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Invasive Aspergillosis in Neutropenic Patients During Hospital Renovation: Effectiveness of Mechanical Preventive Measures in a Prospective Cohort of 438 Patients

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Abstract
Background *Aspergillus* species are the main cause of invasive fungal disease for patients with severe and prolonged neutropenia. Building or renovation works have been shown as one of the major causes of outbreaks of aspergillosis.
Objectives This study aimed to assess the effectiveness of introduction and adaptation by air sampling of mechanical preventive measures on the incidence of invasive pulmonary aspergillosis in neutropenic patients during hospital renovation.
Patients All of the patients admitted for prolonged and severe neutropenia during a renovation period from 2003 to 2008 were prospectively enrolled. Invasive pulmonary aspergillosis (IPA) cases were classified as possible, probable, and proven, according to the 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group criteria. The effectiveness of preventive measures was determined by air sampling.
Results We recorded 705 hospitalizations for neutropenia concerning 438 patients. The majority of hospitalized neutropenic patients was treated for acute leukemia (38.3 %), followed by patients suffering from non-Hodgkin and Hodgkin lymphomas (33 %). The total cumulative incidence of probable and proven IPA was 4.1 %. Risk factors for developing IPA were underlying disease, treatment course at the time of hospitalization, and the mean duration of hospitalization and of neutropenia.
Conclusions In this prospective study, the incidence of invasive pulmonary aspergillosis did not increase in neutropenic patients during a renovation period because of efficient mechanical preventive measures systematically adjusted using the results of air sampling.

Keywords Invasive aspergillosis · Building works · Neutropenia · Prevention · Hematological malignancies

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Introduction

Aspergillus is a genus of spore-forming moulds that are ubiquitous in the environment. Spores can be deposited on all inert surfaces and are resuspended as airborne particles by activities that disrupt them from their reservoir. After inhalation, conidia develop into hyphae, the invasive tissue form of *Aspergillus*. Polymorphonuclears (PN) are essential to limit the development of hyphae [1]. *Aspergillus* remains the primary cause of fungal infections in neutropenic patients with hematologic malignancies [2–6]. In such patients, pulmonary infections lead to invasive pulmonary aspergillosis (IPA). Its prognosis remains poor, especially in hematopoietic stem cell transplantation (HSCT) patients, despite new antifungal treatments [7, 8].

Building construction and renovation within hospitals are one of the primary causes of fungal contamination in indoor environments. [9] The environmental source is unfiltered outside air that enters hospitals through windows and the backflow of contaminated air [10–12].

Air treatment systems, such as high-efficiency particulate air (HEPA) filtration, have been known to reduce airborne fungal contamination and to reduce IPA incidence [13], but these measures alone are not always sufficient in cases of building construction near hematology units.

The Centers for Disease Control and Prevention and the Health Care Infection Control Practices Advisory Committee have provided international recommendations to prevent the risk of health care-associated infections, [14] including the Guideline for Isolation Precautions: Guidelines for Environmental Infection Control in Healthcare Facilities (2003).

There have been scarce and discordant data on the effectiveness of mechanical preventive measures and the parameters used to adapt these measures during indoor hospital building construction.

The aim of this prospective study was to analyze the effectiveness of designed and regularly adapted mechanical preventive measures on the incidence of IPA during construction works that occurred between June 2003 and September 2008 in an occupied hematology and cancer center.

Patients and Methods

Patients

All of the patients who were hospitalized for neutropenia lasting longer than 7 days with a neutrophil PN count less than 500/mm^3 during the renovation work were included.

The Hematology Department of the Henri Becquerel Cancer Center (CC) consists of two hospitalization units: a conventional unit (CU) and an intensive care unit (ICU) for patients undergoing treatments that induce deep and prolonged neutropenia (e.g., allogeneic and autologous transplantation, chemotherapy for acute leukemia). Because the ICU had only 14 beds, many of the included patients with prolonged aplasia were treated in the CU. In the ICU, half of the rooms were equipped with HEPA filtration. This study was approved in January 2003 by ethics committees.

