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Original Article

Monitoring of Particle Environmental Pollution and Fungal Isolations During Hospital Building-Work Activities in a Hematology Ward

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Abstract. Building-work activities could cause dust contamination and fungal spores' dissemination. A significant relationship was found between building-work activities and the incidence of invasive aspergillosis, in profoundly immunocompromised patients.
Renovation-works activities were carried out by four building sites of the hematology ward in a Teaching Hospital without the interruption of clinical activities. These sites were monitored by environmental sampling to determine the particles and fungi count. Clinical surveillance was made using galactomannan antigen test as a proxy for invasive aspergillosis diagnosis. A definitive diagnosis of IA was confirmed by clinical and radiological features.
The galactomannan antigen test showed no significant difference between presence (2,75%) and absence (5,03%) of renovation work activities (p=0,522). During the renovation activities, an increment of IA cases with respect to the control period was not recorded. The particle counts showed higher values of small and big-diameter particles before the renovation works if compared to the end of the activities. It was probably due to the containment measures implemented during and immediately after the final phases of the building site. The Fungi counts showed no significant differences between the phase before and after the renovation activities.
Our findings show that is possible to perform renovation work, during clinical activities, by increasing clinical and environmental surveillance.

Keywords: Renovation activities; Dust contamination; Invasive aspergillosis; Hematology ward; Protective measures.

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Introduction. Construction and renovation activities are an ever-constant phenomenon in Hospitals, causing dust contamination and dissemination of fungal spores. Different studies describe a strict association between dust contamination, as a consequence of building-work activities, and the dispersion of a large number of fungal spores in the environment.[1,2] In particular the *Aspergillus* spores spread in great amount during construction and renovation work. Several work-related aspergillosis outbreaks have been described in literature.[3] *Aspergillus* is a large genus of ubiquitous filamentous fungi, that can cause invasive aspergillosis

(IA) through the inhalation of the airborne conidia.[3,4]

The factors that influence with overall fungi load in building-work activities are: first of all, construction work characteristics (active construction work, greater surface area of construction site and demolition are associated with a higher fungi concentration); later of course, season (lower fungi concentration in cloudy periods if compared to sunny periods), temperature (higher temperature associated with higher concentration) and relative humidity (higher concentration in case of higher relative humidity).[5,6,7,8] The most frequent environmental sources of fungi in building-work activities are: inflow of unfiltered outside air, backflow of contaminated air, unclean air filters, fireproofing materials, air conditioning out of order, duct systems and dust above false ceilings.[9,10] Reports about airborne fungal contamination related to the type of building-work activities and climatic conditions are described also in Italy.[11]

A review estimates that the overall mortality rate of building work activities-associated fungal infections was almost 50%.[12] A significant relationship between fungal contamination of air and surfaces in hematology wards and the incidence of IA has been demonstrated in non-epidemic situations.[2] For the highly immunocompromised patients the mortality rates associated with IA range from 40% to 90%.[13,14] Besides, IA occurs in <5% of autologous and 5%–10% of allogeneic hematopoietic stem cell transplant recipients.[15,16]

Due to the difficulties in performing an early diagnosis, IA is associated with a high mortality rate. In recent years several methods, in addition to clinical and radiological data were developed to earlier diagnose IA, including circulating biomarkers, and among these, serum galactomannan detection has markedly improved the diagnosis of invasive aspergillosis.[17]

Besides, fluid galactomannan quantification in BAL fluid has shown excellent sensitivity and specificity to assist clinical decision-making in confirming or excluding a diagnosis of IA when clinical findings are not clear.[18]

The purpose of the present work is to evaluate the possibility of carrying out renovation activities without stopping the clinical activities in the high-risk ward, such as the Hematology ward, through the environmental monitoring (fungi and particle counts) during different phases of renovation works and measuring the incidence of IA by Fluid Galattomannan Quantification in biological samples and confirming that with the clinical and the radiological features of the patients.

