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Abstract

Purpose of the study

Invasive aspergillosis (IA) is the most prevalent invasive fungal disease (IFD) in neutropenic patients. Environment is the main source of *Aspergillus* spores aerosolization especially during building construction. International guidelines recommend mechanical protection during hospital building works; otherwise the use of antifungal prophylaxis is not clearly indicated.

Our objective was to determine the efficacy of antifungal prophylaxis by posaconazole on IA incidence in acute myeloid leukemia population and to analyse the benefit of this prophylaxis and HEPA-filters during hospital buildings works.

Patients and methods

We included patients treated for acute myeloid leukemia at Brest teaching hospital from January 2009 to December 2015. We compared incidence of IA in the group treated by posaconazole from 2012 to 2015 to the incidence of IA in the first group who did not receive antifungal prophylaxis (from 2009 to 2011). The one-year overall survival was also analyzed using the Kaplan–Meier method.

Results

245 patients were enrolled including 151 treated with posaconazole. 23 IA were diagnosed between 2009 and 2011 (without antifungal prophylaxis), then 31 between 2012 and 2015 (with posaconazole) without statistical difference between the incidence densities (0.34 per 100 hospitalization-days vs. 0.30 per 100 hospitalization-days, p=0.71). Incidence density of IA increased during building works (2.40 per 100 hospitalization-days vs. 0.28 per 100 hospitalization-days, p<0.0001). The incidence density of IA significantly decreased during construction periods when posaconazole prophylaxis was used (1.59 per 100 hospitalization-days vs. 4.87 per 100 hospitalization-days p<0.0001).

Conclusion

Our study suggests, for the first time, the interest of antifungal prophylaxis in addition to HEPA filtration in prevention of IA during hospital building works.

Introduction

Invasive fungal disease (IFD) remains a major cause of morbidity and mortality in immunocompromised patients, in particular patients with prolonged neutropenia after haematological chemotherapy or allogeneic hematopoietic stem cell transplant (HSCT) recipients. Invasive aspergillosis (IA) is the most prevalent IFD. Environment is the main source of *Aspergillus* spores aerosolization especially during building constructions and renovations (1,2). International guidelines recommend that patients at high-risk for IFD be nursed in high-efficiency particulate air (HEPA)-filtered, laminar airflow, positively pressurised rooms with minimum air exchanges ≥ 12 per hour during hospital construction works (3,4).

Kanamori *et al.*(5) reviewed fungal outbreaks linked to construction and renovation of healthcare settings. They selected 49 studies that reported cases of fungal outbreaks related to hospital construction, renovation or demolition. They found that fungal infections linked to construction works seem to be in decline: from 2010 to 2014 only 3 published studies have reported cases (6–8). Protective measures may explain this result. However, a meta-analysis of Eckmanns *et al.* revealed no significant benefit of HEPA filtration on the prevention of fungal infection(9). Additional guidelines are provided to minimize mold exposure during hospital works. Infectious Diseases Society of America (IDSA) and European Conference on Infections in Leukemia (ECIL) recommend antifungal prophylaxis for prolonged neutropenia after acute myeloid leukemia (AML) induction chemotherapy and for allogeneic HSCT recipients with graft-versus-host disease (GvHD) (4,10). Otherwise, the use of antifungal therapy in association with mechanical protection is not clearly recommended during hospital construction/demolition works.

In this context, our primary objective was to determine the impact of antifungal prophylaxis by posaconazole on invasive aspergillosis incidence in AML population. Our secondary objective was to determine the benefit of this antifungal prophylaxis combined with HEPA-filters during hospital building works.

Methods

This was a prospective, monocentric, open, non-randomized study, approved by the Institutional Ethics Committee and identified in Clinicaltrials.gov (N° NCT02900430). The study complies with all local and international ethical and legal requirements. A non-opposition form was authorized by the institutional ethics committee and signed by patients.The inclusion period started on January 1st, 2009 and ended on December 31st, 2015.

Patient eligibility: Any patient admitted to the Department of Clinical Haematology of Brest Teaching Hospital (France) was eligible for this study after signing a non-opposition form if they fulfilled the following inclusion criteria: age ≥ 18 years, diagnosis of AML, patients eligible for an intensive chemotherapy treatment and treated in room equipped with HEPA filtration and laminar airflow. Patients without curative care were excluded from this study.