Data Collection

For each neutropenic patient, the following parameters were prospectively recorded using a computed standardized file: underlying pathology, age and sex, type of treatment, duration of neutropenia, care unit, clinical events (coughing, fever, chest pain, hemoptysis), radiological results, microbiological results of bronchoalveolar lavage, and galactomannan plasma levels. The occurrence of all events due to IPA type or of death was recorded only after the seventh day of hospitalization to exclude community-acquired infections.

Methods

For all neutropenic patients, galactomannan plasma levels were assessed twice weekly. Computed tomography (CT) was performed within the 2 days following the occurrence of fever or respiratory symptoms and of suggestive findings on chest radiography, to specify pulmonary lesions with the aim to early identify IPA. All of the cases were reviewed by a specific multidisciplinary committee called ‘crisis unit’ and were categorized as possible, probable, or proven, according to the 2008 EORTC criteria [15].

Radiological events were defined as interstitial, dense, and limited condensation patterns on chest radiography, which were confirmed by imaging features on chest CT (air crescent sign, dense circumscribed lesions with halo formation).

To confirm probable status, one of the following microbiological assays had to be positive: positive direct examination, presence of mould on sputum or bronchoalveolar lavage with at least two consecutive galactomannan serum dosages. Proven IPA required positive cultures from biopsy in sterile sites (lung biopsy or sinus puncture) and identification.

As soon as the committee validated a diagnosis of IPA, further hospitalizations for the same patient were not recorded.

Airborne *Aspergillus* concentrations were measured weekly by repeated air sampling in each department (patients' rooms, corridors, and nurse posts) and in all areas considered at high risk by the crisis unit. Areas with positive samples were retested after corrective measures. Samples were collected using a Reuter Centrifugal Impaction (RCS®) High Flow Air Center (Biotest Hycon, Germany) loaded with ready-to-use culture media on flexible agar strips with modified Sabouraud Dextrose Agar for yeast and molds, γ-irradiated in double wrapper (SDX-γ®) to determine the total number of fungal spores in the air (Biotest Hycon, Germany).

The samples were then transferred to mycology laboratory. When the cultures were positive, we quantified colonies as colony forming units (cfu) per cubic meter (m^3). Less than 20 cfu/m^3 was considered acceptable results in all the areas except for ICU where 0 cfu/m^3 was required.

Indoor Building Construction, Preventive Measures, and Adaptation by the Multidisciplinary Committee

Our center underwent 5 years of indoor and outdoor renovations, including excavations, collapsing of walls, sanding, and wiring within the hospital from 2003 to 2008.

Because the surrounding areas were at high risk of fungal contamination, a multidisciplinary 'crisis unit', including a hematologist (local referent in fungal diseases), a microbiologist (member of the 'Comité de lutte contre les infections nosocomiales'), a nurse hygienist and the building foremen, was introduced to assess airborne fungal spore levels, establish preventive measures and systematically adjust those measures, and monitore their effectiveness with air sampling and clinical results. Meetings were organized by the committee with all of the trade workers and hospital staff to explain the risks and specifications.

Mechanical preventive measures including the construction of air lock chambers between hospitalization units and building sites were implemented 2 months before the beginning of works. Windows were sealed 1 month before the beginning of the works.

Specific mechanical measures introduced by this committee consisted of isolation of each pollution zone by creating air lock chambers with temporary rigid plastic walls. The partitions were sealed airtight, and mechanical doors and adhesive carpets for collecting dust were placed at the entryways of the units. Surgical masks were required for neutropenic patients when they had to leave their rooms. All of the windows were also sealed in both units. The construction debris was moistened daily with water to minimize dust generation. Rubble containers were covered and quickly removed. Pedestrian traffic was rearranged to avoid visitors and patients crossing near construction work sites.

The committee met to adopt additional protections whenever the contamination of the indoor environment increased or when a risk situation was identified during site visits, such as multiple positive samples in the same area or wall or ceiling destruction. Corrections made included the addition of supplementary isolation chambers between work sites and care units. Air samples were taken again immediately after implementation of the corrective measures.