Materials and Methods. Building renovation works, classifiable as type D construction sites according to the Canadian IPAC, were carried out in the Hematology ward of a Teaching Hospital in Italy between December 2016 and June 2017.[19] During the whole period, the clinical activities were not interrupted. Two hospital rooms have been renovated at a time, in order to allow activities in the rooms adjacent to the building site. A total of four building sites were set up overtime for the renovation works, named Building site 1 (BS1), Building site 2 (BS2), Building site 3 (BS3) and Building site 4 (BS4) respectively (**Figure 1**). During the renovation activities, the following preventive actions were applied, in order to avoid dust dispersion and fungal spores dissemination: each area of activities was isolated with appropriate barriers from the rest of the ward through the construction of an anteroom, and only authorized personnel were required to pass through the anteroom. Ceiling barriers were also applied. The HEPA filter-air extractors were installed as an infection protection measures. As recommended by CDC[20] thought the HEPA filter-air extractors, a negative pressurization of the work area was maintained at all time. The doors of the patient rooms had to be closed all the time and the cleaning shifts were intensified.

Before the beginning of the renovation activities, pressure measures (anteroom vs corridor) were performed with (TESTO-480, TESTO s.p.a.).

At the end of the renovation activities, and before the employing of the patient rooms, proper cleaning procedures were applied.

Environmental monitoring. Environmental sampling was carried out in the patient rooms by a laboratory technician dedicated to this study. Air sampling was conducted with the active volumetric Surface Air System sampler (SAS Super ISO, VWR International Srl). We used plates containing a selective culture medium for fungi (Sabouraud Dextrose Agar, Liofilchem S.r.l, (TE) Italy). The volume of air sampled was 1000 m^3 (1000 liters). The Sabouraud plates were incubated at 25°C for five days, and they were checked daily. The number of colonies recovered on the air sample plates was adjusted for multiple impacts; a positive hole correction was used to determine the likely number of fungi passing through the orifices of the grid. This correction was calculated as reported in the proper instrument user manual according to J. M. Macher.[21] The concentration of airborne fungi was expressed as the number of colony-forming units per cubic meter of air (CFU/m^3). The isolated colonies were also identified by a lactophenol cotton blue wet mount preparation and slides were observed under the optical microscope.

The airborne particle count (APC) in the range size of 0.5-10 μm in diameter was performed using a LIGHTHOUSE HANDHEL 3016 IAQ portable counter (IQ Air, Incen AG, Goldach, Switzerland) according to ISO 14644:2015 part 1.[22] This device had

