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The impact of portable high-efficiency particulate air filters on the incidence of invasive aspergillosis in a large acute tertiary-care hospital

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Background: Worldwide, the frequency of invasive fungal infections has been increasing, with a corresponding increase in the numbers of high-risk patients. Exposure reduction through the use of high-efficiency particulate air (HEPA) filters has been the preferred primary preventive strategy for these high-risk patients. Although the efficiency and benefits of fixed HEPA filters is well proven, the benefits of portable HEPA filters are still inconclusive.

Methods: This was a retrospective study to assess the impact of 48 portable HEPA filter units deployed in selected wards in Singapore General Hospital, an acute tertiary-care hospital in Singapore. Data were extracted between December 2005 and June 2008 on the diagnoses at discharge and microbiological and histological laboratory findings. All patients with possible, probable, or proven invasive aspergillosis (IA) were included.

Results: In wards with portable HEPA filters, the incidence rate of IA of 34.61/100,000 patient-days in the preinstallation period was reduced to 17.51/100,000 patient-days in the postinstallation period ($P = .01$), for an incidence rate ratio of 1.98 (95% confidence interval [CI], 1.10-2.97). In wards with no HEPA filters, there was no significant change in the incidence rate during the study period. Portable HEPA filters were associated with an adjusted odds ratio of 0.49 (95% CI, 0.28-0.85; $P = .01$), adjusted for diagnosis and length of hospital stay.

Conclusions: Portable HEPA filters are effective in the prevention of IA. The cost of widespread portable HEPA filtration in hospitals will be more than offset by the decreases in nosocomial infections in general and in IA in particular.

Key Words: Invasive aspergillosis; high-efficiency particulate air filter; invasive fungal infection.

Worldwide, the frequency of invasive fungal infections (IFIs) has been increasing, with a corresponding increase in the number of ''high-risk'' patients. These high-risk patients include recipients of solid organ transplants and hematopoietic stem cell transplants (HSCTs), those with hematologic malignancies, and others receiving immunosuppressive therapy apart from the increasing pool of patients with human immunodeficiency virus. This increase is due in part to the rapid advances in medicine that have significantly increased the number of patients with critical illnesses who survive for longer periods. The development of intensive chemotherapy protocols for the treatment of solid tumors, aggressive lymphomas, myelomas, and resistant forms of leukemia; the growing number of organ transplantations; and finally, the widespread use of immunosuppressive therapies for a wide spectrum of autoimmune diseases have all contributed to this.[1] Among the IFIs, invasive aspergillosis (IA) is a leading cause of death in this group of severely immunocompromised patients.[2] A large-scale prospective collaborative study has shown that IA accounts for about 42% of all IFIs in patients who underwent HSCT.[3] IA is a rapidly progressive, often fatal infection, with mortality rates ranging from 30% to 95%.[4,5] The mortality rate due to IA has risen steadily, with an 8-fold increase since1970.[6]

Major outbreaks of nosocomial IA have been associated with hospital construction, renovation, and maintenance activities that allow spores to become

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airborne.[7-10] Preventive measures are important to the control of IA, because the diagnosis is difficult and the outcome of treatment is dismal. Reducing exposure by isolating these high-risk patients in rooms equipped with high-efficiency particulate air (HEPA) filters has long been the preferred primary preventive strategy.[11,12]

The effectiveness of HEPA filters in reducing environmental fungal spore counts is well established based on a number of studies.[13-15] Despite the fact that the cause-and-effect relationship between airborne *Aspergillus* spore level and IA is difficult to quantify, it is clear that decreasing the spore level in the air is instrumental to reducing the risk of nosocomial infections.[13] Although HEPA filters do not provide complete protection from fungal infection, some good retrospective studies suggest that it significantly reduces the risk of *Aspergillus* infection.[11,16-21] In addition, some published evidence suggests that HEPA filtration also can significantly reduce the airborne concentrations and/or infection rates for a wide range of other aerosolized pathogens, including methicillin-resistant *Staphylococcus aureus*, *Pseudomonas* spp, mycobacteria, and some viruses.[22-25]

The efficiency and benefits of portable HEPA units are not as well established as those for their fixed counterparts. Even though some studies have demonstrated their usefulness,[26] currently there is little consensus about their efficacy in field conditions.[27-29] Although the ability of portable HEPA units to reduce *Aspergillus* spore levels has been well studied, the degree of reduction in IA incidence does not seem to be of clinical relevance for high-risk patients.

