Review of Fungal Outbreaks and Infection Prevention in Healthcare Settings During Construction and Renovation

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Hospital construction and renovation activities are an ever-constant phenomenon in healthcare facilities, causing dust contamination and possible dispersal of fungal spores. We reviewed fungal outbreaks that occurred during construction and renovation over the last 4 decades as well as current infection prevention strategies and control measures. Fungal outbreaks still occur in healthcare settings, especially among patients with hematological malignancies and those who are immunocompromised. The causative pathogens of these outbreaks were usually *Aspergillus* species, but Zygomycetes and other fungi were occasionally reported. *Aspergillus* most commonly caused pulmonary infection. The overall mortality of construction/renovation-associated fungal infection was approximately 50%. The minimal concentration of fungal spores by air sampling for acquisition of fungal infections remains to be determined. Performing infection control risk assessments and implementing the recommended control measures is essential to prevent healthcare-associated fungal outbreaks during construction and renovation.

Keywords. fungal outbreaks; *Aspergillus*; healthcare-associated infections; construction; renovation.

Numerous fungal outbreaks have occurred in healthcare settings and have been a serious threat to immunocompromised hosts [1]. Construction and renovation activities can cause serious dust contamination and disperse large amounts of fungal spores, and construction activity has been reported to be an independent risk factor for invasive fungal infections [1, 2]. A previous review revealed that construction or renovation activities within the hospital or in surrounding areas accounted for approximately half of the sources of healthcare-associated *Aspergillus* outbreaks [2]. Hospital construction and renovation activities are an ever-constant phenomenon [2], and the cost of hospital construction is expected to be nearly $200 billion dollars by 2015 in the United States [3]. It is estimated that 5000 deaths due to construction-related infections occur each year in healthcare settings [4].

The goal of this review article was to (1) examine fungal outbreaks that were related to hospital construction, renovation, and/or demolition over the last 4 decades; and (2) offer infection prevention and control measures in healthcare facilities based on previous experiences, evidence, and guidelines.

SEARCH AND SELECTION CRITERIA

To select relevant articles, we searched the published literature in PubMed using the following keywords [All Fields]: (aspergillosis OR Aspergillus OR Zygomycetes OR Mucor OR mycoses OR mycosis OR fungi) AND (hospital OR healthcare OR nosocomial) AND (construction OR renovation) AND (outbreak OR contamination OR infection OR prevention OR control). From 1974 through 2014, 158 references were carefully reviewed. Additional reports were also identified through the references cited. Finally, 49 studies [5–53] were

selected for the analysis, including all cases of outbreaks that were related to hospital construction, renovation, or demolition. We excluded non-English publications, reported cases of contaminations or *Candida* species only, and reports that did not include human infections. We used each author's definition in the selected articles to classify construction, renovation, demolition, and excavation. Definitive outbreaks (pseudo-outbreaks were not included) are summarized in Table 1.

FUNGAL OUTBREAKS ASSOCIATED WITH CONSTRUCTION AND RENOVATION AT EACH 5-YEAR TIME PERIOD

The trend of outbreaks that were related to construction, renovation, and demolition by 5-year period of publication from 1970 to the present is shown in Figure 1. The first report was published in 1976 [5], and the reported cases of outbreaks increased gradually. There were 7–10 articles of outbreaks associated with construction, renovation, and demolition in each 5-year period during 1985–2009; however, in the last period, 2010–2014, there were only 3 published studies that had been conducted before 2010. This reduction in reported outbreaks may represent improved infection control that resulted in fewer outbreaks or publication bias (by authors or journals) given the large number of previously published outbreaks.

SETTINGS WHERE FUNGAL OUTBREAKS AND INFECTIONS OCCURRED, AND PATIENT POPULATIONS AT RISK

Healthcare-associated fungal outbreaks have been reported throughout the world [2]. In this review of English-language studies that focused on construction and renovation, the United States accounted for 47% (23/49 articles), followed by European countries, including the United Kingdom (8%), Italy (8%), and France (8%). University hospitals were the most common (35%) settings. Tertiary care hospitals and university hospitals have often implemented the most medically advanced treatment in a given era (eg, cancer chemotherapy, immunosuppressive therapy, and transplant), which likely accounts for the overrepresentation of academic centers because of their highly susceptible patient populations.