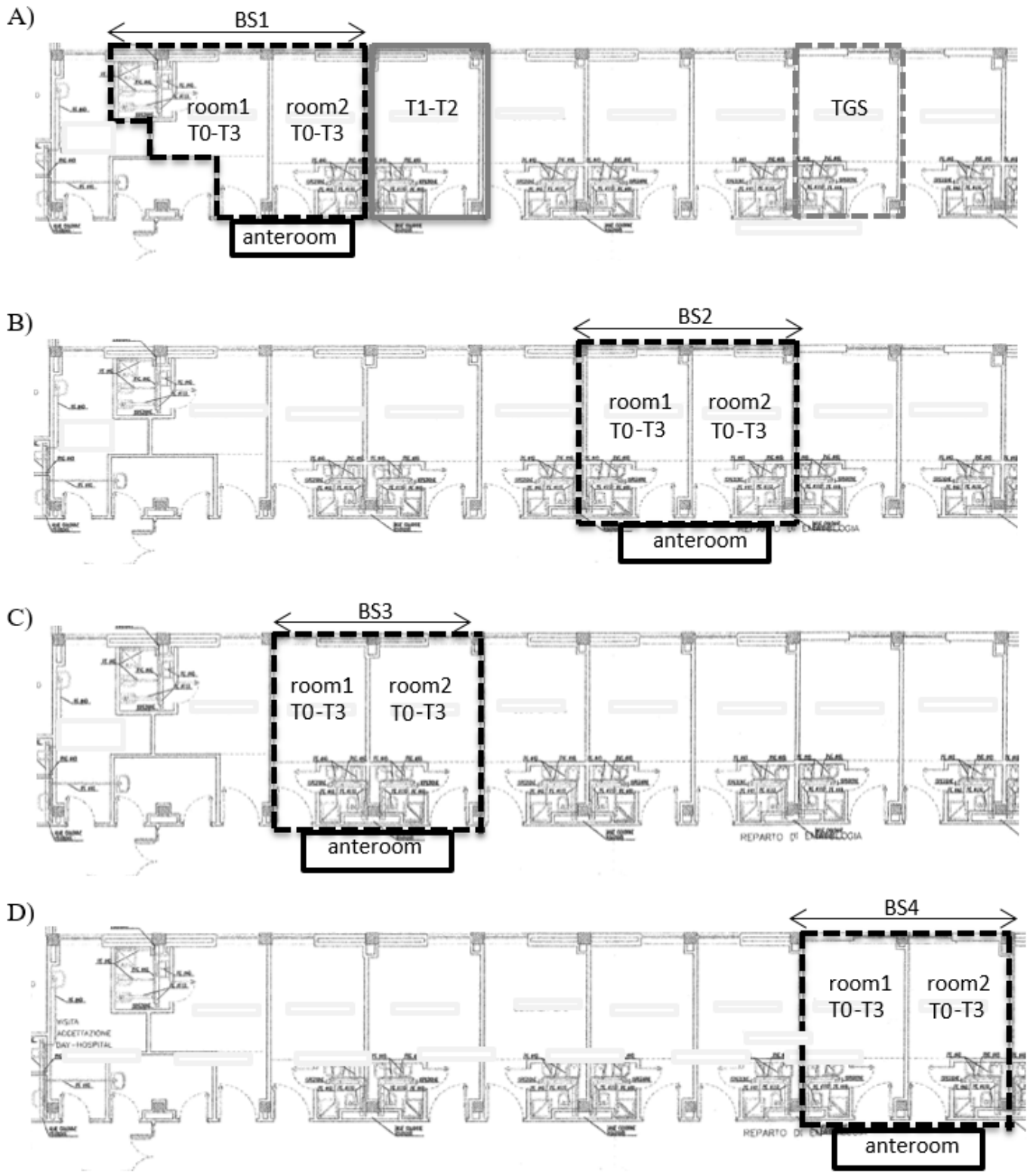

Figure 1. Plan of Hematology ward under renovation activities. **A)** Building site 1 (BS1): the area marked by the black traced lines indicates the rooms undergoing restructuring (room1 and 2) and the phases in which environmental monitoring is carried out (T0 and T3 phases). The anteroom indicates the filter area accessible only to authorized personnel. The area outlined by the gray rectangle shows the rooms in which environmental monitoring is carried out during the initial and terminal phases of the construction site (T1 and T2 respectively). The area delimited with gray rectangle identifies the room in which environmental monitoring is carried out 1 week before the start of the works and which allows to define the Time of golden standard (TGS) value. **B)** Building site 2 (BS2) **C)** Building site 3 (BS3) and **D)** Building site 4 (BS4); the area marked by the black traced lines indicates the rooms undergoing restructuring (room1 and 2) and the phases in which environmental monitoring is carried out (T0 and T3 phases).

a storage capacity up to 3000 records. The data can be normalized to m^3. The sampler was positioned at the height of about 1 m above the floor, at the potential height of a patient's "breathing area zone" in bed.

The monitoring activities in the building site (BS1, BS2, BS3, and BS4) were performed in several phases,

as reported below and shown in **figure 1**:

*Building site 1 (**Figure 1 A**):*

1. Time of Gold Standard phase (TGS): 1 week before the start of the renovation activities, particles and fungi counts were performed. The environmental monitoring in the TGS phase was performed in the farthest room respect to room object of renovation activities. TGS phase was useful to determine the "baseline value" of particles and fungi.
2. T1: At the beginning of the renovation activities. The environmental monitoring (particles and fungi counts) was carried out "at rest" with the furniture but without patients inside in the room next to the building site.
3. T2: At the end of the period of construction, before the sanification of renovated rooms and after the removal of the anteroom. The environmental monitoring was performed in the same patient's room of T1 phase.
4. T3: after the sanification of the renovated rooms. Environmental monitoring was performed "at rest" in the renovated rooms with furniture but without the patient.