MATERIALS AND METHODS

Singapore General Hospital (SGH), the largest acute tertiary-care teaching hospital in Singapore, caters to a large segment of high-risk patients. To augment its armamentarium against IFIs, SGH acquired about 48 portable HEPA filtration units (HealthPro 150; IQAir, INCEN AG, Blumenfeldstrasse 15, CH-9403 Goldach, Switzerland) during a period of major renovation. These were installed in certain wards starting in December 1, 2006. The wards chosen were W42A, W54D, W55B, W56, W64E, and W72, which cater to patients of different specialties. This study aimed to estimate the effectiveness of these portable HEPA units in deceasing the incidence of IA in SGH.

This was a retrospective study, with data extracted for the period December 2005 to July 2008. We used a standardized data extraction form and reviewed medical records and radiographic, microbiological, and pathological reports. We extracted information from the confirmed discharge diagnosis and results from microbiology culture, histopathologic and cytopathologic diagnosis, and radiology reports. The case definition included all proven, probable, and possible cases of IA using the consensus case definition published by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG).[30] Although these definitions were developed for immunocompromised patients with cancer, in the present study they included all patients who fulfilled the necessary criteria.

''Proven'' was defined as histology showing *Aspergillus* sp hyphal tissue invasion in a site with evidence of tissue damage or positive *Aspergillus* sp culture from a normally sterile but clinically abnormal site. ''Probable'' was defined as a combination of positive *Aspergillus* sp culture or cytology from respiratory secretions in a patient with a clinically compatible picture and one of the host factors. ''Possible'' was defined as a combination of either positive *Aspergillus* sp culture or cytology or clinically compatible picture and one of the host factors.[30]

IA has a poor prognosis; in the patients who responded, there was a least a 50% chance of relapse with subsequent courses of immunosuppression. Thus, multiple readmissions with a primary or secondary diagnosis of aspergillosis are a definite possibility. In this study, only patients with newly diagnosed aspergillosis were included. Incidence rates were calculated with patient-days as the denominator. The incidence rate ratio (IRR) was used to compare the effectiveness of HEPA filters between different ward groups.

The galactomanan assay, a serologic test for IA, was made available in SGH starting on July 9, 2007. The results from this test were not taken into account for the present study for various reasons, including its availability only in the later half of the study period and its suboptimal performance in patients receiving antifungal prophylaxis, patients with graft-versus-host disease, and recipients of a solid organ transplant.[3]

Statistical methods

Variables of interest were expressed as frequencies with percentages. Differences between groups were evaluated using the χ^2 test. The simultaneous contributions of several factors to the risk of IA were analyzed using multiple logistic regression models and the maximum likelihood ratio method. Analyses were performed using SPSS version 17 (SPSS Inc, Chicago, IL). A P value $<.05$ was considered significant.

RESULTS

A total of 134 cases of IA were diagnosed and managed during the study period in all ward groups in SGH. These include 6 cases of proven IA, 77 cases of

probable IA, and 51 cases of possible IA. All 51 cases of possible IA did not have microbiological confirmation but were diagnosed based on the presence of host factors, clinical signs, and radiologic features. The estimated annual incidence of IA in SGH was 10.59 per 100,000 patient-days for the year 2006, 10.29 per 100,000 patient-days for 2007, and 8.56 per 100,000 patient-days for 2008 (as of June).

In the wards in which portable HEPA filters were deployed (group I), the incidence of IA of 34.61/100,000 patient-days during the preinstallation period decreased to 17.51/100,000 patient-days during the postinstallation period ($P = .01$). The relative risk (RR) of IA in the preinstallation period compared with the postinstallation period was 1.98 (95% confidence interval [CI], 1.10-2.97). In wards with only fixed HEPA filters during the entire study period (group II), the incidence rate almost doubled during the study period. No change was seen in wards with no HEPA filtration (group III) (Table 1).