Susceptible populations for healthcare-associated *Aspergillus* infections included patients with the following characteristics: hematological malignancies, allogeneic hematopoietic stem cell transplant (HSCT), solid organ transplant (renal and liver), high-dose steroid therapy, neonates, other malignancies, chronic lung disease, residing in intensive care units (ICUs), and thoracic surgery [2]. The main risk factors for healthcare-associated mucormycosis were prolonged steroid therapy, solid organ transplant, diabetes mellitus, prematurity, and hematological malignancies [54].

In this review, hematologic malignancies or bone marrow transplant accounted for 53% of reports by underlying diseases, and construction-related fungal infections occurred infrequently among rheumatology patients, patients after surgery, premature infants, and nephrology and dialysis patients (Table 2).

FEATURES OF FUNGAL OUTBREAKS AND INFECTIONS AND THOSE CAUSATIVE PATHOGENS

The primary infection site was mainly lower respiratory tract in healthcare-associated *Aspergillus* outbreaks as air was the major transmission route of fungal spore, whereas surgical site infections and skin infections were rarely described [2]. Of the 41 articles reporting *Aspergillus* infection only, the major site of *Aspergillus* infection was lung only (19 articles [46%]), followed by lung with other sites (8 articles [20%]), skin/wound (3 articles [7%]), sinus with other sites (1 article), eye (1 article), and disseminated (1 article). An outbreak of *Aspergillus fumigatus* endophthalmitis after cataract surgery during construction has been described [32]. The causative pathogens of fungal outbreaks and infections were usually *Aspergillus* species, including *A. fumigatus*, *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger*, but occasionally Zygomycetes and other fungi, which was similar to a previously published article [55]. Six construction-related cases of healthcare-associated pulmonary mucormycosis due to *Mucor indicus* or *Cunninghamella bertholletiae* have been reported [9, 34], although it was difficult to differentiate healthcare-acquired from community-acquired mucormycosis, as most of those infections in hospitalized patients are sporadic in nature [56].

Furthermore, there were 4 articles of pseudo-outbreaks associated with construction and renovation, including a pseudo-epidemic of *Sporothrix cyanescens* pneumonia due to bronchoscopy material contaminated by dust created during renovation of the bronchoscopy suite [57]; pseudo-fungemia of *Aspergillus* species and *Penicillium* species from contamination of plates that had been inadvertently left open to air on a workbench area connected to locations outside the laboratory during renovation [58]; pseudo-epidemic of *A. niger* cultures traced to specimen contamination in the laboratory during construction [59]; and pseudo-outbreak of *Aspergillus sydowii* keratitis due to environmental contamination of culture media following construction in an ophthalmology ward [60].

Invasive aspergillosis is an independent predictor of mortality, and the overall case-fatality rate among the published reports was 58%, ranging from 25% in cutaneous cases to 88% in disseminated or central nervous system cases [61, 62]. Death attributable to mucormycosis differed from 50% to 100% by each report [54]. This review revealed that the overall mortality of fungal outbreaks and infections associated with construction

Table 1. Characteristics of Fungal Outbreaks and Infections Associated With Construction, Renovation, and Demolition