Collected data: For each patient, we collected the following clinical and biological data: age, sex, type of AML (de novo or secondary), date of diagnosis, karyotype (according to the 2008 revision of the World Health Organization (WHO) classification(11)), presence of pulmonary comorbidity or other immunosuppression, duration of neutropenia with polymorphonuclear neutrophil (PMN) count ≤ 0.5G/L (in days), duration of hospital stay (in days). During the follow-up, invasive aspergillosis (IA) was diagnosed according to EORTC definitions (12). Serum galactomannan detection was performed twice a week during neutropenia time and all patients with a fever lasting more than 5 days under antibiotics therapy were screened by chest CT scan to search IA. If an IA was suspected, a treatment with intra-venous voriconazole was administrated without delay. We noted the overall survival at 1 year from AML diagnosis.

Prophylactic therapy: Allogeneic patients received antifungal prophylaxis with fluconazole during neutropenia period. Patients treated for AML received posaconazole prophylaxis (syrup 200mg 3 times a day) during induction, salvage chemotherapy or GVH treatment from January 1st, 2012 to December 31st, 2015.

Environmental air sampling

Environmental samplings were carried out in the patients' rooms by a laboratory technician. Air sampling was conducted with the MAS-100 biocollector (Merck®, Darmstadt, Germany) using Sabouraud chloramphenicol plates in the rooms (under the laminar airflow and in the bathroom). Surface samplings were conducted using a biocontact applicator (Oxoid, Dardilly, France) in 5 places of the room and in 2 places of the bathroom. We also carried out environmental sampling in the corridors of hematology department to assess fungal contamination outside HEPA filtration. Environmental samplings were carried out in the rooms after each patient exit. The number of sampling varied from 3 to 8 per year for each room. Sampling was performed in the corridors before the beginning of hospital building works, every week during the building works and at the end.

Periods of hospital construction, renovation, or demolition near the Department of clinical Haemotology were noted.

Evaluation criteria: Our primary objective was to evaluate the impact of posaconazole prophylaxis on the incidence density of IA and the one-year overall mortality per period of study (from 2009 to 2011 versus from 2012 to 2015). The incidence density of IA was calculated by the ratio between the number of IA cases and the number of neutropenic days for all patients, even if they underwent many times in hospital. All episodes were collected: possible, probable and proved IA. Our secondary objective was to determine the efficiency of standard preventive measures, HEPA filtration and antifungal prophylaxis in healthcare settings by the comparison of IA incidence according to hospital building works periods.

Statistical analysis: All statistical analyses were performed using the R software (version 2.12.1). Percentages were compared using the Chi square test or Fischer test. Comparison of means was performed using Mann-Whitney Wilcoxon tests. Means were noted with the standard deviation. All tests were performed two-sided, and a p-value less than 5% was considered significant. Overall survival was analyzed using the Kaplan–Meier method. Differences between the survival curves of the tested groups were assessed by means of a log-rank test with a 0.05 significance level.

Results

Population: Two-hundred and forty-five patients with AML were enrolled: 94 and 151 patients during each phase of the study. The clinical characteristics of patients were similar in each period and are summarized in Table I. The mean age was 55.9±13.3 years and 54.2±13.8 years respectively (p=0.40). The sex ratio did not differ (p=0.37). The main underlying haematological malignancy was de novo AML (72.3% and 70.2%; p=0.72) with an intermediate karyotype (60.9% and 55%). Twelve and eighteen patients had undergone allogeneic hematopoietic cell transplant procedure (p=0.98). The average length of neutropenia per hospitalization was 27.9±14.4 and 26.5±11.0 days for each period (p=0.21). The median length of stay (LOS) significantly decreased during the second period of the study from 30.6 days to 27.8 days (p=0.04).

Invasive aspergillosis: Twenty-three episodes of IA were diagnosed between 2009 and 2011, then 31 between 2012 and 2015 (Table II). No statistical difference was found between the incidence densities (0.34 per 100 hospitalization-days and 0.30 per 100 hospitalization-days; p=0.71). IA were mainly classified in possible IA (n=8 and 15 respectively) and probable IA (n=14 and 15) according to EORTC guidelines. Only 1 proved IA was diagnosed at each period of the study. Most of diagnostics were done during induction chemotherapy period (n=16 for each period, 69.6% and 51.6% respectively; p=0.23). No difference was found between the two groups for salvage chemotherapy (p=0.69), allogeneic stem cell transplant

procedure (p=0.18) and during graft-versus-host treatment (p=0.74). None IA was diagnosed during consolidation chemotherapy in the first phase of the study, contrary to the second period of the study (n=9; p=0.004). Details are shown in Table II.