During the 31-month study period, there were 29,603 admissions in wards W42A, W54D, W55B, W56, W64E, and W72 (group I). A total of 52 patients developed IA (3 proven, 23 probable, and 26 possible cases) in these wards during the study period. Because these cases of possible IA formed a substantial proportion of the total cases (50%) and were not managed differently from proven or probable cases, we included them in our final analysis. The recent EORTC/MSG consensus statement also recommends considering the use of probable and possible IA diagnoses in epidemiologic studies.

A precise way to estimate the impact of portable HEPA filters would be to limit the study population to severely immunocompromised patients admitted in these wards. Because the present study is a retrospective study using an administrative database, evaluating how many of the 29,603 admissions in these wards met the host factor criteria set by the EORTC/MSG was impracticable. Thus, all admissions were taken into account.

Table 2 summarizes characteristics of the patients admitted to these wards during the preinstallation period (period I) and the postinstallation period (period II). The distribution of diseases during the 2 periods was not significantly different, with the sole exception of the number of diabetic patients admitted ($P < .00$).

Among other factors, patient age and sex, the underlying disease condition, and the duration of hospital stay could influence the effect of these portable HEPA filters on the development of IA. Our univariate analysis suggested no significant associations between age and sex and the occurrence of IA (Table 3).

Disease conditions were grouped in such a way that patients admitted with a malignant condition, all transplantation recipients, and patients with agranulocytosis as a discharge diagnosis formed a single susceptible group, and the remaining patients composed the reference comparison group. The patients in the susceptible group had a 7-fold greater risk of acquiring IA compared with the reference group (odds ratio [OR], 6.92; 95% CI, 3.97-12.06; $P < .00$). The longer the length of stay, the greater the risk of IA; in those with a stay exceeding 4 weeks, the risk was increased by about 83-fold (OR, 82.7; 95% CI, 31.64-216.65; $P < .00$). Although the length of stay depends heavily on underlying disease condition, an extended length of stay increases the risk of exposure to *Aspergillus* spores and thus the risk of acquiring IA.

In multivariate logistic regression analysis using all cases of proven, probable, and possible IA, the risk of acquiring IA was significantly lower in the presence of portable HEPA filters (adjusted OR [aOR], 0.49; 95% CI, 0.28-0.85; $P = .01$), adjusted for presence of an immunosuppressive condition and length of hospital stay (Table 4). There was no significant interaction between length of stay and the presence of an immunosuppressive condition. Patients who were admitted to these wards after the installation of portable HEPA units had an ~51% lower risk of acquiring IA. When the analysis was restricted to only the proven and probable cases, a nonsignificant reduction in risk of 16% was seen (aOR, 0.84; 95% CI, 0.39-1.84; $P = .67$) (Table 5).

DISCUSSION

Worldwide, the number of high-risk patients is constantly rising, as is the risk of IFIs. IFIs constitute a constant threat to these already-compromised patients. During the study period, the incidence rate of IA doubled in wards with fixed HEPA filters (group II), reflecting the worldwide trend. In contrast, in wards which portable HEPA units were deployed demonstrated a significant drop in incidence, of about 50%, in the postinstallation period. This intervention helped keep the overall incidence in check. The annual incidence of IA remained fairly constant during the entire study period in SGH.

A number of studies have demonstrated the efficiency of portable HEPA units in reducing indoor *Aspergillus* spore counts but have been inconclusive in terms of their ability to prevent the occurrence of IA. This is because the efficiency of these units depends to a large extent on other factors, including room configuration, unit placement, and the unit's ability to recirculate all of the room air. The present study was initiated to guide the decision making process regarding future purchase and deployment of these portable HEPA filtration units. Instead of limiting our study group to severely

Table 1. Incidence rates and RRs of IA in different ward groups during the study period

Ward group	Ward type	Incidence rate (per 1000 patient-days) Period I (December 2005 to November 2006)	Period II (December 2006 to June 2008)	*P* value	RR (95% CI)
Group I	Wards with portable HEPA filters deployed December 2006	0.35	0.17	.013	1.98 (1.11-3.51)
Group II	Wards with only fixed HEPA filters during the entire study period	0.16	0.31	.061	0.51 (0.28-0.93)
Group III	Wards with no HEPA filtration	0.088	0.075	.623	1.17 (0.44-3.10)