Author, Year	Patient Population	No. of Patient Infected	No. of Patient Deaths	Type of Infection (Site)	Type of Fungi	Reservoir or Source	Airborne Fungal Level(s)	Molecular Typing	Control Measures
Aisner, 1976 [5]	Cancer patients	8	Unknown	*Aspergillus* infection (lung, pharyngeal, or maxillary sinus)	*Aspergillus* spp. (predominantly *A. niger*, *A. flavus*, *A. fumigatus*)	Fireproofing material sprayed wet during construction	Unknown	Unknown	Unknown
Arnow, 1978 [6]	Immunosuppression (renal transplant)	3	1	*Aspergillus* infection (lung)	*A. fumigatus*, *Aspergillus* sp.	Renovation, spores on dust from false ceiling tiles above transplant unit	Airborne spores >200 cfu below renovation	Unknown	Impermeable plastic barriers, immunosuppressed patients moved to other floors, horizontal surfaces, vacuumed, damp mopped, and dusted
Sarubbi, 1982 [8]	Hospitalized patients (acute nonlymphocytic leukemia for 1 infected)	1	1	Invasive *Aspergillus* infection (lung)	*A. flavus*	Construction, defective ventilation and air filtration	8 *A. flavus*/positive room, control 1 *A. flavus*/positive room-settle plates	Unknown	Pre-filters and filters in ventilation system replaced
Lentino, 1982 [7]	Immunosuppressed patients with renal allograft recipients or hematologic malignancy	10	4	Invasive *Aspergillus* infection (lung)	*Aspergillus* sp.	Road construction for access to the new hospital, contaminated window air conditioners in renal transplantation ward	400–2800 *Aspergillus* spores/cm^2 from air conditioner filter	Unknown	Unknown
Krasinski, 1985 [9]	Premature infants	2	2	Fungal infection (lung)	*Aspergillus* sp., Zygomycetes, *Rhizopus indicus*	Renovation of adjacent special care unit and demolition of wall, mold in dust above a false ceiling	0.88 fungi per hour per settle plate compared to 0.22 fungi per hour per settle plate in construction free area	Unknown	Patients moved from area of construction, additional dampers placed in air ducts, impervious dust barriers erected, area above false ceiling and ventilation ducts vacuumed, replaced HEPA filters, air ducts and environmental surfaces disinfected
Opal, 1986 [10]	Immunocompromised (lymphoreticular malignancy, high-dose corticosteroid therapy or disseminated carcinoma)	11	11	*Aspergillus* infection (disseminated)	*A. flavus*, *A. fumigatus*, *A. niger*, *Aspergillus* sp.	Hospital renovation and construction	5.9 ± 0.7 *Aspergillus*/m^3 inside construction site compared to 1.2 *Aspergillus*/m^3 outside construction site	Unknown	Copper-8 quinolinolate, airtight plastic and dry wall barriers about the construction site, HEPA filters in patients room, and negative pressure in construction area
Barnes, 1989 [14]	Children undergoing BMT	6	6	Invasive *Aspergillus* infection (lung)	Unknown	Building work installing a laminar air flow system to the unit	133 cfu/m^3 of *A. fumigatus* in the BMT unit during building work	Unknown	Laminar air flow isolation
Humphreys, 1991 [19]	Severe patients in the ITU	2	2	Invasive *Aspergillus* infection (lung)	*A. fumigatus*, *A. flavus*	Building work in an area adjacent to the ITU, disturbance of spores in fibrous insulation material above the perforated metal ceiling	Sampling after building work completed, but no molds isolated	Unknown	Improved hospital design, satisfactory ventilation, thorough regular cleaning of environmental surfaces, and relocation of patients

Table 1   continued.

Author, Year	Patient Population	No. of Patient Infected	No. of Patient Deaths	Type of Infection (Site)	Type of Fungi	Reservoir or Source	Airborne Fungal Level(s)	Molecular Typing	Control Measures
Brincker, 1991 [18]	Acute leukemia	10	4	*Aspergillus* infection (lung)	Unknown	Indoor building renovation, Increased spores in ward locations with heavy traffic of patients and staff	At least 11.2 *Aspergillus* per 24h-settle plate	Unknown	Unknown
Flynn, 1993 [20]	BMT recipients, acute myeloid leukemia, or disseminated choriocarcinoma	4	4	*Aspergillus* infection (lung)	A. terreus	Hospital renovation, entry of fungal organisms from corridors, stairwells, elevator, shafts serving the ICU and renovation areas due to the negative air pressure gradient	Fungal spores >71/m^3 at elevator shafts during renovation	Unknown	Reestablished positive pressure and unidirectional airflow
Iwen, 1994 [22]	Neutropenic patients who underwent high-dose chemotherapy	5	Unknown	Invasive *Aspergillus* infection (unknown)	A. fumigatus, A. flavus	Hospital construction, increase in molds in the air occurred in the patient rooms and corridor adjacent to construction staging area, windows in the adjacent corridor as the most likely source of mold contamination	0.14 cfu fungi per hour per settle plate (before construction) to 0.40 cfu fungi per hour per settle plate (after construction)	Unknown	Special care unit closed to incoming patients, window casements, plumbing penetrations, electrical outlets, and other sources for potential air leaks visually examined and sealed, HEPA filters replaced, each room terminally cleaned with subsequent follow-up testing by air-settling plates
Buffington, 1994 [21]	Acute leukemia or aplastic anemia	7	6	Invasive *Aspergillus* infection (unknown)	A. flavus, A. fumigatus, Aspergillus sp.	Construction activity, staff and visitors frequently walking through breezeway by the construction	Unknown	Randomly amplified polymorphic DNA (6 different pattern, similar pattern banding from case patient, healthcare worker, and environmental source)	Laminar air flow rooms with HEPA filters, air intake ducts decontaminated with formaldehyde vapor
Loudon, 1994 [23]	Hematologic malignancies (acute lymphoblastic leukemia, acute myeloid leukemia, lymphoma, Hodgkin's disease)	7	5	Invasive *Aspergillus* infection (lung)	A. fumigatus, A. flavus	Extensive building work was ongoing on the ground floor beneath the hematology unit, *Aspergillus* for showerhead	Unknown	Silver staining of sodium dodecyl sulphate-polyacrylamide gels, immunoblot fingerprinting, and random amplification of polymorphic DNA (3 cases indistinguishable)	Itraconazole prophylaxis

Table 1 continued.

