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ORIGINAL ARTICLE

Fungal infections after haematology unit renovation: evidence of clinical, environmental and economical impact

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Abstract

Objective and methods: The Haemato-Oncology Unit, Hospital S. Joao, suffered extensive refurbishing intervention in order to adapt for autotransplant patients. Eight new individual rooms with central HEPA filtration system were built. All patients admitted in the department during 14 months prior to and 14 months after renovation works were enrolled. A total of 403 admissions were considered and a detailed analysis of all patients with fungal infections, air quality and antifungal consumption were evaluated in order to study clinical, environmental and economical impact after unit renovation. *Results:* Patients with acute myeloid leukaemia submitted to induction treatment were the most susceptible to acquisition of fungal infections. Fungal infections were reduced after installation of HEPA filters in individual rooms, particularly proven and probable fungal infections. No patients were diagnosed with proven or probable mould infection in the period after the unit renovation and no deaths were registered among patients with the diagnosis of possible fungal infection. Considering the group of patients diagnosed with fungal infection, the average of hospitalization was reduced 3 d in the latter period. The new high-protected rooms showed a reduction of 50% and 95% of airborne fungi, respectively in the first week and after the second week. The consumption of voriconazole and caspofungin was reduced, respectively, 66% and 59% and the final cost with antifungal therapy was reduced by 17.4%. *Conclusions:* Autotransplant patients may be under higher risk of infection, however, the installation of high-protective measures may efficiently prevent fungal infections in these patients. Renovation of haematology unit resulted in major clinical, environmental and economical improvements. The definition of reference values for airborne agents in hospital facilities remains urgent.

Key words acute leukaemia; antifungal therapy; fungal infection; high efficiency particulate air filters; indoor air quality

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Patients with haematological diseases are usually under intense suppressive therapies, which affect their immune status and frequently cause neutropenia and increase the risk of infection (1–3). Nosocomial fungal infections are often associated to considerable mortality and longer stay in intensive care units, being responsible for extremely high healthcare costs (1, 4, 5). The implementation of preventive infection control measures, particularly the high efficiency particulate air (HEPA) filters, may reduce the incidence of fungal infections like invasive aspergillosis (6–9). However, this reduction was not consistently observed in all clinical units (10–12). A systematic review has recently reported no significant advantages of HEPA filters in reduction of the mortality rate among haematological patients (13).

The Department of Clinical Haematology of Hospital S. Joao, Porto, initiated bone marrow autotransplant interventions in 1996, particularly in the Neutropenic Patients Unit. In order to increase the department's transplant capacity, the Haemato-Oncology Unit had

undergone restructuring works to build eight isolation rooms with HEPA filters and positive pressure central system. Are these protective measures enough to prevent fungal infections in patients admitted for autotransplant? Were clinical and environmental variables improved and patients admitted in a safer unit? The main objective of the current study considered the detailed analysis of the clinical data of all patients with fungal infections admitted at Haemato-Oncology Unit, before and after renovation works. We intent to verify if a more protected environment may be correlated with clinical improvements regarding fungal infection in risk patients admitted in haematological units. The incidence of yeast and mould infections in haematological patients, mortality rate and related risk factors was evaluated. The assessment of indoor air quality and antifungal consumption were also considered, before and after unit renovation.