Statistical Analysis

The primary end point was the rate of positive diagnoses of IPA during hospitalizations. Subjects characteristics were compared between the two groups (regardless of aspergillosis diagnosis). For qualitative variables, the Chi-square test and Fisher's exact test were used. For variables with more than two categories, if either the Chi-square test or Fisher's exact test was significant, Bonferroni's correction was applied to highlight the differences between the classes in pairs. Quantitative variables were compared between groups using the Mann–Whitney test.

The comparison of the amount of *Aspergillus* between both units was performed using the

Table 1 Description of hospitalizations

	Hospitalizations ($n = 705$)	
	Number	%
Unit		
Intensive care unit	191	27.1
Conventional unit	514	72.9
Reason for hospitalization		
Autologous stem cell transplant	249	35.3
AML induction	146	20.7
AML consolidation	127	18.0
Allograft	58	8.2
Chemotherapy for lymphoma	56	7.9
ALL induction	39	5.5
ALL consolidation	5	0.7
Other	25	3.5
Duration of hospitalization (days)		
Median (min; max)	23 (7; 174)	
Duration of neutropenia (days)		
Median (min; max)	13 (7; 140)	
Characteristics ($n = 102$)		
Possible	84	82.3
Probable	17	16.7
Confirmed	1	1.0

AML Acute Myeloblastic Leukemia, *ALL* Acute Lymphoblastic Leukemia

Table 2 Characteristics of patients at the time of inclusion

	Patients ($n = 438$)	
	Number	%
Sex		
Male	253	57.8
Female	185	42.2
Age at inclusion (months)		
Median (min; max)	54 (16; 80)	
Status		
Alive	187	42.7
Dead	224	51.1
Lost	27	6.2
Pathology		
AML	135	30.8
NHL	123	28.1
Myeloma	88	20.1
ALL	33	7.5
Hodgkin lymphoma	22	5.0
CLL	16	3.7
Myelodysplastic syndromes	5	1.1
Others	16	3.7

AML Acute myeloblastic leukemia, *ALL* Acute lymphoblastic leukemia, *NHL* Non-Hodgkin lymphoma, and *CLL* Chronic lymphoid leukemia

nonparametric Mann–Whitney test with an α risk of 5 %. All of the analyses were performed using SAS software, version 9.3 (SAS Institute Inc.).

Results

Demographic Characteristics

During the renovation period from June 2003 to September 2008, 705 hospitalizations for prolonged neutropenia were considered (Table 1), affecting 438 patients. The majority of the patients were admitted to the CU ($n = 514$, 72.9 %). The demographics of the patients are shown in Table 2. There was a slight male predominance, and the median age was 54 years. The mean hospital stay for prolonged neutropenia was 23 days (range 7–174 days). Median duration of neutropenia during each stay was 13 days (from 7 to 140 days), with most of the hospitalized neutropenic patients being treated for acute leukemia [30.8 % acute myeloblastic leukemia (AML), 7.5 % acute lymphoblastic leukemia (ALL)], corresponding to 185 stays for induction chemotherapy and 132 for consolidation chemotherapy. The next most common diseases were non-Hodgkin and Hodgkin lymphomas ($n = 123$ and $n = 22$, respectively), with myeloma ($n = 88$) being the third most prevalent disease because of neutropenia that was induced during auto-HSCT. The remaining 37 patients presented with heterogeneous hematological malignancies, including myelodysplastic syndromes ($n = 5$) and chronic lymphocytic leukemia (CLL) ($n = 16$). Fifty-eight allogeneic stem cell transplantations were performed. There were 249 admissions for high-dose chemotherapy, followed by autologous HSCT. The median number of hospitalizations was 1 ($n = 286$), with 93 patients admitted twice, 31 admitted three times, 9 admitted four times, and 19 admitted more than 5 times (Table 2).