Author, Year	Patient Population	No. of Patient Infected	No. of Patient Deaths	Type of Infection (Site)	Type of Fungi	Reservoir or Source	Airborne Fungal Level(s)	Molecular Typing	Control Measures
Anderson, 1996 [25]	Immunocompromised pediatric patients with leukemia or neuroblastoma	6	Unknown	Nosocomial *Aspergillus* infection (lung, blood, pericardial fluid, or cardiac vegetation)	*A. fumigatus, A. terreus, A. flavus, A. niger, Aspergillus* sp.	Defective disposal conduit door and dispersal of contaminated aerosol from the ward vacuum cleaner	62 *Aspergillus*/m^3 close to vacuum cleaner during use	Unknown	Disposal door sealed, vacuum cleaner replaced by a machine of higher efficiency, itraconaole prophylaxis
Loo, 1996 [28]	Patients with leukemia or BMT	36	17	Nosocomial *Aspergillus* infection (lung, sinus)	*A. flavus, A. fumigatus, A. niger*	Archaic ventilation system in hospital which could not filter the *Aspergillus* spores that were disturbed and dispersed to patient-care areas during construction activity	6.77 *Aspergillus* sp./m^3 during the epidemic period	Unknown	Portable HEPA filter air purifier units, application of copper-8-quinolinolate formulation, windows sealed, existing perforated ceiling tiles replaced with the easy-to-clean, non-perforated tiles, vinyl-faced aluminum tiles, horizontal dust-accumulating blinds replaced with vinyl, opaque, roller shades, ventilation systems meticulously maintained, patient rooms cleaned regularly, patients moved to another area of the hospital and housed in single rooms with doors closed
Thio, 2000 [35]	Patients with leukemia or BMT	21	6	Invasive *Aspergillus* infection (sinus and other)	*A. flavus*	Construction of a new building adjacent to the oncology center, negative pressure in the oncology unit	0.8–18 *A. flavus*/ 1,000L	Randomly amplified polymorphic DNA (2 of 5 patient samples and 5 environmental samples identical)	Use of wet buffing to clean all floors, N95 masks to protect neutropenic patients outside filtered areas, portable HEPA at entrance, change of traffic patterns into the unit, windows and exterior walls resealed, doors to patient rooms kept closed, hospital construction policy developed, closing central stairwell
Lai, 2001 [37]	Patients undergoing BMT and neutropenia	2	2	Invasive *Aspergillus* infection (lung)	*Aspergillus* sp., *A. flavus*	Construction below the unit, but no link to the construction by air sampling	0.5–5.9/0 *Aspergillus* cfu/m^3, 5.9–23.6/0.4- > 11.6 other filamentous fungi cfu/m^3 (precleaning/postcleaning)	Unknown	BMT unit closed, air intake ducts cleaned, HEPA filters replaced, double plastic coverings across the entryways to construction sites, stairwell sealed with negative pressure, carpeting replaced by vinyl flooring, prophylactic amphotericin B
Burwen, 2001 [36]	Neutropenic patients in hematology-oncology ward	6	Unknown	Invasive *Aspergillus* infection (lung, blood, ear tissue, and other)	*A. flavus*	Internal construction on a new west wing adjacent to the hematology-oncology ward and renovation of patients' room	Unknown	Randomly amplified polymorphic DNA (patient isolate matched an environmental, two environmental isolates matched)	Unknown

Table 1   continued.

