operating room to repair 2 additional minor liver lacerations. After the operation, the abdominal wound dehisced. Persistent fevers with leukocytosis prompted a third surgery on 29 October. The abdominal wound showed no signs of infection, but purulent peritoneal fluid and blood cultures grew *A. fumigatus.* On 2 November, mold was identified on the open abdominal wound. Debrided tissue showed invading septate hyphae and an aspergillum with phialides radiating from a conidiophore, which was diagnostic of *A. fumigatus* (figure 1).

METHODS

The index case was identified during a third postoperative period. Given the unusual nature of the wound infection, and because of concerns about potential patient-to-patient transmission [15, 39], an outbreak investigation was begun. Inpatients were included if *Aspergillus* species were recovered from samples from usually sterile sites or if there was histopathological confirmation of septate hyphal elements noted during examination of biopsy specimens obtained by an invasive technique. This definition is consistent with consensus definitions for proven deep-tissue fungal infection due to molds [13]. Patients with only probable or possible invasive *Aspergillus* infection, per published criteria [13], or who had positive cultures of specimens obtained within 24 h after admission, were excluded. In addition, outpatients with culture specimens positive

for *Aspergillus* species were excluded. Cases were identified by hospital medical records from 1 March 1999 through 1 March 2001. Pathology databases and clinical microbiology laboratory records were analyzed. Medical history, diagnosis, culture and pathological evidence of disease, therapy, therapeutic outcome, dates of hospitalization, room location, evidence of procedures or surgeries, and dates and locations of procedures or surgeries were abstracted. In addition, engineering records were reviewed during the same 2-year period to identify construction or renovation projects.

To assess potential environmental contamination, settle plates were placed in the Coronary Care Unit (CCU) and operating rooms shortly after the index case was identified. Sabouraud dextrose agar plates were opened to air for ~1 h, sealed, and incubated at 30°C for up to 4 weeks. Mold colonies were identified using lactol-phenol cotton blue. Clinical and environmental isolates of *A. fumigatus* were compared by random amplification of polymorphic DNA (RAPD) using 2 primers with satisfactory discriminatory power (R108, 5′-GTATTGCCCT-3′; and Opc 10, 5′-TGTCTGGGTG-3′), as described elsewhere [40, 41].

Several additional patients with invasive *Aspergillus* infection meeting the case definition were identified early in the investigation (see below). These patients had also undergone surgery in October 2000, which suggested that the hospital operating theater was a potential source of infection. The operating theater occupied 1 floor of the hospital. Rooms were connected by a central corridor for delivering supplies and outer corridors for the movement of personnel. Each half of the operating theater was supplied with filtered air from independent north and south ventilation systems. These air-handling systems were located below the operating theater and connected to operating rooms by complex ductwork. Two main air intakes were located at the north and south sides of the building. For the north system, each room had an individual in-line custom filter with 97% efficiency for particles ≥ 3 μm in diameter. An exception was the orthopedic room, for which a separate in-line filter was rated at >99% efficiency. The south system consisted of 2 main filter banks with 97% efficiency. Both air-handling systems were continuously monitored by computer for pressure changes across filters. Data logs for these filters were reviewed.

All operating rooms received 15 air exchanges per hour through individual variable airflow volume (VAV) units located in the ducts just downstream from final filters. VAV units allow adjustment in room air exchange rates via airflow dampeners and air temperature control via water-jacketed radiative elements. Dampeners in these units were activated by motion detectors in operating rooms when no movement occurred in a room for >30 min, reducing air exchange by ~25% as an energy conservation measure.

A multichannel portable counter (Met One Laser Particle Counter, model 3313; Pacific Scientific Instruments) was used to measure airborne particles ≥ 0.3, ≥ 1, ≥ 3, ≥ 5, or ≥ 10 $\mu m/m^3$. Measurement of particles ≥ 3 μm was used as a surrogate for *Aspergillus* conidia bioaerosols. A confined-space color camera with a wide-angle lens and video recorder (SeeSnake Model KD-200; Ridge Tool) was used to survey ductwork that could not be directly visualized. Diffusers, ductwork, and other selected duct materials were cultured for *Aspergillus* by swabbing 2-cm^2 areas of selected materials using moistened culturettes.