Methods

Unit conditions and study population

The renovation works and installation of central HEPA filters at the Haemato-Oncology Unit started at November 2004, being the new rooms available for admission of patients in June 2005. Renovation works occurred into the Haemato-Oncology Unit separated from the main hall of the unit by a barrier (door). No additional measures were considered. The installed air filtration HEPA system was based on a polyester pre-filter G4 (initial efficiency of 70%) replaced every 15 d, a polyester fine filter F8 (24×24 inches; flow of 4500 $m^3\ h^{-1}$; Luwa GmbH, Frankfurt, Germany) replaced every 6 months and the HEPA filter H13 of polyester and fiberglass (glued type with a flow of 4200 $m^3\ h^{-1}$; Camfil Farr, Trosa, Sweden) replaced once a year. HEPA air filtration system was turned on continuously 24 h per day, being turn off only for filter replacement, and it was adjusted to 15–20 air exchanges per hour. Additional protective conditions were added to the new rooms like the existence of an anteroom with HEPA filters installed along the entrance to each room (during door opening prevents air flow into patient room, also preventing the access of non-authorized people), water filtration and the systematic use of protective sterile clothes (the unit staff or visitors must wear sterile gown, shoe covers, head cap and surgical mask). The department availability comprised 12 beds before renovation works (one room each for six men and six women, respectively, both without air filters or other protective measure) and 14 beds after the unit renovation (two rooms with three beds each, both without air filters or other protective measure, plus the eight new individual rooms equipped with HEPA filters and positive air flow). Additional protective measures like extensive hand disinfection were part of the staff routines. Patients and unit staffs were continuously alerted to a higher risk of infection during renovation works and stressed to keep the wards maximally isolated from the exterior air. During that period, visitors and unit staff must nevertheless wear surgical facial mask into the rooms with no protective measures, the doors and windows were always kept closed, the patients only leaving the room for clinical exams and to use toilet facilities. In such cases, patients must wear N95 NIOSH facial mask (Kimberly-Clark SL, Madrid, Spain), as recommended (14). All patients admitted in the department from April 2004 to July 2006 were monitored, corresponding to the period before and during the works (14 months) and the period of 14 months immediately after the renovation works. The Haemato-Oncology Unit admitted patients with all types of acute leukaemia and the most severe cases of lymphoma/myeloma malignancies in the northern region of Portugal. Data regarding haematological disease, admission diagnosis, length of stay at hospital, duration of neutropenia, acquired infections, therapeutic protocols and origin of infection were registered.

Definition of hospital-acquired infection

The definition of invasive fungal infection was established in three levels, proven, probable and possible, according to previous consensual criteria (15). Hospital-acquired yeast infections or nosocomial infections were defined following the isolation and diagnosis of infections after the initial 48 h after admission in the haematology unit, according to Centers for Disease Control and Prevention (CDC) (16) and other reports (17). Prolonged fever corresponded to the persistence of fever for more than 4 d and refractory to broad-spectrum antibacterial treatment, while prolonged neutropenia corresponded to neutropenia longer than 10 d (15). The incidence of fungal infections was determined considering the number of admitted patients diagnosed with fungal infection against the total number of admissions.

Antifungal consumption

The antifungal agents requested by the Haemato-Oncology Unit during the 28 months surveillance period were quantified and the consumption associated to amphotericin B, both deoxycholate and liposomal formulation, fluconazole, voriconazole and/or caspofungin was evaluated. The same price was considered for each antifungal formulation in the periods before and after renovation works, in order to avoid false comparisons due to antifungals price adjustments along the 28 months.

Environmental surveillance

The conventional volumetric air sampling method using the Andersen one-stage sieve impactor was used for air surveillance. This standard method is recommended to collect and quantify airborne fungal species. Eighteen impactor air samples with six different impact volumes of air (14, 28, 56, 84, 140 and 280 L) were collected in each room, at a flow of 28 L/min, as recommended (18). Larger air volumes were not collected due to dehydration of agar culture medium for prolonged air exposure. Impactor air samples were cultured using the DG18 medium (19, 20) and incubated at 25°C and 37°C, during 10 d. Results were expressed as number of colony-forming units per cubic meter (CFU/m^3) of analyzed air. Regression through the origin was applied to the data and the concentration of CFU in the analyzed air determined from the slope of the regression line. For each room, the total number of colonies was plotted against the volume of analyzed air. Identification of fungal colonies was based upon macro and microscopic morphological aspects, accordingly the standard mycological methods (21). Sample collection was conducted in phases of four consecutive weeks each (sampling phases performed every 3 months), before and after the renovation works.