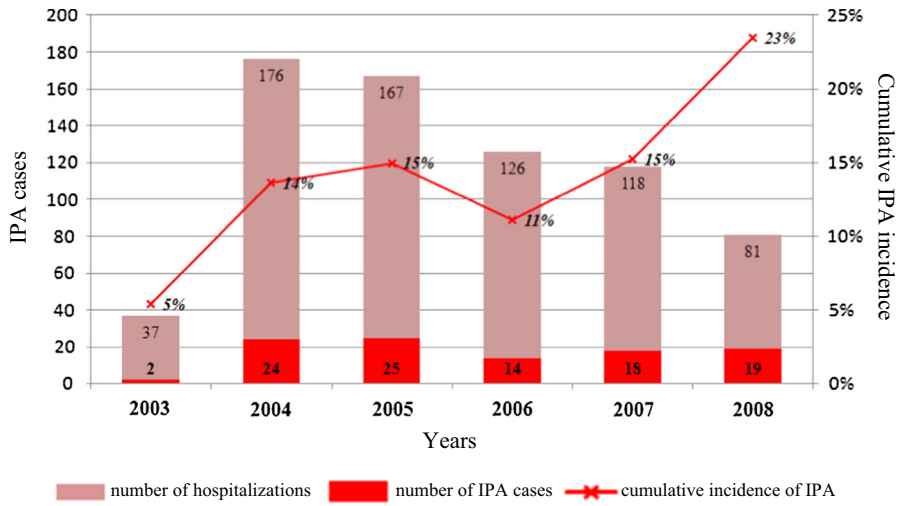

Fig. 1 Number of cases of invasive pulmonary aspergillosis during the construction period. Because work began in June 2003, the results for this year were not significant. There was no significant difference in the occurrence of IPA during the building renovation period. The cumulative incidence of IPA is expressed as a percentage on the *red curve* and was steady over time. (Color figure online)

Characteristics of the IPA Cases

The number of hospitalization per year and cumulative incidence of IPA remained stable all along the building period (Fig. 1).

Among the 438 patients in the study, 17 developed probable IPA and one developed proven IPA, corresponding to an overall cumulative incidence of 4.1 % (Table 3). During the period of the study, 84 patients were diagnosed with possible aspergillosis, leading to a total (possible, probable, proven IPA) cumulative incidence of 23 %. There was a slight increase in incidence at the end of the renovation period in April, May, and August of 2008, but this increase was not statistically significant ($p = 0.1058$).

A chest scanner was used in 84 of the cases of aspergillosis (82.3 %). The incidence was steady over the renovation period (Fig. 1). All of the aspergillosis cases were invasive pulmonary, but one was disseminated, with cerebral lesions. Concerning serum galactomannan, all patients with probable and proven aspergillosis had at least two galactomannan dosages positive in serum.

The underlying disease in the IPA-positive group was primarily AML. In the AML group, the cumulative incidence of probable IPA was the highest (5.9 %). Probable IPA only concerned induction courses, with an incidence of 5.5 cases per 100 induction courses. There were no probable IPA cases in the ALL group. Among the patients who underwent allogeneic HSCT, 12 IPA cases were recorded, with 11 possible and only one probable aspergillosis, corresponding to a cumulative probable/proven IPA incidence of 1.7 % in this subpopulation.

During the construction period, the only proven case received high-dose chemotherapy followed by autologous stem cell transplantation for non-Hodgkin lymphoma.

Among the 249 autologous transplant recipients, the overall cumulative incidence of probable/proven IPA was 2 %.

At the end of the study, 187 patients had survived, 224 had died, and 27 had been lost to follow-up. There was a significant difference in survival between infected and non-infected patients. Among the patients who had developed IPA, 64 % were deceased versus 47 % in the non-infected group. The leading cause of death was disease progression, but fungal infections were responsible for eight deaths.

In multivariate analysis, comparing patients who developed IPA and those who did not, the underlying disease (leukemia was the most common, $p < 0.0001$), the treatment course at the time of hospitalization, and the mean duration of hospitalization and of neutropenia were significantly associated with the onset of IPA (Table 3). But the hospitalization unit (CU or ICU) was not significantly associated with the incidence of IPA in our study.