RESULTS

The record review identified 294 *Aspergillus*-positive cultures among 227 unique patients. There were no patients with positive histopathological findings for hyphal elements who were not listed among the culture reports. For these 227 patients, there were 5, in addition to the index case patient, who matched

Table 1. Patients with invasive *Aspergillus* infection identified by record review.

Patient	Age, years	Sex	Procedure	Site of infection	*Aspergillus* species	Immuno-compromised	Comorbidities	Clinical outcome
1	52	F	Repair of liver laceration	Wound, peritoneum, blood	*A. fumigatus*	No	Obesity, HTN, DM, anemia, GERD, hyperlipidemia, hypothyroidism	Death
2	48	F	AKA, revision	Amputation stump	*A. flavus*	No	ESRD, DM, HTN	Hospital discharge
3	56	M	Peritoneal dialysis catheter placement	Peritoneum	*A. fumigatus*	No	ESRD, HTN, DM, osteoarthritis	Hospital discharge
4	42	F	Renal allograft, pancreas transplant	Renal allograft	*A. fumigatus*	Yes[a]	ESRD, DM	Hospital discharge
5	46	M	Pulmonary valve autograft	Mediastinum, aortic valve, aortic graft	*A. fumigatus*	No	Aortic insufficiency	Death
6	72	F	CABG	Sternum, mediastinum	*A. flavus*	No	CAD	Hospital discharge

NOTE. AKA, above-knee amputation; CABG, coronary artery bypass graft; CAD, coronary artery disease; ESRD, end-stage renal disease; GERD, gastroesophageal reflux disease; HTN, hypertension; DM, diabetes mellitus.

[a] Renal allograft/ pancreas transplant recipient.

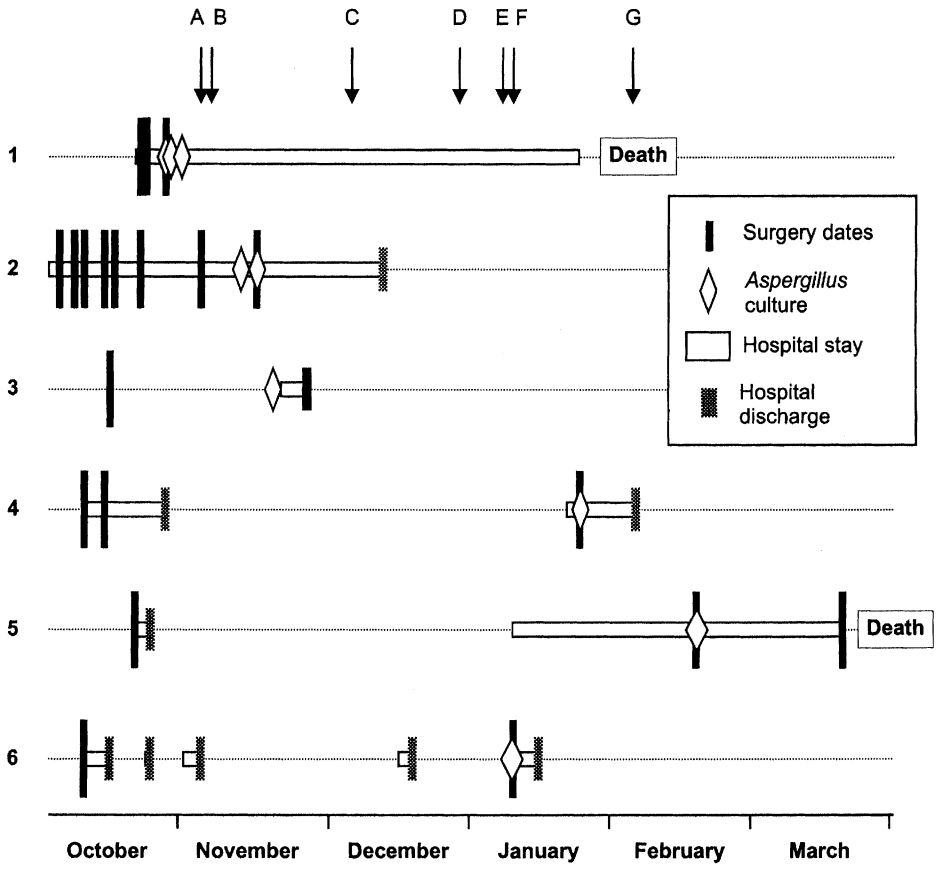

Figure 2. Timeline representing the outbreak period. *A,* Placement of operating room settle plates. *B,* Placement of Coronary Care Unit settle plates. *C,* Operating room final filters changed. *D,* Particle counts on final filters performed to ensure proper function. *E* and *F,* Particle count measurements performed in operating theater. *G,* Closed-space video camera used to visualize interiors of ventilation ducts.