Influence of hospital works: Results of environmental sampling are presented Table III. These periods of hospital building works were marked by significant contamination of the corridors. So, for example, in 2015, 15/32 (46.8%) of the samples carried out in the corridors during hospital building works were contaminated by fungi. After cleaning up the work area, the rate of contaminated sample was significantly reduced (1/29, 3.5%, p<0.0001). We identified three periods of hospital works: from October to November 2011, from May to July 2013 and from April to May 2015 (Figure 1). During hospital work periods, there were 8 IA for 333 hospitalization days (incidence density=2.4 per 100 days). Apart from work periods, there were 47 IA for 16746 hospitalization days (incidence density=0.28 per 100 days). IA incidence density significantly increased during works periods (p<0.0001).

We also compared IA density incidence during building works periods according to posaconazole prophylaxis. Without posaconazole prophylaxis, IA incidence density was 4 for 82 hospitalization days (4.87 IA per 100 hospitalization days). With posaconazole prophylaxis, IA incidence density significantly decreased to 4 IA for 251 hospitalization days, (1.59 per 100 hospitalization days, p<0.0001). Posaconazole prophylaxis during hospital work periods seems to reduce the IA incidence density.

Outcome: One-year overall survival was estimated for patients with IA at 60% compared to 76% for patients without IA. The hazard ratio (HR) was 0.63 (95%IC= [0.33; 1.04]; p=0.075) (Figure 2A). No statistical difference was found between one-year survival of patients according to the period of study (respectively 65% and 78%, HR=0.63 95%IC= [0.38; 1.0]); p=0.065) (Figure 2B). Posaconazole prophylaxis had no impact on overall survival in our population.

Discussion

Hospital building works are periods at risk to disseminate fungal spores in the environment of patients(1,2). It is admitted that construction/demolition works are a risk factor for IFD but the incubation duration of IFD in the context of nosocomial acquisition of the fungus remains unknown(2–4). International guidelines recommend caring in protected areas the higher-risk patients: prolonged neutropenia after leukemia chemotherapy and allogeneic HSCT recipients with GvHD (3,4). Environmental sampling from air, water and surfaces may be performed during hospital building works. Antifungal prophylaxis was recommended by IDSA and ECIL guidelines for AML patients during induction/reinduction chemotherapy and for allogeneic HSCT recipients with GVH disease after *Cornely* and *Ullmann* studies(13,14). Following these recommendations, some authors published real-life study or meta-analysis that showed a decrease of IA incidence with the antifungal prophylaxis but no benefit on overall survival(15–17). There are few studies dealing with antifungal prophylaxis efficacy during hospital building works(6).

In our study, the primary objective was to determine if posaconazole prophylaxis brought a benefit regarding the IA incidence and the overall survival in AML population. This study had some selection bias, as we compared two successive periods of times without randomization of patients, but we did not observe significant difference of invasive aspergillosis incidence density (p=0.71) with posaconazole prophylaxis. The efficacy of posaconazole prophylaxis could be decreased due to a poor oral absorption. We often noted digestive disorders in patients relating with severe mucositis, nausea/vomiting or diarrhoea. The oral suspension and multiple drug interactions (proton pump inhibitors, immunosuppressants) could also explain this poor absorption, as previously described(18–22). Moreover, as the therapeutic drug monitoring of posaconazole was not often available in our centre, the target concentrations were not regularly controlled(23,24).

We noted high level of IA incidence because of large criteria of diagnosis (possible, probable and proved IA). In the literature, only probable and proved IA were considered. The IA rates

differ with environmental conditions (country), hospitalization conditions (HEPA or no-filter rooms) and according to the included population (AML, myelodysplastic syndrome, allogeneic HSCT recipients), so the comparison between studies is difficult. We observed a high level of IA diagnosis in our AML population despite the use of HEPA-filters rooms (>20% when possible, probable and proved IA were considered, >10% for probable and proved IA). Our patients lived in rural conditions and could be colonized by *Aspergillus* conidies.

We chose to present the results using the incidence density rather than the incidence of IA, in order to be more representative of daily risk factor. Hence, each neutropenic length and each work building length were recorded. The IA incidences were also calculated but we did not find significant difference between the incidence densities according to the study period (p=0.46 – Table II). Our study is probably not enough powerful to demonstrate a significant difference.