Air Sampling Results

Concerning air samples, a slight increase in the levels of airborne fungal spores was noted in October and

Table 3 Characteristics of invasive pulmonary aspergillosis according to hospitalizations

	IPA according to hospitalization ($n = 705$)					p
	Negative ($n = 603$)		Positive ($n = 102$)		Total ($n = 705$)	
	n	%	*n*	%	*N*	
Reason for hospitalization						**<0.0001**
Autologous transplantation	224	90	25	10	249	
AML induction course	111	76	35	24	146	
AML consolidation course	120	94	7	6	127	
Allogeneic transplantation	46	79	12	21	58	
Chemotherapy for lymphoma	44	79	12	21	56	
ALL induction course	35	90	4	10	39	
ALL consolidation course	5	100	0	0	5	
Other	18	72	7	28	25	
Hospitalization unit						0.5687
Intensive care unit	161	84	30	16	191	
Conventional unit	442	86	72	14	514	
Duration of hospitalization (days)						**<0.0001**
Median (min; max)	22 (7; 95)		33 (10; 174)		23 (7; 174)	
Duration of hospitalization (days)						**<0.0001**
(7–17 days)	158	97	5	3	163	
(17–33 days)	326	86	51	14	377	
(33–174 days)	119	72	46	28	165	
Duration of neutropenia						**<0.0001**
Median (min; max)	12 (7; 75)		17 (7; 140)		13 (7; 140)	
Total	603	86.0	102	14.0	705	

In adjusted analysis, reason for hospitalization (AML induction course) and duration of hospitalization and neutropenia were strongly correlated with the cumulative incidence of IPA. The unit type was not associated with infection risk due to the preventive measures implemented, which increased the protection for patients hospitalized in the conventional unit

IPA Invasive Pulmonary Aspergillosis, *AML* Acute Myeloblastic Leukemia, and *ALL* Acute Lymphoblastic Leukemia

Bold characters correspond to the parameters significantly associated with the risk of developing an IPA

November of 2006, but there was no impact on aspergillosis incidence.

Airborne spore levels ranged from 0 to 30 CFU/m^3. There was an increased number of positive samples in the standard unit CU compared to the ICU ($p < 0.0001$). In the ICU, there were no positive samples, but the CU airborne spore concentrations varied between 0 and 12 CFU/mm^3. All samples were realized after the risk factor for correction, and contaminated source suppression showed a decrease in the rate of airborne *Aspergillus* spore level. There was a single peak at 30 CFU/m^3 with no clinical consequences, and there was no difference between the standard unit and intensive care unit with regard to IPA incidence. The airborne spore concentrations varied according to seasons and were the greatest during autumn; however, there was no correlation between the evolution of airborne spore concentrations in the range detected during construction and the incidence of aspergillosis.

Discussion

To our knowledge, we are reporting the largest prospective survey cohort with prolonged neutropenia during a hospital renovation period. This survey also covers the longest time frame reported.

Importance of Protective Environment Measures for All Neutropenic Patients

The cumulative incidence was 4.1 %, accounting for both probable and proven IPA. The cumulative incidence was steady throughout the entire renovation period, with a cumulative incidence of probable IPA of 5.9 % during induction treatment for patients with acute myeloblastic leukemia and 1.7 % for HSCT; both conditions described, at risk, patients. In our study, the only case of proven aspergillosis was in a young man treated with high-dose chemotherapy, followed by an autologous stem cell transplantation. The cumulative incidence of IPA among this subpopulation during the renovation period was 2 %. The emergence of chronic lymphoproliferative malignancies as a risk factor was already highlighted. In 2011, Lortholary et al. [16] reported the results of a multicentre prospective study conducted by the 'Surveillance des Aspergilloses Invasives en France' (SAIF) network from 2005 to 2007. This study included 305 patients with hematological malignancies, and it only recorded probable or proven IPA. Similar to our study, the primary underlying disease was acute leukemia. Chronic lymphoproliferative disorders represented the second largest group of underlying malignancies, accounting for 21.6 % of infected patients.