Statistical analysis

SPSS 13.0 (SPSS Inc., Chicago, IL, USA) application was used for data elaboration and analysis. Student's *t*-test for paired and two independent samples was used during statistical analysis. The comparison of infection incidence in the periods before and after renovation works was performed determining *z*-values, the population considered at normal distribution. Alpha was set to 0.05 and all reported *P*-values were two tailed.

Results

Haematological malignancies and fungal infections

A total of 403 admissions (198 before and 205 after the renovation works), corresponding to 221 patients (119 women and 102 men), were made to the Haemato-Oncology Unit during the 28 months surveillance period. Patients' age ranged between 15 and 86 years old (average of 54 years old). The haematological patients admitted at the unit corresponded to 75 patients with acute myeloid leukaemia (33.9%), 25 with acute lymphoblastic leukaemia (11.3%), 4 with blast crisis of chronic myeloid leukaemia (1.8%), 4 with chronic lymphoblastic leukaemia (1.8%), 5 with myelodysplastic syndrome (2.3%), 1 with plasma cell leukaemia (0.5%), 11 with Hodgkin lymphoma (5.0%), 51 with non-Hodgkin lymphoma (23.1%), 35 with multiple myeloma (15.8%) and 10 with aplastic anaemia (4.5%). The admissions of both periods are more detailed in Table 1.

Table 1 Admissions, duration of neutropenia, unfavourable outcome and fungal infections in haematological patients, before and after unit renovation

	Before renovation	After renovation
Admissions	198	205
Non-neutropenia	51	43
Short neutropenia	68	74
Long neutropenia	79	88
Deaths	16	8
Fungal infections (FI)	13	10
Yeasts[1]	3	0
Moulds[1]	3	0
Possible FI	7	10

[1]Proven and probable infections.

The incidence of fungal infections in haematological patients admitted at unit was 6.6% and 4.9% ($P = 0.001$), respectively, in the periods before and after the renovation works, corresponding to 0.33 patients per 100 d before works and 0.26 patients per 100 d after installation of protective measures (Table 1). These fungal infections also corresponded to 0.64 infections per 100 d of neutropenia before renovation and 0.49 infections per 100 d of neutropenia in the latter period. Mould infections, proven and probable, were significantly reduced after the renovation works (incidence of 1.5% and 0%, respectively, before and after renovation; $P < 0.001$), as well as proven yeast infections (incidence of 1.5% and 0%, respectively, before and after renovation; $P < 0.001$). The details of the patients diagnosed with proven and probable fungal infections are described in Table 2. Patients 1 and 6 stayed at haematology unit during the construction period, while the other four patients were admitted and left the unit before this period. Pre-construction period showed more fungal infections compared to construction period (incidences of 9.5% vs. 3.7%) probably due to the decrease of admitted patients for treatments causing longer expected neutropenia. After the unit renovation, there were no proven or probable fungal infections, being diagnosed 10 cases of possible fungal infection (in the previous period of 14 months, seven cases were diagnosed, Table 1). Of the previous 17 cases, three were PCR positive for *Aspergillus fumigatus*. However, this test is not still accepted as microbiological criteria. Nevertheless, it was especially relevant to the fact that there were no deaths in patients with the diagnosis of possible fungal infection in the latter period against three patients with poor outcome in the first 14 months (Table 1). More severely ill patients

Table 2 Data from haematological patients diagnosed with proven and probable fungal infections (all patients presented fever for more than 4 d, submitted to broad-spectrum antibiotics)