the case definition (table 1). Among these patients, the first sample for *Aspergillus* culture was obtained on 29 October and the last on 21 February 2001. Surgical procedures included revision of an amputation stump, insertion of a peritoneal dialysis catheter, renal and pancreas transplantation, coronary artery bypass grafting, and placement of a pulmonary artery autograft. Two of the 6 patients died. All diagnostic cultures were from operative specimens of closed sterile anatomic spaces that were only open to air in the operating theater (figure 2). Four cases were due to *A. fumigatus,* and 2 were due to *A. flavus.* Of 6 patients, only 1 received immunosuppressive therapy and then only after surgery. No single hospital ward or unit housed all patients; each, however, had been to the operating theater during the period of 13–25 October 2000. No hospital construction or renovation projects took place during this month.

On 6 November 2000, settle plates for 3 operating rooms failed to yield *Aspergillus* species. On 9 November, additional plates in the room of patient 2 and at other CCU areas yielded several isolates of *A. fumigatus,* other *Aspergillus* species, and diverse molds. *A. fumigatus* isolates from settle plates and clinical isolates were compared by RAPD PCR (figure 3). Although DNA banding patterns for several isolates appeared similar when a single primer was used, no 2 isolates showed identical patterns when both primers were compared. These findings suggested that no 2 isolates were related and that a single-point source of contamination was unlikely.

Despite the negative results for settle plates from the operating theater, the exclusive occurrence of *Aspergillus* infections among surgical patients led to a closer examination of air quality in this area. Operating rooms where patients had undergone surgery were supplied air by north and south air-handling systems. Data logs for these systems indicated that no final filters needed replacement. Despite this, all filters for both air-handling systems were replaced on 6 December.

Air quality was subsequently evaluated through quantitative particle counts. Air samples from both north and south air-handling systems were assayed for particles ≥ 3 μm in diameter at air intakes and ducts downstream of final filters. Each new filter functioned at or above 97% efficiency for particles in this size range. Compared with particle counts immediately downstream of final filters, measurements in operating rooms and