Author, Year	Patient Population	No. of Patient Infected	No. of Patient Deaths	Type of Infection (Site)	Type of Fungi	Reservoir or Source	Airborne Fungal Level(s)	Molecular Typing	Control Measures
Oren, 2001 [38]	Acute leukemia	31	8	Invasive *Aspergillus* infection (lung)	*Aspergillus* sp.	Extensive hospital construction and indoor renovation	15 *Aspergillus*/m³ at construction site	Unknown	Amphotericin B prophylaxis, and HEPA system
Raad, 2002 [39]	Neutropenic patients with hematologic malignancy	113	Unknown	Nosocomial invasive *Aspergillus* infection (lung)	*A. fumigatus, A. terreus, A. flavus*	Hospital construction (low-intensity construction and high-intensity construction)	5–29 fungi/m³ in outdoor air during low-intensity construction, 1–71 fungi/m³ in outdoor air during high-intensity construction and 1–2 fungi/m³ in indoor air	Unknown	Physical barriers using floor-to-ceiling dry wall or plastic barriers, protected environment with laminar air-flow rooms, HEPA filter, use of high-efficiency filtration masks for patients when leaving rooms
Yonemori, 2002 [40]	Acute leukemia	4	0	Invasive fungal infection (lung)	Unknown	Demolition and excavation near new building	65 fungi/m³ at construction area; 10 fungi/m³ in patient rooms	Unknown	Windows sealed, use of portable open horizontal laminar-air-flow apparatuses placed at bedside of neutropenic patients, itraconazole prophylaxis
Panackal, 2003 [42]	Renal transplant recipients	4	4	Invasive *Aspergillus* infection (unknown)	*A. fumigatus*	Inappropriate barriers between construction site and ward, frequent trafficking of staff between the construction and patient care areas, few respiratory protection	Unknown	Restriction fragment length polymorphism (genotype matched between 2 patients and 2 environmental isolates, but no match between environmental and clinical isolate)	Recommend application of CDC guideline such as: appropriate placement of impermeable barriers, the use of HEPA filters in HVAC, N95 respirator use for patients in contaminated areas, preventing traffic between construction and patient care areas, and elevator for exclusive use of construction workers and debris removal
Ahmad Sarji, 2006 [44]	Child patients with leukemia and other malignancies undergoing chemotherapy	14	9	Fungal infection (lung, blood, sinus, liver, spleen, kidney, skin)	*Candida* sp., *Aspergillus* sp., *Fusarium* sp., *Chrysosporium* sp., *Mycelium* sp., *Monilia* sp., *Phaecilomyces* sp.	Soil disturbance at adjacent building construction work	659 fungi /m³ at treatment room	Unknown	Identifying high-risk patients, anti-fungal prophylaxis
Berthelot, 2006 [45]	Highly immunocompromised patients with hematological malignancies	15	8	Invasive *Aspergillus* infection (lung)	*A. flavus, A fumigatus*	Hospital building work and demolition	3.7% - 15.2% (frequency of environmental samples containing *A. fumigatus* per year)	Unknown	Use of temporary barriers during work, watering of soil during demolition work, reduction of pedestrian traffic in construction areas, maintaining negative pressure, and wearing of high-efficiency filtration masks by immunosuppressed patients

Table 1   continued.

Author, Year	Patient Population	No. of Patient Infected	No. of Patient Deaths	Type of Infection (Site)	Type of Fungi	Reservoir or Source	Airborne Fungal Level(s)	Molecular Typing	Control Measures
Pini, 2008 [50]	Acute leukemia	7	Unknown	Invasive *Aspergillus* infection (lung)	*A. fumigatus, Aspergillus* sp.	Renovation work	2.98 *A. fumigatus*/m^3 corridor between the wards, 0.09 *A. fumigatis*/m^3 in restricted access rooms	Unknown	Multiple-bed rooms without HEPA filtration but restricted access to visitors and other particular behavioral measures (ban on plants, flowers, and opening windows)
Chang, 2008 [49]	Leukemia, multiple myeloma, and high-grade lymphoma	6	2	Nosocomial invasive *Aspergillus* infection (lung, mediastinum)	*A. fumigatus*	Hospital construction in and around the vicinity of the day oncology building	No fungal growth by air sampling in the inpatient facility, day-oncology and pharmacy	Unknown	Unit relocation, impermeable barriers at construction site, face-masking and voriconazole prophylaxis among high-risk patients
Chabrol, 2010 [51]	Acute leukemia	25	6	Invasive *Aspergillus* infection (lung, sinus, brain, disseminated)	*A. fumigatus, A. flavus, A. terreus*	Construction or renovation work	1–10 *Aspergillus*/m^3 (during building work)	Unknown	HEPA filters without any laminar air flow room, and prophylaxis with voriconazole or caspofungin
Pokala, 2014 [53]	Children with acute leukemia	50	10	Invasive fungal diseases (lung, sinus, and other)	*Scedosporium* sp., *Rhizopus* sp., *Phoma* sp., *Exoserohilum* sp., *Bipolaris* sp., *Fusarium* sp., *Aspergillus* sp., *Candida* sp.	Major renovation with excavation of the grounds for construction of a new tower connected to the existing buildings	Unknown	Unknown	Windows of the existing adjacent building re-sealed, education for construction crews, air handling systems optimized using HEPA filters, use of N-95 respirator, valet parking service for all oncology patients immediately adjacent to the hospital entrance, fluconazole or voriconazole prophylaxis