Building site 2:

According to the results of the environmental monitoring of the BS1 site, the environmental monitoring of TGS and T2 phases were not performed for BS2. Phases monitored in the BS2 were reported below (**Figure 1 B**).

1. T0: before the beginning of renovation works within the room object of renovation activities.
2. T3: after the sanification of the renovated rooms. Environmental monitoring was performed "at rest" in the renovated rooms after cleaning and before patient occupancy.

Building site 3 and *Building site 4* were monitored for the same phases reported for BS2 (**Figure 1 C** and **D**)

IA at-risk group patients classification: The clinical data of the patients hospitalized in the Hematology ward during the renovation work from December 2016 to June 2017 (case period) and one year later from December 2017 to June 2018 (control period) were reviewed to identify any cases of IA.

The patients were categorized as: i) no evidence of risk (group 1), ii) increased risk (group 2), iii) high risk (group 3) and iiii) very high risk (group 4), according to their degree of immunocompromise as reported in the box1 of Talento et al. (i.e. degree of neutropenia, graft versus host disease, number of allogeneic and autologous HSCT, etc.[23] If more than one risk groups were identified within a specific cohort, the higher risk group was selected (group 4).

Differences in the percentage of at-risk group categorization during the case and the control period were evaluated through the chi-squared test or Fisher exact test, as appropriate. A probability of $p<0,05$ was considered statistically significant. All statistical tests were two-sided. Statistical analysis was performed using Stata IC 14 for Mac (Intercooled Stata 14 for MacIntosh, Stata Corporation Lakeway, USA, 2015).

Therapeutic regimens: Antifungal prophylaxis was performed mainly with posaconazole (300mg/day), and in few cases with fluconazole (400mg/day). The antifungal treatment was carried out with amphotericin B (3mg/kg/day) or caspofungin (50mg/day) and voriconazole (400mg/day). In case of febrile neutropenia, empiric antimicrobial treatment was performed with piperacillin/tazobactam generic formula (13.5 mg/day).

Galactomannan detection: Positivity to galactomannan in bronchoalveolar lavage (BAL) and serum galactomannan antigen test were used as a proxy for invasive aspergillosis (IA) diagnosis. Serum specimens from patients admitted to Hematology ward were collected between December 2016 and May 2017 (case period) and between December 2017 and May 2018 (control period). These clinical samples were routinely sent to a microbiological laboratory for galactomannan (GM) detection. The GM test was performed according to the manufacturer's instructions for the Platelia Aspergillus kit (Bio-Rad Laboratories, CA, USA). The optical density (OD) value for each hole of the plate was read, and the GM detection value in the serum or BALF samples was derived as follows: specimen OD value divided by standard OD value. A serum GM value of 0.5 or higher was considered positive.[24] If GM detection was negative in the serum of patient with high suspicious of IA, also the bronchoalveolar lavage (BAL) was collected, and the Galactomannan antigen test was performed. The GM positive tests were correlated with clinical and radiological features for the definitive diagnosis of IA.

Statistical Methods: The percentage of positive samples was calculated considering the only samples positive to GM for the single patient: if the serum of a specific patient was negative to GM, while BAL was positive to GM, we considered only BAL sample and not the serum.

Differences in percentage during case and control period were evaluated through the chi-squared test or Fisher exact test, as appropriate. A probability of $P<0,05$ was considered statistically significant. All statistical tests were two-sided. Statistical analysis was performed using Stata IC 14 for Mac (Intercooled Stata 14 for MacIntosh, Stata Corporation Lakeway, USA, 2015).

Results. Between December 2016 and June 2017, four building sites (BS1, BS2, BS3, and BS4) were carried out for a total of 8 patients' rooms involved in the renovation activities of the Hematology ward. Each building site involved two rooms (room1 and room2) at a time (**Figure 1**). We registered differential pressures of about 5 Pa between the anteroom vs the corridor for all four BS.