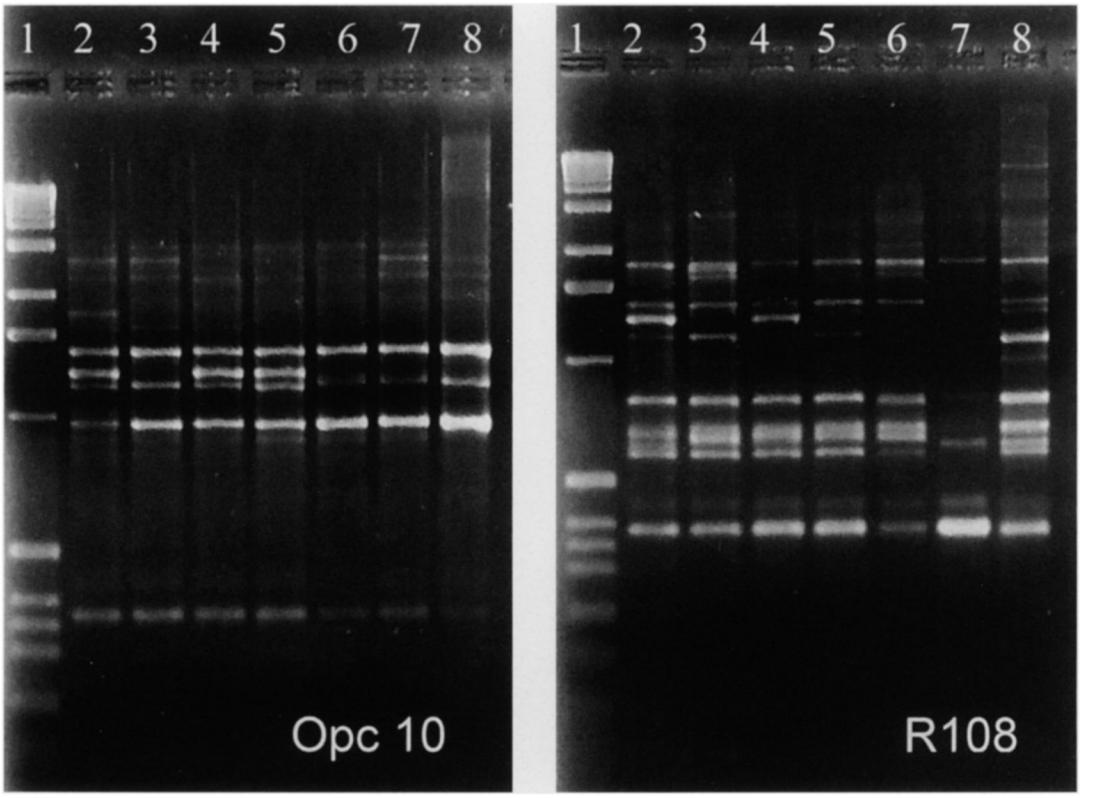

Figure 3. Random amplification of polymorphic DNA analysis of *Aspergillus fumigatus* isolates. Hybridization profiles using primers R108 and Opc 10: *Lane 1,* size marker; *lane 2,* peritoneal fluid, patient 1; *lane 3,* Coronary Care Unit environmental isolate; *lane 4,* patient with pulmonary aspergillosis in room near patient 1; *lane 5,* peritoneal fluid, patient 3; *lane 6,* iliac artery, patient 4; *lane 7,* aortic graft, patient 5; and *lane 8,* control sample 98-407. Although several isolates show similar DNA patterns when only 1 primer was used, none are identical when patterns generated by both primers are compared.

hallways ~1 m below diffusers fed by both air-handling systems had 3–1000-fold increased concentrations of ⩾3-μm particles (table 2).

This unexpected increase in conidia-sized particles in the operating theater prompted an investigation of ductwork downstream of the final filters. Portions of ductwork were visualized using a confined-space camera. Flecks of foil and bits of fiberglass insulation were found in several ducts (figure 4). When VAV units were disassembled foil-covered fiberglass insulation was found that was wet, had deteriorated, and become blackened. This factory-installed interior insulation was designed for noise reduction. Many diffusers and associated grates were rusted, indicating condensation in air-handlers. Cultures of deteriorated insulating material, ductwork, and operating room and hallway diffusers yielded a wide variety of molds. *Aspergillus* species were recovered from 8 (14%) of 56 specimens from the south air-handling system (7 *A. fumigatus* and 2 *Aspergillus niger* isolates) and 4 (17%) of 23 specimens from the north system (1 *A. fumigatus* and 3 *A. flavus* isolates).

Subsequently, 107 of >500 VAV units were inspected in other operating suites or clinical areas where patients at risk for *Aspergillus* infection received care. All units had interior insulating material, but minimal evidence of deterioration was found in only 6 units. Remediation was begun in May 2001 and completed 4 months later. Repairs consisted of removing interior insulating material, coating interior surfaces of VAV units with a fungicide (Foster 40-20; Foster Products), and cleaning diffusers. In general, airborne particle counts in the 1.0–10-μm range were reduced for remediated units, ducts, and diffusers (data not shown). Through May 2003, no additional postsurgical *Aspergillus* wound infections occurred in the hospital.

DISCUSSION

This investigation of invasive *Aspergillus* infections among postsurgical patients identified mold contamination in an operating theater air-handling system. This outbreak was due to insulation in VAV units that had deteriorated after becoming wet. These units were located downstream of final filters, and, therefore, conidia released from mold growing on insulation were not filtered out before entering the operating theater. The source of this outbreak was identified through use of a closed-space video camera that allowed visualization of otherwise inaccessible ductwork.

Table 2. Airborne particle counts in operating rooms.