Irrespective the IA diagnosis, the one-year overall survival did not significantly differ (p=0.075). We made a sensitivity analysis excluding possible cases and we found the same results: the hazard ratio (HR) was 0.80 (95%IC= [0.48; 1.31]; p=0.38) The IA occurrence was a severe complication for the patients because of their possible consequences (delay in chemotherapy, more sensibility for opportunist infection in particular others IFI). The prognosis of IA seemed to be improved by the use of intra-venous voriconazole but this medication must be administrated quickly after the onset of pathology(25). The ECIL-3 and 5 guidelines recommend a change of antifungal classes to prevent and treat an IA occurred with a prior exposition of an azole prophylaxis (10,26,27). In our centre, our choice was to use the intra-venous voriconazole because of the poor absorption of posaconazole syrup and the recurrent undersoding. Our approach was to check patients by galactomannan twice a week and by chest CT scan for any febrile neutropenia occurring more than 5 days or if patients had a positive galactomannan (index >0.5). Intra-venous voriconazole was also started in a pre-emptive strategy.

During the study, we collected 1937 samples: 1229 under the laminar airflows, 618 in the bathrooms and 80 in the corridors of the hematology department (Table III). Very few air sampling carried out under laminar flows were contaminated (1.2%). At the same time, 28.75% of environmental samplings made in the corridors retrieved fungus such as *Aspergillus fumigatus* and *Aspergillus versicolor*. Destruction works have contaminated environment in the hematology department but not in rooms equipped with HEPA filtration. These results are consistent with those of Barreiros *et al.* who studied the *Aspergillus* conidia concentration in air corridors, in rooms without filters and in rooms with HEPA filters before and after a demolition of hospital wing. They showed that the higher concentration of *Aspergillus* spores was in non-protected areas (corridors, rooms without filters). Fungal concentration did not increase in rooms with HEPA filters. In their study, high-risk patients were cared in rooms with HEPA filters and no increase of IA incidence was noted. These authors did not precise the use of antifungal prophylaxis. Our results showed a downward trend in the rate of IA incidence density when posaconazole prophylaxis is used during hospital building works, but our study lacks of power and should be confirmed by a larger study.

Our results suggest that posaconazole prophylaxis could prevent IA during hospital building works period. Even if areas with HEPA filtration are not impacted during works, fungal contamination of patient's rooms can be done via the visitors.

Although we did not find an overall decrease in invasive aspergillosis with posaconazole prophylaxis, the use of this therapeutics during higher risk periods (AML induction or GvHD), such as building works periods, appears to be efficacious and should be recommended. For the others patients (AML consolidation, aplasia, myelodysplastic syndrome), our study does not allow to conclude on the interest of the prophylaxis during building works, because of the weakness of included cases. Each centre should survey their IA incidence rates and decide according to the ECIL guidelines (incidence > 8%) (26).

Conflict of interest: None reported.

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Figure 1: Work periods according to posaconazole prophylaxis