In **figure 2** the results of the particle counts were reported. **Figure 2** shows the levels of APC at different phases, both in the presence (phase TGS, T1 and T2) and in the absence of the renovation activities (phase, T0 and T3). The APC values (0.5 µm, 1.0 µm, 5.0 µm and 10 µm) of the T0 phase (**Figure 2 A-C-E-G**) are higher respect of the values observed in the T3 phase (**Figure 2 B-D-F-H**). The APC values of the T1 phase

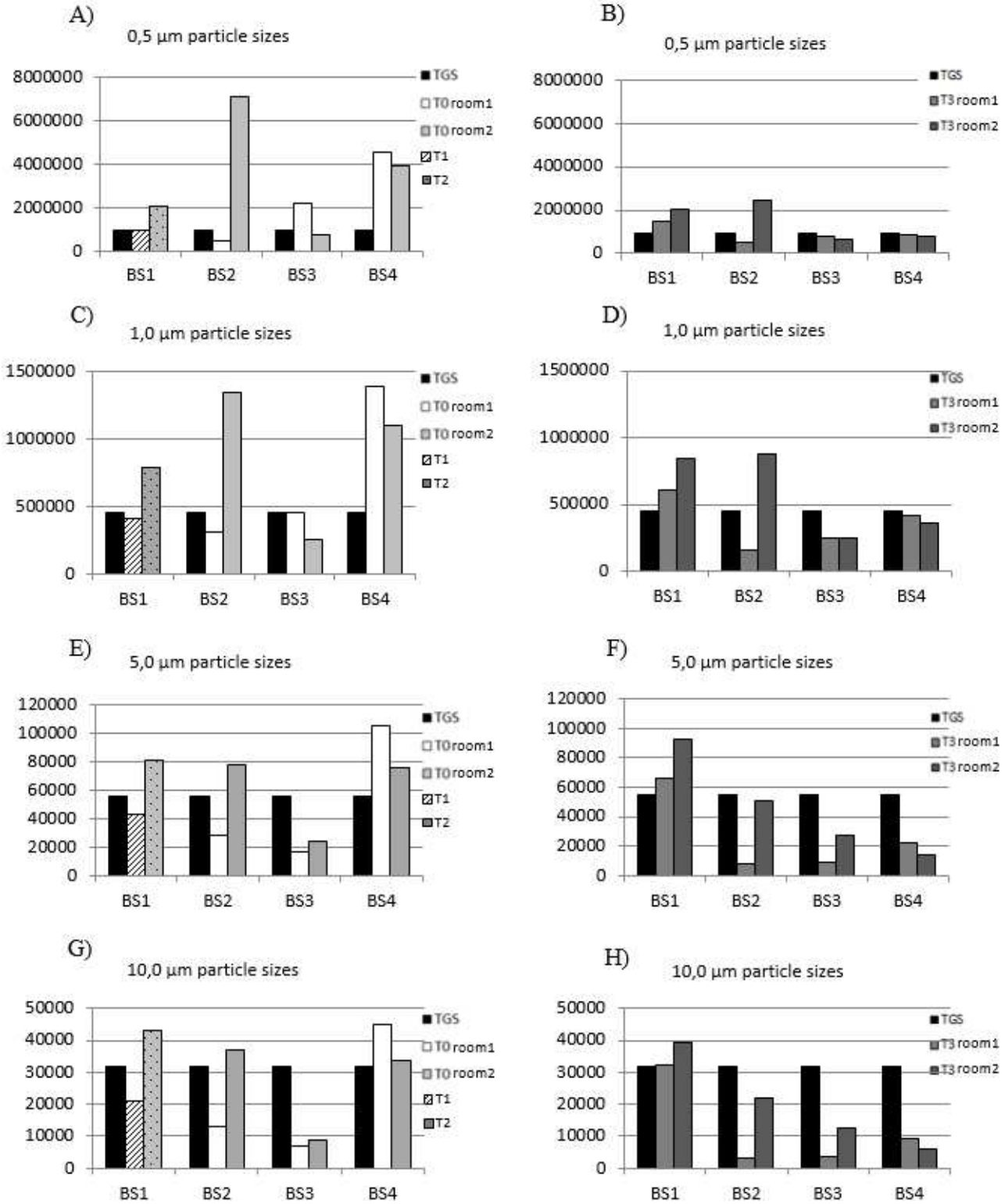

Figure 2. Bar graphs show the results of the airborne particle count (APC). Particle size is reported in the title of each graph. The phases at which the particle count is carried out are indicated in the legend: T0 before the beginning of the renovation activities (**A-C-E-G**), T1 and T2 initial and terminal phases of the renovation activities (**A-C-E-G**), and T3 after the sanification of the renovated rooms (**B-D-F-H**). Time of golden standard (TGS) represents the baseline value of particle count recorded 1 week before the start of renovation activities.