Isolation of Sites Resulted in a Low Incidence of IPA

In France, Nicolle et al. [17] conducted a prospective, observational study on invasive aspergillosis in hematology units between 2004 and 2009. In this study, 4,073 patients were hospitalized, and the cumulative incidence of invasive aspergillosis was 3.1 %. In the AML and ALL patients, the cumulative incidences were 4.4 and 2.2 %, respectively. These results were similar to our observations, as our incidences of probable IPA in AML and ALL were 5.9 and 0 %, respectively, confirming the effectiveness of our protective measures. Indeed in our study, there was an increased risk of air contamination because of the works in progress.

The data on the cumulative incidence of aspergillosis during either renovation or construction have been scarce and conflicting. In our cohort, when focusing on probable and proven IPA, the rates were 3.9 and 0.2 %, respectively. Berger et al. [18] reported the incidence of aspergillosis in patients undergoing HSCT during an outdoor demolition project. In this study, there was no IPA during the building period compared with the period before, most likely due to the increase in preventive measures with the installation of an air filtration HEPA system immediately before the beginning of construction. Unfortunately, there was no air sampling. Moreover, the reconstruction project only lasted 1 year.

In the setting of building renovations, the role of air filtration (notably HEPA filtration) has been an important proven factor in reducing aspergillosis incidence. Bénet et al. [13] reported the effectiveness of environmental control exposure during a renovation period. This construction occurred over 1 year in some French hematology units. One of these units (unit B) did not benefit from mechanical preventive measures, such as HEPA air filtration, during the first phase of the construction, and the patients were eventually transferred to a more protective environment with HEPA filtration. Among 356 patients admitted from 2005 to 2006, there were 21 cases of invasive aspergillosis, which corresponded to a global cumulative incidence of 13.9 %. After relocation of the patients in unit B to an intensive care unit, the incidence decreased to 1.6 %. When considering probable IPA, we observed an incidence of 3.9 %, which was similar to the incidence of 3.4 % (total incidence in the three hematology units) observed in the study by Bénet et al. [13] after relocation of their patients to a protective environment. In our study, similar results were obtained but we did not enroll only leukemia patients.

In our study, there was no increase in the incidence of invasive pulmonary aspergillosis throughout the entire construction period. As reported by others [19, 20], we found that preventive measures were sufficient to prevent invasive pulmonary aspergillosis in neutropenic patients. In 2006, Vonberg et al. [9] published a review of nosocomial aspergillosis. They reported that air was the most important contamination source and that major site of infection was the lower respiratory tract. In 49 % of cases of nosocomial aspergillosis, either indoor or outdoor construction work was suspected to be the source of the contamination. In our study, we only diagnosed respiratory tract infections, with only one case complicated by cerebral localization. The 'crisis unit' adapted the

preventive measures as often as necessary to ensure the separation between the construction sites and the care units. Both the creation of a multidisciplinary committee and the adaptation of specific mechanical preventive measures during renovation have been recommended by the Centers for Disease Control and Prevention (CDC) and the Healthcare Infection Control Practices Advisory Committee (HICPAC).

There were some limitations to our study. First, it was monocentric, which may have caused a bias of center effect. However, considering the levels of probable and proven aspergillosis noted here, our results are similar to those reported in previous studies. Another limitation was due to the fact that we did not measure the concentration of fungal spores in the air before the beginning of the renovation period, so it was impossible to compare our results with the previous period. Although the *Aspergillus* spore concentration in the air varies among studies, the incidence of IPA in our study was similar to that reported in other studies. Likewise, we did not monitor the IPA incidence before the building restoration work period.

To conclude, we performed the first prospective study that included all neutropenic patients (taking into account chronic lymphoid disorder patients) hospitalized during a hospital renovation period, and we confirmed that mechanical preventive measures, when adapted by a multidisciplinary committee, may be highly effective and sufficient to prevent outbreaks of invasive aspergillosis during indoor and outdoor building construction.

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Conflict of interest The authors received funding from Pfizer Pharmaceuticals to collect the data. However, Pfizer did not participate in either the data analyses or the writing.

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