Abbreviations: BMT, bone marrow transplant; CDC, Centers for Disease Control and Prevention; CFU, colony-forming unit; HEPA, high-efficiency particulate air; HVAC, heating, ventilation, and air conditioning; ICU, intensive care unit; ITU, intensive therapy unit.
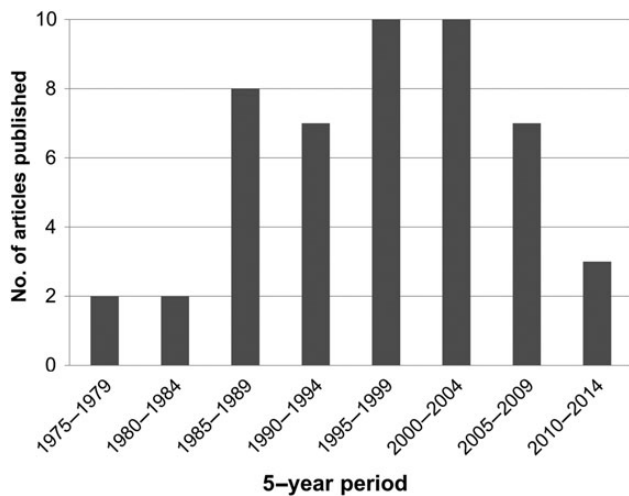
Figure 1. Trend of fungal outbreaks and infections associated with construction, renovation, and demolition.

and renovation among the published reports was 48%, ranging from 12.5% after surgery to 67% in rheumatology patients, premature infants, or nephrology and dialysis patients (Table 2). Thus, the mortality of fungal outbreaks and infections was substantially high but varied greatly according to underlying conditions and infection types.

RESERVOIRS AND SOURCES OF FUNGI OUTBREAKS AND INFECTIONS ASSOCIATED WITH CONSTRUCTION AND RENOVATION

Construction was the most common type of source in this review (38 articles [78%]), followed by renovation (19), demolition (4), and excavation (3). The data on reservoirs and sources are summarized in Table 1. Environmental sources in construction-related settings were described as follows: inflow of unfiltered outside air, backflow of contaminated air, air

filters, fireproofing materials, air conditioners, duct systems, and dust above false ceilings [55], thereby enabling fungal spores to be aerosolized and disseminated throughout hospital areas. *Aspergillus* species can also be isolated from hospital water samples and be involved in invasive aspergillosis [52, 63, 64]. However, it remains unclear how *Aspergillus* species isolated from hospital water contribute to nosocomial waterborne *Aspergillus* infections, and there are no criteria for determining water contamination levels that have been correlated with a risk of fungal infections.

LABORATORY TESTING, AIR SAMPLING, AND MOLECULAR TYPING IN INVESTIGATION OF FUNGAL OUTBREAKS AND INFECTIONS

In the special settings of construction and renovation, several studies described the monitoring of *Aspergillus* species using quantitative polymerase chain reaction (PCR) of air samples [65, 66] or serum *Aspergillus* galactomannan in pediatric patients with allogeneic stem cell transplant [67]. Although *Aspergillus* infections were finally diagnosed at autopsy in many articles reviewed, the diagnosis of invasive aspergillosis during a patient's lifetime remains difficult. Clinical signs and radiological findings for *Aspergillus* infections can be nonspecific, and in less invasive testing methods, there are diagnostic limitations for conventional culture methods and serum biomarkers (eg, galactomannan and $[1{\to}3]$-β-D-glucan assays) due to the low sensitivities and for clinical implementation of PCR assays because of the potential environmental contamination of *Aspergillus* DNA [68–72]. Recently, detection of *Aspergillus* antigen by the lateral-flow device as a point-of-care test [73] or *Aspergillus* secondary metabolite signature in breath by thermal desorption–gas chromatography/mass spectrometry [72] may be promising, but further investigation is needed.