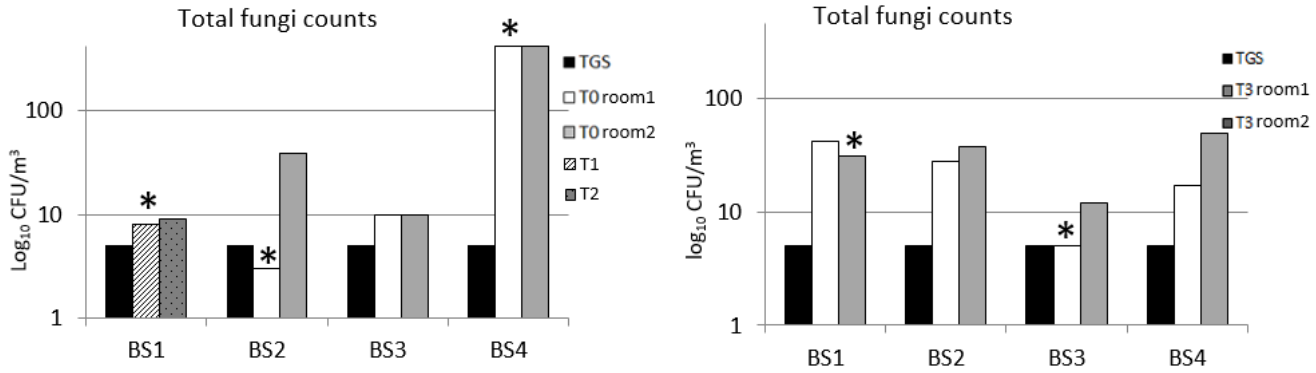

Figure 3. Total fungal counts were reported along the Y-axis from different building sites (BS1, BS2, BS3 and BS4). a) phases T0 (before the beginning of renovation activities), T1 at the beginning of activities and T2 at the end of activities and before the sanification procedures. The values of fungi total count for BS4 were b) phases T3 after the sanification of the renovated rooms. The presence of *Aspergillus* spp. was indicated by asterisk.

is lower than the T2 phase and similar to the TGS values.

Specifically, the APC values of the analyzed particles (**Figure 2 A-C-E-G**) in the T2 phase of BS1, BS2 (room2), BS3 (room1) and BS4 (room1 and room2) are higher than the TGS value, with the exception of the room1 of the BS3 (**Figure 2 C-E-G**). Regarding the APC values of the T3 phase (**Figure 2 B-D-F-H**), the BS1 (room1 and room2) and BS2 (room2) for APC of 0.5 µm and 1.0 µm were higher than TGS values.

Airborne fungi counts were reported in **figure 3**. The airborne fungal trend in the phases before the beginning of renovation activities (T0) and in the phases after renovation (T3), shows a higher airborne dispersion of fungi in T3 phase. Nevertheless, a very high concentration of fungi was observed in T0 phases of BS4. The asterisk reported in **figure 3**, indicated the presence of *Aspergillus* spp. A very low concentration of *Aspergillus* spp. was detected: 1 UFC/m^3 for BS1 (T1-room1 and T3-room2), 1 UFC/m^3 for BS2 (T0-room1), 1 UFC/m^3 for BS3 (T3-room1) and 2 UFC/m^3 for BS4 (T0-room1). Considering the importance of the categorization in at-risk groups for IA during the hospital construction/renovation works,[24] we classified the patients in at-risk groups during the control period and the renovation activity period (case period) as reported in **table 1**. The percentage of patients categorized at risk group 4 was higher during the case period (51,92%), respect to the control period (33,09%). This difference was statistically significant (p=0.004).