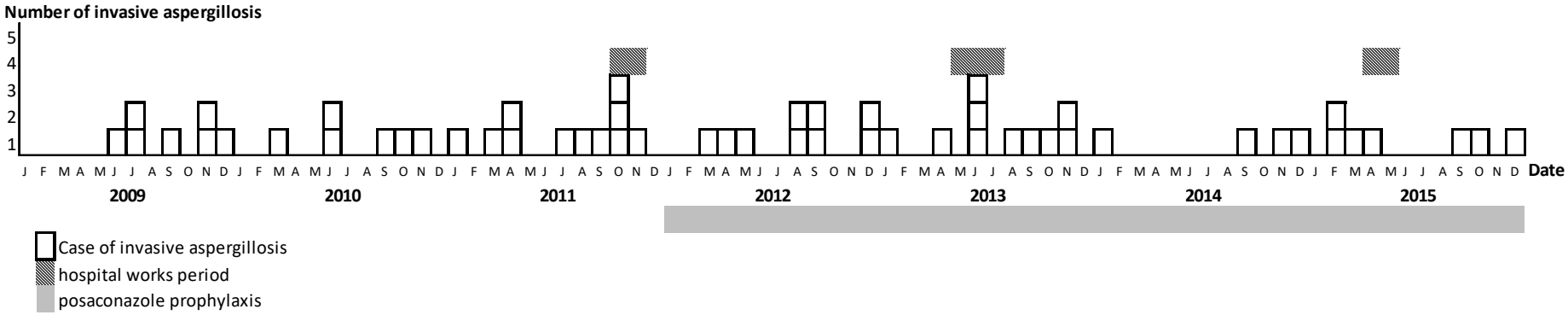
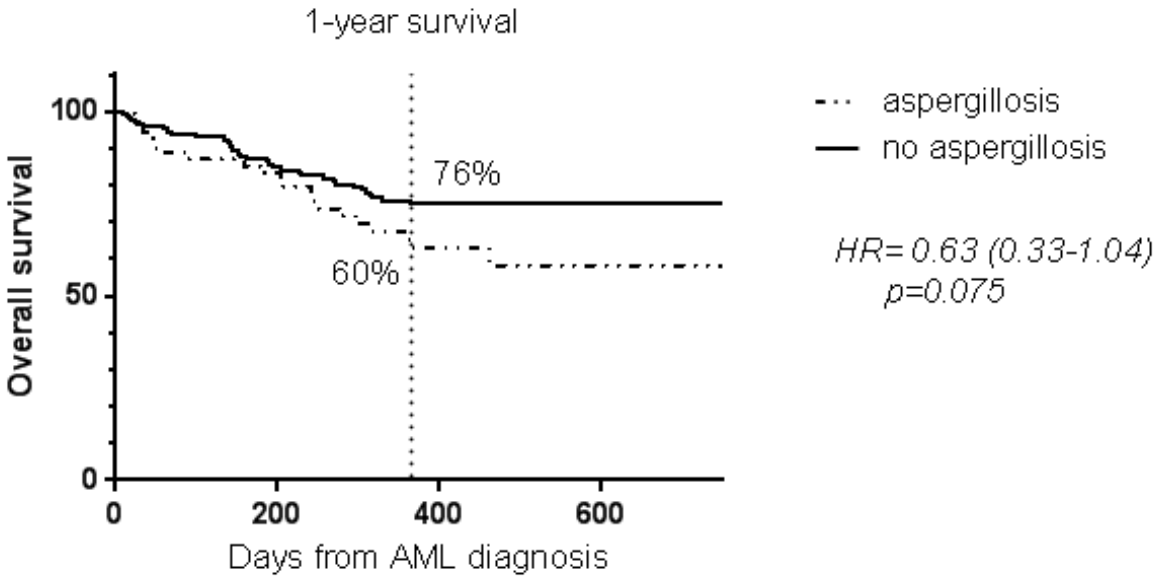
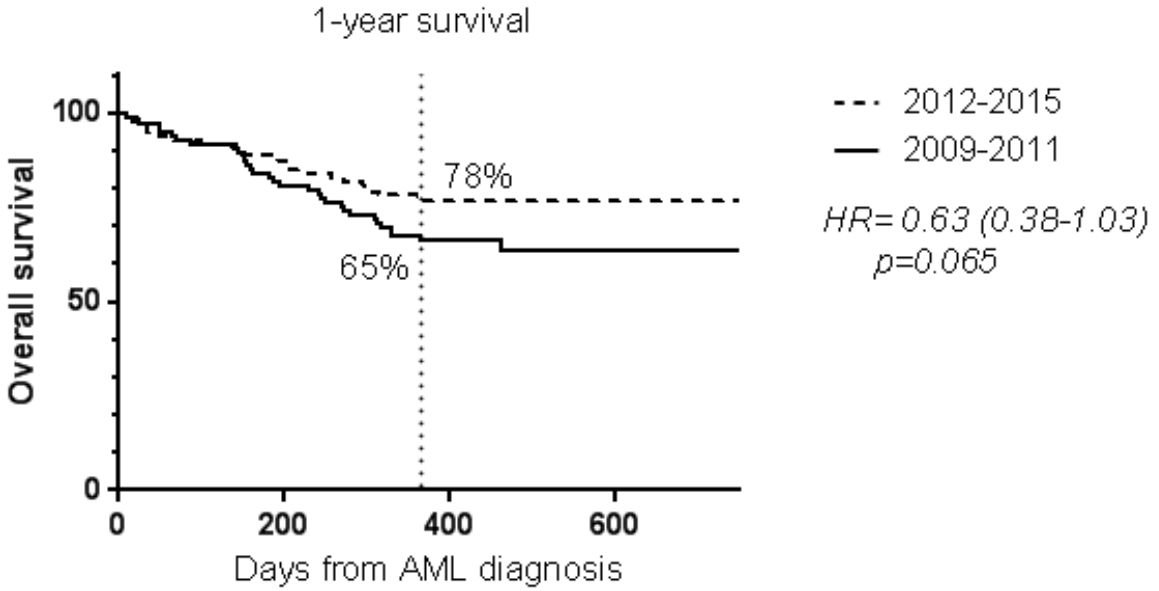


Figure 2 : Kaplan-Meier estimates of overall survival



A : Overall survival at 1 year according to aspergillosis diagnosis.