Operating theater	Mean no. of ≥3.0-μm particles/m³ ± SD, by site: At final filter	Mean no. of ≥3.0-μm particles/m³ ± SD, by site: At diffusers	log_{10}-fold change
North air-handlers[a]			
Room 1	1 ± 1	209 ± 61	2.3
Room 2	3 ± 1	43 ± 13	1.2
Room 3	1 ± 1	131 ± 36	2.3
Room 4	2 ± 2	455 ± 177	2.3
Room 5	2 ± 1	312 ± 212	2.3
Room 6	6 ± 8	292 ± 110	1.7
Room 7	6 ± 3	73 ± 35	1.1
Room 8	4 ± 1	656 ± 409	2.2
Hallway 1	2 ± 4	501 ± 271	2.3
Hallway 2	1 ± 0	1695 ± 564	3.2
Hallway 3	1 ± 1	728 ± 410	3.0
South air-handlers[b]			
Room 9	19 ± 12	98 ± 44	0.6
Room 11	19 ± 12	76 ± 13	0.5
Hallway 4	19 ± 12	910 ± 886	1.7
Room 13	16 ± 5	46 ± 19	0.3
Room 12	16 ± 5	75 ± 62	0.6
Hallway 5	16 ± 5	150 ± 132	0.9

[a] Mean no. of ≥3.0-μm particles/m³ ± SD, 921 ± 23.
[b] Mean no. of ≥3.0-μm particles/m³ ± SD, 2093 ± 238.

The 6 patients who met the case definition for this outbreak had *Aspergillus* infection at anatomic sites that had only been open to air during surgery. Because we could not contact all patients who had undergone surgery during the outbreak period in October 2000, we cannot eliminate the possibility that additional patients may have sought care at other health care facilities. Missing patients, however, would not likely detract from the conclusions of this investigation.

The recognition of higher airborne particle counts in operating rooms in the size range of *Aspergillus* conidia (2–4 μm), compared with counts immediately downstream of final filters, led to the discovery of deteriorating insulation in VAV units. Inspection of the operating theater air-handling system also revealed rust on diffuser grates and moisture in ducts indicative of long-standing condensation. Only VAV units supplying operating rooms contained wet, contaminated insulation. The predisposition for insulation in these units to deteriorate may have been due to moisture generated when colder temperatures used in operating rooms created condensation in ducts. Presumably, moist insulation was contaminated with *Aspergillus* conidia not removed by final filters. Fiberglass insulation readily supports the growth of *Aspergillus* species, but only in the presence of >50% humidity [42]. We speculate that, in October 2000, a short-lived "bloom" of *Aspergillus* species may have released large quantities of conidia into the operating theater air at points beyond the final filters. The reason for a self-limited bloom is not clear, but it may be associated with the lower humidity that came with cooler weather after October. Although only a small percentage of cultures from VAV units, ductwork, and diffusers were positive for *Aspergillus* species, these tests were performed months after the outbreak had terminated.

Although local weather conditions may have played a role in the outbreak, in previous studies, it has been difficult to associate outdoor concentrations of *Aspergillus* conidia with seasons or the weather [39, 43, 44]. During September and early October 2000, the weather at the hospital was extremely hot (~35°C–41°C) and dry. During the week before the sur-

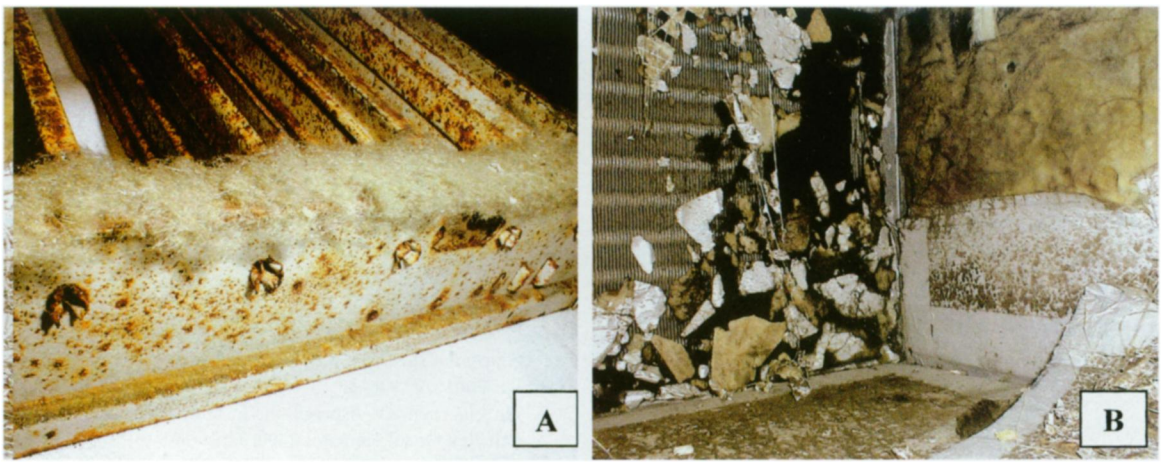

Figure 4. *A,* Operating room diffuser showing fiberglass fragments from insulation blown downstream from a variable airflow volume (VAV) unit. Severe rusting is indicative of intermittent or chronic condensation. *B,* Interior view of a VAV unit showing deterioration of foil-lined fiberglass insulating material.