During the period of the renovation activities, patients were monitored to track putative hospital-acquired aspergillosis. Currently, serum Galactomannan (GM) detection is considered a microbiological diagnostic criterion for fungal infection in neutropenic patients, according to the guidelines of the 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).[23] Recently, bronchoalveolar lavage fluid GM detection was also strongly recommended in the 2016 Infectious Diseases Society of America guidelines as a test providing high-quality evidence in neutropenic patients.[25,26] .During the case period, namely between December 2016 and May 2017, and during the control period (December 2017 and May 2018) a total respectively of 104 and 139 clinical samples were collected and analyzed to detect GM.

Ninety of the 104 samples were collected from the blood of patients and 14 from BAL. A total of 4 samples were positive to GM assay (3.85%): 2 samples from blood and 2 samples from BAL. During the control period of 139 samples: 17 were collected from BAL and 122 from blood. Of these, a total of 8 samples were positive to GM assay (5.76%), 6 samples from BAL and 2 samples from the blood.

As reported above, 4 and 8 patients were positive to the GM tests during the case and the control period, respectively. Six of 12 patients positive to GM test, were treated with piperacillin/tazobactam generic formula. For 10 patients (3 patients in the case period and 7 patients in the control period), IA diagnosis was

Table 1. Categorization of risk-groups for IA.

	Group 1. No evidence of risk	Group 2. Increased risk	Group 3. High risk	Group 4. Very high risk
case period	2,14% (3/104)	35,58% (37/104)	9,62% (10/104)	51,92% (54/104)
control period	1,44% (2/139)	41,01% (57/139)	24,46% (34/139)	33,09% (46/139)

confirmed by radiological and clinical data. The 2 patients that showed positivity to GM assay, but a not supported IA diagnosis by radiological and clinical data, were simultaneously subjected to the antimicrobial treatment. Excluding the false positive to GM test, the rate of patients that shown positivity to GM during the control period in hematology ward was slightly higher (5,03%) than the rate of patients positive to galactomannan during the building work activities (2,75%). This difference was not statistically significant (P=0,5227).

The standard practice of antifungal chemoprophylaxis is supported by studies conducted in specific high-risk patient populations, especially those receiving treatments for hematological malignancies.[27,28] According to European guidelines,[29] during the case period, a total of 25 patients were subjected to antifungal prophylaxis and/or treatment. Three of these showed positivity to the GM test. For the remaining 22 patients, who underwent antifungal prophylaxis and/or treatment, the diagnosis of IA was never confirmed by the clinical and radiological features. Surprisingly, we found out the same results during the control period.

Discussion. Demolition, construction and/or renovation works in Hospitals, may pose a severe risk to the patients, in particular, those immunocompromised patients.[30,31] Our study was conducted in the Hematology ward of a large teaching hospital in Rome during the renovation activities. During the renovation works, the care activities were maintained. To restructure the ward, it was necessary to carry out four building sites (BS1, BS2, BS3, and BS4) sequentially (**Figure 1**).

Our findings show that the APC values in the four building sites were higher in the T0 phase if compared to the values recorded in the T3 and TGS phases. This is especially true for particles with smaller diameters (0.5-1.0 μm) because smaller particles persist longer in the air. This trend can be justified by the fact that during the construction activities the HEPA filter-air extractors were kept on night and day, and at the end of the renovation activities, very accurate and exclusively wet cleanings were performed. Furthermore, before final sanitization, sterile water was sprayed into the air in order to precipitate more quickly the bigger particles that are those that potentially contain microorganisms.

These containment activities meant that the APC values after the renovation activities were better than those registered immediately before the renovation works began.

High levels of all APC values in the T0 phase were detected for the BS4. It could be because all the furniture had been removed, but probably the sanitizing procedures were not effectively carried out, as demonstrated by the presence of dust at the time of particle counts. Instead, the values of the T3 phase of the BS4 were comparable with the values of the other building sites.