Air sampling may be used to measure airborne fungal levels inside and outside of hospitals before, during, and after

Table 2. Fungal Infections and Associated Mortality by Each Underlying Disease During Construction, Renovation, or Demolition

Underlying Diseases	No. of Articles Published	No. of Patients Infected	No. of Patients Died	Mortality, No.[a] (%)
Hematologic malignancies or bone marrow transplant	26	414	148	131/288 (45.5)
Other malignancies, transplant, and/or immunosuppressed patients	13	105	38	38/60 (63.3)
Patients in intensive care unit	3	8	2	2/4 (50)
Rheumatology patients	2	6	4	4/6 (66.7)
After surgery	2	8	1	1/8 (12.5)
Premature infant	2	3	2	2/3 (66.7)
Nephrology and dialysis patients	1	3	2	2/3 (66.7)
Total	49	547	197	180/372 (48.4)

[a] Articles in which the number of patients infected or died was unknown were excluded for mortality calculation.

Table 3. Bundle of Key Methods for Preventing Filamentous Fungal Infections Associated With Renovation/Construction Activities

1. Hospital epidemiology (infection control) should be notified by plant engineering prior to any renovation/construction activities in the healthcare facility.
2. Conduct an ICRA for all renovation/construction activities: implement recommended prevention strategies as guided by the ICRA.
3. Focus prevention efforts on control of airborne dissemination of fungal spores (eg, barriers, containment, air handling, portable HEPA filters).
4. Consider impact of renovation/construction on the involved hospital unit plus adjacent units on the same floor, and hospital units on floors above and below the renovation/construction activities.
5. Maintain surveillance for healthcare-associated filamentous fungal infections during renovation/construction. Investigate any cases to see if they are related to renovation/construction and determine if prevention efforts need to be revised.
6. Visit renovation/construction sites regularly to assure compliance with recommended prevention activities.

Source: Adapted from the Centers for Disease Control and Prevention. Guidelines for Environmental Infection Control in Health-Care Facilities. Available at: http://www.cdc.gov/hicpac/pdf/guidelines/eic_in_HCF_03.pdf. Accessed 2 January 2015.
Abbreviations: HEPA, high-efficiency particulate air; ICRA, infection control risk assessment.

construction by identifying viable airborne fungal spores [1]. Air sampling may be useful in inspection of ventilation performance, maintenance, and cleaning of airflow systems, construction activities, and epidemiologic investigation and research purposes, but microbiologic air sampling and environmental culture are not routinely recommended [55]. Although air sampling has been performed in many studies, there are no standardized methods that are comparable in terms of performance, data collection and analysis, and interpretation (eg, type of air samplers, sampling sites and time, air volume, airflow rate, ecological condition [1]). In addition, there are only limited studies showing a direct relationship between fungal spore concentration by air sampling and human fungal infections in healthcare settings during construction and renovation [37]. In fact, airborne fungal levels varied greatly, and even <1 colony-forming unit $(CFU)/m^3$ could be associated with an *Aspergillus* outbreak among immunocompromised patients [2]. In this review focused on construction and renovation, 22 of 49 (45%) articles conducted air sampling, and airborne fungal levels ranged from 1 to 659 CFU/m^3. Several investigators have provided a time series over several years in which they assessed a relationship between healthcare-associated filamentous fungal infections and construction and renovation [45, 52, 53, 74]. In some cases, an increase in fungal infections with an increase in fungal spores occurred during the time period of renovation and construction [14, 22, 28]. Although renovation and construction can be associated with outbreaks, the correlation is

imperfect (ie, outbreaks may occur without renovation/construction, whereas renovation/construction may occur without an outbreak). An article reported fungal infections despite no fungal growth by air sampling [49]. Thus, the minimal airborne concentration of spores needed for acquisition of fungal infections remains to be determined.

Unlike most bacterial outbreaks in healthcare settings, multiple fungal strains can cause construction-related outbreaks because *Aspergillus* species are ubiquitous in nature [75]. In addition, the incubation period of invasive aspergillosis remains unclear, and thus it is impossible to definitively conclude that *Aspergillus* infections resulted from construction activities. Notably, a recent whole-genome sequencing analysis of serial *A. fumigatus* clinical isolates showed dynamic alterations in the genome within its host [76]. In this review, only 5 (10%) articles applied molecular typing, mostly random amplified polymorphic DNA (4 articles), to their investigations. Furthermore, if molecular typing is performed and reveals multiple distinguishable fungal strains within a patient cluster, the possibility of a nosocomial outbreak cannot be excluded as invasive fungal cases could be caused by a variety of unrelated strains [2]. Therefore, the value of *Aspergillus* typing to facilitate epidemiologic investigations remains undetermined. The lack of genotypic matches between the environmental and clinical isolates may be related to the genetic diversity of *Aspergillus* species in the environment.