geries associated with this outbreak were performed, cooler temperatures (~12°C–13°C) and frequent rain developed. Immediately before the first surgery linked to the outbreak, temperatures warmed again (~32°C–33°C), and the rain continued. These conditions may have promoted condensation in air ducts in the operating theater. In November, temperatures returned to a seasonable range and the weather became drier. These latter conditions may not have supported the growth of *Aspergillus* species as well as those in October 2000 and could explain, at least in part, the spontaneous cessation of cases after October.

No correlation was found between particle counts in specific operating rooms and the rooms in which case patients underwent surgery. This negative association may simply have been due to our measurement of airborne particle counts after the outbreak had already spontaneously terminated. It appears that the first case patients were exposed to *Aspergillus* species during surgery in October 2000, days to weeks before the index case was identified on 2 November 2000. In retrospect, by the time the outbreak was recognized, "real time" measurements of conidial counts in the operating theater may not have been helpful if increased concentrations that caused the outbreak had already abated.

Nosocomial transmission of *Aspergillus* infection occurs most often during or after hospital construction or renovation, and usually in severely immunocompromised patients. The development of postoperative invasive *Aspergillus* infection, however, is unusual [18, 20] (it is reviewed in [21]). Most surgery-associated infections arise from contaminated dressings or, as was the situation here, airborne contamination of wounds in the operating theater. This investigation is the first to implicate VAV units in the nosocomial transmission of fungal infections. These devices are recommended by the American Institute of Architects in recent *Guidelines for Construction and Equipment of Hospitals and Medical Facilities* [45], and they are commonly installed in hospitals to improve energy efficiency through airflow and temperature control. The guidelines, however, specify that VAV units should not be used downstream of humidification systems or be allowed to interfere with air exchanges in patient care areas. Liners in VAV units are usually installed to decrease noise generated by turbulent airflow across dampers. Although, in general, no material should be installed in ductwork beyond final filters, special liners have historically been permitted in VAV units. In this hospital, airflow and filter pressure were appropriately monitored, and the design of the hospital's air-handling systems complied with current guidelines [46].

Genetic testing has been used to investigate the epidemiology of nosocomial *Aspergillus* infection. PCR identification techniques, such as RAPD analysis, have documented nosocomial transmission of *Aspergillus* species [20, 34, 38–41]. Analyses of large numbers of environmental and hospital-associated isolates indicate that marked genetic diversity among *A. fumigatus* populations is typical [46, 47]. The heterogeneity of airborne spores likely explains why, in this outbreak, patients were infected with different strains. We elected not to compare *A. fumigatus* isolates recovered from insulating material and ductwork with clinical isolates because of the prolonged period between the outbreak and collection of air-handler samples for culture. Identical genetic isolates may provide good evidence for a point source, but to effectively eliminate a point source from consideration requires genotyping multiple *A. fumigatus* isolates from each patient and a large number of environmental isolates. This was not possible in this outbreak.

Aspergillus species are infrequent but serious causes of nosocomial infection. Although contamination of air-handling systems is uncommon [22, 35–37], this outbreak suggested that some modification in current air quality guidelines may be necessary for critical patient care areas, such as oncology wards, intensive care units, and operating theaters. Current guidelines for operating theaters only address total air exchanges per hour, air filtration efficiency, filter location, and monitoring systems to measure pressure drops across filters and air exchange rates [45, 48]. The routine use of airborne particle counts to monitor air quality is not currently recommended. Instead, avoidance of fungal contamination is sought through good construction and maintenance practices [48]. Despite the appropriate implementation of these guidelines by this hospital, an outbreak of *Aspergillus* infection still occurred. Facilities using VAV units in air-handlers for clinical areas where patients are at risk for nosocomial infection may wish to verify that interior insulating liners are not present or are in good condition. Under certain conditions, as might occur with excessive moisture, these materials can deteriorate and become an attractive substrate for mold growth. As described here, this can lead to serious invasive fungal infection in immunocompetent patients.

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