	Neutropenia (days)	Haematological disease	Diagnosis of fungal infection	Fungi detected	Level[1]	Outcome
Patient 1	20	Acute myeloid leukaemia	CT scan suggesting fungal infection, negative antigen test, positive biopsy to *A. fumigatus*	*Aspergillus fumigatus*	Proven, deep tissue	Alive
Patient 2	27	Acute myeloid leukaemia	Positive cultures from blood and bronchial secretions to *C. glabrata*	*Candida glabrata*	Proven, fungemia	Died
Patient 3	22	Acute myeloid leukaemia	Positive blood culture	*Saccharomyces cerevisiae*	Proven, fungemia	Alive
Patient 4	20	Acute myeloid leukaemia	Positive cultures from catheter and blood	*Candida parapsilosis*	Proven, fungemia	Alive
Patient 5	27	Acute myeloid leukaemia	Two CT scans suggesting fungal infection, three positive cultures to *A. fumigatus*, two positive antigen tests, one positive PCR test	*Aspergillus fumigatus*	Probable	Died
Patient 6	6	Non-Hodgkin lymphoma	Symptoms of lower respiratory tract infection and pleural infusion, two positive cultures from bronchial secretions to *A. fumigatus*	*Aspergillus fumigatus*	Probable	Alive

CT, Computerized tomography.
[1]According to Ascioglu *et al.* (15).

were admitted during the latter period in the new protected wards compared to the wards without HEPA filters. The 10 cases of possible fungal infection detected after the renovation works corresponded to 7 patients admitted in the new rooms with HEPA filters and 3 patients admitted in the other rooms without air filtration. Haematological patients with expected prolonged neutropenia (more than 10 d) or submitted to autotransplant were preferentially admitted in the new rooms. All patients diagnosed with fungal infection stayed at least 3 wk into the haematology unit and were frequently neutropenic for longer periods (the average was 23 d in both studied phases), being simultaneously under administration of large spectrum antibiotics due to the systematic isolation of other microbial agents from clinical samples and/or central venous catheters.

Patients with acute myeloid leukaemia submitted to the induction treatment were more susceptible to acquisition of fungal infections, both yeast and mould infections, compared with patients with other haematological malignancies and/or submitted to other treatments. A single case of probable mould infection was detected in a patient diagnosed with non-Hodgkin lymphoma (patient 6 shown in Table 2), being also found during the entire study a single case of possible fungal infection in each group of haematological patients admitted with acute lymphoblastic leukaemia, myelodysplastic syndrome, aplastic anaemia and non-Hodgkin lymphoma. Thirty-eight autotransplants were successfully performed after the renovation works; these patients were never diagnosed with a fungal infection. *A. fumigatus* was the most frequent and detected mould during the 28 months surveillance period, being registered a single case of possible infection by Mucorales in a patient admitted before the unit renovation. The three described yeast infections were all caused by different organisms. Two cases were classified as nosocomial yeast infections (patients 2 and 3; Table 2).

Economical impact

Considering the group of patients diagnosed with all fungal infections, the average of hospitalization days was reduced 3.4 d in the latter period. Patients with a proven or probable fungal infection stayed from 21 to 75 d in haematology unit (average of 41 hospitalization days). Although there was also a reduction in the number of patients diagnosed with a fungal infection, the administration of some antifungal agents did not follow this tendency. The consumption of voriconazole and caspofungin in the Haemato-Oncology Unit was reduced 66% and 59%, respectively, in the period after the renovation works, while increased the use of deoxycholate amphotericin B, liposomal amphotericin B and fluconazole (Table 3). The final cost with antifungal therapy was reduced by 17.4% (around €71 000) during the second arm of the study. The usual choice for empiric antifungal therapy of moulds was an amphotericin B formulation,

Table 3 Consumption of antifungal agents before and after renovation of haematology unit (number of packs)

Antifungal and formulation	Before	After	Difference (%)
Deoxycholate amphotericin B (50 mg)	580	921	+59
Liposomal amphotericin B (50 mg)	759	990	+30
Fluconazole (200 mg), capsules	691	3342	+484
Fluconazole (2 mg mL^{-1}), intravenous formulation (200 mL)	124	180	+45
Voriconazole (200 mg), capsules	454	330	−28
Voriconazole (200 mg), intravenous formulation	138	7	−95
Caspofungin, intravenous formulation	382	158	−59

being the second line therapy mainly an association of drugs using voriconazole and/or caspofungin. For yeast infections, the first choice was regularly fluconazole and the alternative caspofungin or liposomal amphotericin B. Liposomal amphotericin B was administered at 3 mg kg day^{-1}. The daily defined dose of the other antifungals administered to patients was similar in both periods and established according to standard therapeutic protocols.