Fungi counts showed no distinct differences between the T0 phase and the T3 phase concerning the TGS, and in any case, the recorded values were slightly higher than the value of the TGS phase. Except for T0 phase of BS4, which showed a very high level of fungi contamination in comparison with the other building sites. These data were in accordance with the APC values registered in the same phase, and it could be explained as reported above. Even if there are no numerical threshold guidelines available for *Aspergillus* spp. Counts a threshold of <5 cfu/m^3 inward areas without high-efficiency particulate air (HEPA) filtered rooms have been suggested.[32]

During the renovation activities, colonies of *Aspergillus* spp., were isolated both in T0 phase than in T3 phase; a slightly decreasing trend is observed in the number of colonies observed in the phase T3 (2 CFU/m^3) with respect to the total number of colonies observed in the T0 phase (a total of 4 CFU/m^3) respecting the threshold of <5 cfu/m^3.[32]

The at-risk groups' categorization showed a higher percentage of the very high risk patients (group 4) for IA during the case period (51,92%) respect the control period (33,9%). The detection of galactomannans in serum and/or BAL of patients admitted during the case period (2,75%) and the control period (5,03%) did not show any statistically significant correlation between the presence of the renovation activities compared to the absence of these. The GM test is the most rapid detection method for IA diagnosis; nevertheless, false positive could be observed in patients simultaneously treated with piperacillin/tazobactam generic formula.[33] Our study shows that for 2 patients the positivity to GM test was not confirmed by clinical and radiological data suggesting an alleged interference between antimicrobial agent and the GM detection assay.

Over the past decade, a decreased incidence of IA has been seen in the Hematological patients, due to improved preventive measures of isolation and antifungal prophylaxis.[34]

Because of antifungal mold, active prophylaxis and/or treatment decreases the sensitivity of serum GM assay, clinical and radiological data of patients that were negative to GM test, were analyzed in order to find out the alleged false negative. All the patients that showed negative results to GM test had a clinical and radiological feature that confirms a negative diagnosis of IA.

Renovation works represent a major environmental risk factor, necessitating protective measures that have to be implemented.[35] In the literature, renovation activity was linked to increased airborne *Aspergillus* contamination.[3] Our results showed that if the appropriate protective measures for the containment of

dust dispersions, were adopted, the renovation activities may co-exist with those of assistance practices, also in a ward that accommodate patients at very high risk for invasive aspergillosis (group 4). The compliance of all the containment measures such as i) the construction of filter areas accessible only to authorized personnel, ii) the presence of an extractor with HEPA filters working day and night, iii) the maintenance of adequate differential pressures and iiii) the implementation of the procedures of sanitization with further activities such as the nebulization of sterile water on air in order to precipitate the bigger particles that otherwise would take longer to settle.

Although the particle counts are carried out in clean rooms, according to the ISO 14644:2015 part 1,[21] in order to it assign a specific internationally recognized ISO classification, its application in environments other than in the cleanrooms made possible to monitor the dust dispersion trend during the different phases of the construction and/or renovation activities. Thus, we think that this count can be useful also for environmental monitoring.

Conclusions. Environmental monitoring (particle fungi count) of pre (T0) and post (T3) renovation activities can be a useful tool to verify if the site activities have worsened the quality of the environment, and possibly to drive clinicians towards closer surveillance of patients admitted to the ward undergoing restructuring. This study suggests the importance of a multi-professional approach, involving clinicians, hygienists, nurses, and technicians, that regularly meet to share evidence on environmental monitoring programs, and results on hospital-acquired infection incidence. The categorization of the at-risk group,[24] according to the degree of patients before the beginning of renovation activities, could be a useful method to potentially reduce the risk of IA during the renovation works. Environmental data can be correlated with clinical data in order to preventively evaluate an IA and then proceed quickly in treating the patient before the onset of clinical deterioration.

Authors' Contributions. DILM and SV contributed equally to this work and wrote the original draft; WR and PL reviewed, edited, and supervised, UM, SS and VA contributed to the revision of the final manuscript, AB, FP, RT, BF, and MW contributed reagents/materials/analysis tools, DILM performed statistical data analysis. All authors contributed to the revision of the final manuscript.

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