INFECTION PREVENTION AND CONTROL MEASURES IN SPECIAL HEALTHCARE SETTINGS OF CONSTRUCTION AND RENOVATION

Infection prevention and control measures used to prevent and terminate outbreaks are summarized in Table 1. Recent guidelines regarding infection prevention and control in construction and renovation activities have been published [77–79]. A multidisciplinary coordination team and elaborate planning are essential to prevent airborne fungal infections before/during/after construction and renovation activities in healthcare facilities [78]. The environmental surveillance for immunocompromised patients and high-risk units during construction and renovation are also recommended by several guidelines [77, 80]. A bundle of preventive measures for fungal infections associated with renovation/construction activities is summarized in Table 3. Construction activities can be safely conducted if a bundle of preventive measures is employed with cooperation and coordination among team members who are involved in infection prevention and control for construction projects [81]. It is important for infection control departments to ensure that hospital engineering staff notify them of the planned work activities and seek advice from them preemptively for all hospital

construction and renovation. Furthermore, education of construction workers, engineers controlling indoor air quality and ventilation, and healthcare personnel caring for high-risk patients is necessary to mitigate dust and moisture intrusion from construction sites into patients' areas. Regular monitoring and feedback on compliance with infection control guidelines in and around construction site are also critical [78].

The risk assessment before construction and renovation is implemented to identify potential exposures of susceptible patients to dust and moisture for prevention of airborne infections and to mitigate potential risks [78]. The infection control risk assessment (ICRA) is a multidisciplinary, organizational, documented process using the risk matrix based on construction project types (eg, type A: small noninvasive and inspection; type D: major demolition and construction) and patient risk groups (eg, low risk: office areas and public areas; highest risk: ICUs, oncology, and transplant units). The matched matrix helps to determine the class of infection control precautions that should be followed. Details of the ICRA are available at http://www.ashe.org/advocacy/organizations/CDC/pdfs/assessment_icra.pdf. Infection control risk mitigation recommendations are developed as specific measures for obviating transmission of airborne biological contaminants in construction activities.

Protective measures include relocating high-risk patients, wet cleaning, sealing off the construction site and avoiding unnecessary traffic, and using air filtration adequately [49, 77]. The Centers for Disease Control and Prevention guideline recommends high-efficiency particulate air (HEPA) for high-risk patients as the HEPA filter system can reduce fungal spore counts from the environment of healthcare facilities during construction and renovation and may help prevent fungal outbreaks in combination with other environmental control measures [1, 77]. However, a meta-analysis revealed no significant improvement of HEPA filtration in the prevention of death among patients with hematological malignancies and severe neutropenia, although there were possible publication bias and limitations that no studies were blinded or had control subjects [82]. Further investigations are needed to clarify whether specific control measures contribute to preventing healthcare-associated fungal infections in construction and renovation.

Because antifungal prophylaxis is recommended by the Infectious Diseases Society of America for immunosuppressed patients, including neutropenic patients and HSCT recipients, under certain conditions [83], physicians are likely to administer antifungal prophylaxis among those patients, whether or not construction and renovation are ongoing. Although the practical use of antifungal drugs for prophylaxis is beyond the scope of this review, pharmacokinetics/pharmacodynamics, spectrums, interactions, and adverse effects should be considered in administering antifungal drugs properly. Several previous studies described the usefulness of antifungal prophylaxis during construction and renovation [49, 51], but no randomized controlled studies exist in such a special condition. On the other hand, voriconazole prophylaxis did not prevent healthcare-associated environmental mold infections among approximately 40% of pediatric patients with leukemia who had received this prophylaxis and had exposure to hospital construction with excavation that was related to the increased risk of developing mold infections despite the recommended prospective measures, suggesting the need for monitoring compliance with infection preventive strategies [53].

CONCLUSIONS

We reviewed outbreaks and infections with medically important mycotic agents during construction and renovation over the last 4 decades, and summarized current infection prevention and control strategies. Construction-related fungal cases among recently published articles seem to be in decline, presumably due to introduction of guidelines and policies regarding infection prevention and control and dissemination of antifungal prophylaxis, but fungal outbreaks and infections under special circumstances still continue to occur in healthcare settings, especially among patients with hematological malignances and those who are immunocompromised. Further research is required to address the unresolved issues on air sampling and molecular typing for investigation of sources, and specific control measures. It is important for infectious disease physicians and infection preventionists in collaboration with building contractors and other associated departments to appropriately implement risk assessment and mitigation measures and prevent healthcare-associated fungal outbreaks and infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

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