Environmental surveillance

Higher values of *A. fumigatus*, *Aspergillus flavus* and *Aspergillus niger* were detected in the cultures incubated at 37°C, while the other fungal species were mostly detected at 25°C. The air surveillance of the clinical unit disclosed values of total fungi ranging from 22 to 278 CFU/m^3 (average of 131 CFU/m^3) in the rooms without air filtration system along the 28 months surveillance period. In the same wards, *A. fumigatus* ranged between 0.7 and 19.3 CFU/m^3 (average of 8.5 CFU/m^3). The haematology main hall was not monitored during the entire study, including the construction period. Airborne quality was assessed exclusively in patients' wards throughout the study, being all rooms considered. Staff and patients were continuously alerted to keep wards maximally isolated from outdoor air. No significant differences were found during the renovation works considering airborne fungal levels into such wards ($P > 0.05$). However, the levels of *A. fumigatus* increased from 8.5 to 12 CFU/m^3, during the construction period. The new rooms with HEPA filters showed a gradual improvement of the air quality since the first week (Fig. 1). The total airborne fungi decreased from 70 CFU/m^3 (reduction of 50%) in the first week to less than 7 CFU/m^3 (reduction of 95%) in the following weeks. *Aspergillus fumigatus* yielded 1.4 CFU/m^3 in the first week but it was not detected thereafter. Similar corresponding airborne values were detected in the entrance hall (also with HEPA filters) that conducted to the patient protected rooms (data not shown).

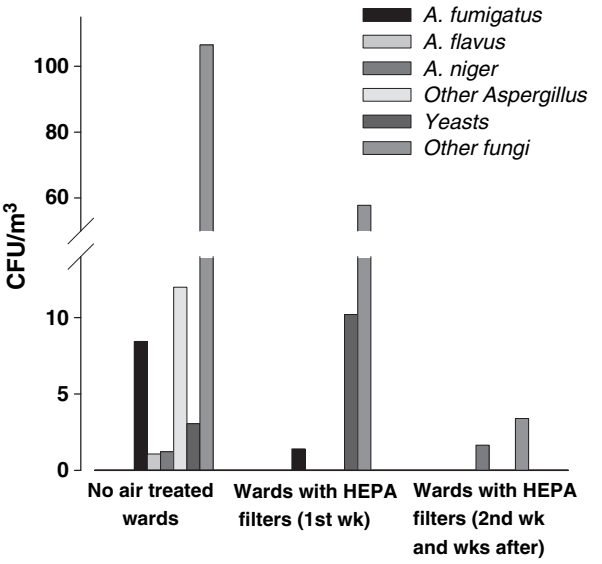

Figure 1 Colony-forming units per cubic meter (CFU/m^3) of fungi detected during air quality surveillance in haematology unit after renovation works. Other fungi included mostly *Penicillium* sp. and rare isolates of *Mucor* sp., *Alternaria* sp. and *Scedosporium* sp. Values of *Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus niger* were detected in the cultures incubated at 37°C, while the other fungal species were mostly detected at 25°C.