B : Overall survival at 1 year according to the study period and posaconazole exposition.

Table 1: Characteristics of included patients.

	1th period 2009-2011 (N=94), No. (%)	2nd period 2012-2015 (N=151), No. (%)	P Value
Age (mean ± SD)	55.9 ± 13.3	54.2 ± 13.8	0.40
Male to female ratio	1.18	0.93	0.37
Haematological malignancies			0.72
• De novo AML	68 (72.3)	106 (70.2)	
• Secondary AML	26 (27.7)	45 (29.8)	
Karyotype			0.84
• Favorable	10 (10.6)	20 (13.2)	
• Intermediate	57 (60.9)	83 (55.0)	
• Adverse	24 (25.5)	42 (27.8)	
• Unknown	3 (3.2)	6 (4.0)	
Comorbidity			
• Pulmonary	30 (31.9)	50 (33.1)	0.84
• Immunosuppression	40 (42.6)	68 (45)	0.70
○ Allogeneic hematopoietic cell transplant recipients	12 (12.8)	18 (11.9)	0.98
Number of hospitalization	223	368	
• Hospital stay (in days)	6829	10250	
• Median length of stay (in days)	30.6	27.8	0.04
Neutropenia per chemotherapy seances (in days, mean±SD)	27.9±14.4	26.5±11.0	0.21
Number of chemotherapy per year (mean±SD)	2.3±1.4	2.1±1.3	0.15

AML= acute myeloid leukemia ; SD=standard deviation

Table 2 : Characteristics of invasive aspergillosis

	1th period 2009-2011 (N=94), No. (%)	2nd period 2012-2015 (N=151), No. (%)	P Value
Invasive aspergillosis	23 (24.5)	31 (20.5)	0.46
• Possible	8 (8.5)	15 (9.9)	0.32
• Probable	14 (14.9)	15 (9.9)	0.36
• Proven	1 (1.1)	1 (0.7)	0.98
• Probable or proven	15 (16.0)	16 (10.6)	0.22
Chemotherapy of IA diagnosis			0.053
• Induction	16 (69.6)	16 (51.6)	0.23
• Consolidation	0	9 (29)	0.004
• Salvage	3 (13)	3 (9.7)	0.69
• Allogeneic stem cell transplant	3 (13)	1 (3.2)	0.18
• Graft-versus-host	1 (4.4)	2 (6.5)	0.74
Incidence density (per 100 hospitalization-days)	0.34	0.30	0.71
Invasive aspergillosis incidence	24.5%	20.5%	0.47

IA= invasive aspergillosis

Table 3: Environmental samplings in the protected area of department of clinical haematology

Year	Under laminar airflow (HEPA)		Bathroom (HEPA)		Corridors of hematology department	
	Air sample	surface sample	Air sample	surface sample		
	No of contaminated samples	No of contaminated samples	No of contaminated samples	No of contaminated samples	No of samples	No of contaminated samples
2009	1/72 (1.40%)	1/349 (0.29%)	4/72(5.56%)	0/140 (0%)	0	
2010	4/33 (12.12%)	3/194 (1.55%)	12/41 (29.27%)	8/81 (9.88%)	2	2/2 (100%)
2011	0/49 (0%)	2/175 (1.14%)	3/48 (6.25%)	2/72 (2.78%)	5	0/5 (0%)
2012	0/18 (0%)	0/38 (0%)	2/11 (18.18%)	0/6 (0%)	0	
2013	0/22 (0%)	3/105 (2.86%)	1/18 (5.56%)	0/38 (0%)	2	0/2 (0%)
2014	0/11 (0%)	1/70 (1.43%)	0/10 (0%)	1/30 (3.33%)	2	0/2 (0%)
2015	0/18 (0%)	0/85 (0%)	3/17 (17.64%)	2/34 (5.88%)	69	21/69 (30.43%)
Total	5/223 (2.24%)	10/1016 (0,94%)	25/217 (11.52%)	13/401 (3.24%)	80	23/80 (28.75%)