Discussion

Construction and renovation works are a well-known risk factor for mould infections (6, 22, 23). *Aspergillus* infections resulting from failure in air filtration systems have been reported (24, 25). Other studies have reported a reduction of *Aspergillus* infections after the installation of HEPA filters and/or by the existence of physical barriers that limit the access of airborne conidia to the clinical units (6–9). The installation of HEPA filters in the individual rooms did not completely prevent fungal infections in the haematological patients admitted in our clinical unit, although its incidence was reduced by 25%. HEPA filters had shown in other studies a reduction of airborne fungi to less than 10 CFU/m^3 (26) and a reduction of mould infections in haematological patients (7). After unit renovation, the new rooms with HEPA filters showed a large improvement of air quality compared with the non-treated rooms, as well as a clinical positive impact – no proven or probable fungal infections were registered in the latter period and no deaths associated to possible fungal infections were reported, even considering the 38 autotransplants performed in the unit during this period. During the construction period, a small increase of airborne *A. fumigatus* was found

but there was no significant clinical impact compared with the previous months, conversely to what had been shown in other locations (6, 22, 23). Even after the installation of HEPA filters, it was possible to find moulds into protected wards, particularly *Penicillium* sp., but these species are not commonly pathogenic, with the exception of *Penicillium marneffei*. *Aspergillus* species were rarely found, particularly *A. fumigatus*. Sherertz *et al*. had reported no *A. fumigatus* infections in clinical environments with less than 0.1 CFU/m^3 (27). However, reference airborne fungal values are still not defined, as well as it is not yet established the sampling air frequency that should be performed in clinical units. Confirming previous reports (4), a higher number of fungal infections were reported among patients with acute myeloid leukaemia. These patients were commonly associated to prolonged neutropenia and longer hospital stay. Incidence of invasive aspergillosis had been previously associated with an increasing number of hospital admissions per year (5, 28). Possible confounders may be detected in this study, namely regarding patients' age, patient's genetic predisposition for infection, severity of haematological malignancy and mortality rate of a unit external group. All patients staying more than 24 h in Haemato-Oncology Unit were included in this study (criteria for admission were similar in both periods) and previous mentioned factors occasionally may not be equally distributed in both compared groups (before vs. after unit renovation). However, the presented main results and values were similar to previous reports and focus different aspects, all indicative of clinical and environmental improvements after installation of protective measures.

The incidence of yeast infections was lower after renovation works, both classified as nosocomial and community-acquired infections. It is relevant that the new eight rooms were individual rooms therefore reducing inter-patient, medical staff–patient and visitor–patient contacts. Yeasts are usually present in the human internal milieu, being some nosocomial infections a clear consequence of host neutropenia and further invasion by the endogenous fungal agent.

The economical benefits of the haematology unit renovation were shown by the reduction of the hospitalization days in a particular group of patients – hospitalization costs are commonly described the most important healthcare costs (5, 29–32) – and the reduction of the expenses with antifungal agents into the unit. The larger consumption of both amphotericin B formulations and fluconazole in the latter period was most probably related to the antifungal prophylaxis administered to patients with acute myeloid or lymphoblastic leukaemia under longer neutropenia (more admissions in this period, as shown in Table 1). The administration of antifungal prophylaxis was a clinician decision and it was mostly employed in acute leukaemic patients under longer neutropenia periods, being sometimes also related to clinical history of invasive aspergillosis. Unit policy regarding prophylaxis or treatment of fungal infections was not modified during the studied period, fluconazole for yeast and amphotericin B for mould infections.

In accordance with previous studies (4, 27, 33), patients staying in hospital under prolonged neutropenia (more than 10 d) and with longer stay than 3–4 wk are more susceptible to develop fungal infections, usually associated to the isolation of other microbial agents and administration of a large spectrum of antibiotics. Patients submitted to autotransplant may be under higher risk of infection in haematological units, nevertheless, the installation of high-protective measures may efficiently prevent fungal infections in these patients, as we had shown in this study. It is urgent to understand the presence and transmission of fungal agents in protected clinical environments in order to improve health and well-being of patients submitted to immunosuppressive treatments and staying longer at hospitals.

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Conflict of interest

The authors declare no conflict of interest.

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