Table 2. Comparison of characteristics of patients admitted to group I wards (W42A, W54D, W55B, W56, W64E, and W72) in the preinstallation and postinstallation periods

Variable	Period I preinstallation	Period II postinstallation	*P* value
Total admissions	11,514	18,089	
Age, years			
0-39	1485	2141	.02
40-64	5729	8903	.60
65 and older	4300	7045	.65
Female sex, n (%)	4646 (40)	7204 (40)	.56
Length of stay, days			
0-7	7644	11723	.20
8-14	2394	3931	.12
15-28	1034	1682	.40
29 and above	442	753	.18
Diagnosis, n (%)			
All malignant neoplasms	849 (7.37)	1349 (7.46)	.80
All organ transplants	109 (0.95)	153 (0.85)	.37
Aplastic anemias/agranulocytosis	60 (0.52)	99 (0.55)	.77
Diabetes mellitus	626 (5.44)	776 (4.29)	.00
Opportunistic mycoses	6 (0.05)	21 (0.12)	.08
Unspecified immune deficiency	3 (0.03)	3 (0.02)	.58
Pyrexia of unknown origin	18 (0.16)	34 (0.19)	.53
Septicemias	51 (0.44)	84 (0.46)	.79
Systemic lupus erythematosus	25 (0.22)	22 (0.12)	.05
Cytomegalic inclusion disease	17 (0 .15)	16 (0.09)	.14
Others	9750 (84.68)	15,532 (85.86)	.43

NOTE. Values are frequencies in percent. *P* values of χ^2 test for heterogeneity in the distribution of factors between the 2 groups.

immunocompromised patients, we included all patients admitted to these wards and attempted to limit confounding due to the differences in level of immunosuppression by adjustment based on the discharge diagnosis. Such inclusion is in line with the view of many experts, who recommend the general housing of all patients in rooms equipped with HEPA filter units, even though this approach is expensive.

Published studies on the effectiveness of portable HEPA filters lack statistical significance, because they are limited to severely immunocompromised patients. Engelhart et al[26] studied the effect of 3 portable HEPA units in an 18-bed hematology-oncology unit over a 1-year period. They reported just a 33% reduction in spore count and no cases of IFI in patients housed in rooms with portable HEPA filters, but their findings were of no statistical significance. A systematic review by Eckmanns et al[21] also reported the impact of HEPA filtration on the incidence of IFI, with a pooled RR of 0.57 (95% CI, 0.13-2.53); however, in all of the studies selected for that review, the results were not statistically significant. Our study, with 48 units evaluated for more than 2-1/2 years, with 52 cases of IA, clearly overcomes this limitation. The ~51% reduction in incidence with an RR of 1.98 provides strongly evidence of the benefit of these units.

Mantadakis and Samonis[27] in a review paper supported the usefulness of HEPA filtration in reducing spore counts and reducing the risk of nosocomial IA, but questioned the cost-effectiveness of this preventive strategy using portable HEPA units. In our study, the use of portable HEPA units was associated with a significant reduction (~51%) in the incidence of IA. At SGH, each portable HEPA unit carried an installation cost of $900

Table 3. Analysis of the impact of patient characteristics and portable HEPA filters on the incidence rate of IA

Characteristic	OR (crude)	95% CI	*P* value
Sex			
Female	Ref		
Male	1.26	0.71-2.23	.426
Age, years			
0-39	Ref		
40-64	1.08	0.50-2.34	.837
65 and above	0.36	0.14-0.93	.035
Diagnosis			
Others	Ref		
With malignancy/posttrans-plantation/agranulocytosis	6.92	3.97-12.06	.000
Length of stay, days			
0-7	Ref		
8-14	4.29	1.36-13.52	.013
15-28	21.48	7.80-59.16	.000
29 and above	82.79	31.64-216.65	.000
Portable HEPA filters			
Absent	Ref		
Present	0.50	0.29-0.87	.014

Table 4. Logistic regression analysis of the impact of patient characteristics and HEPA filtration on the incidence rate of IA (including all proven, probable, and possible cases of IA)

Characteristic	aOR	95% CI	*P* value
Portable HEPA filters			
Absent	Ref		
Present	0.49	0.28-0.85	.011
Length of stay, days			
0-7	Ref		
8-14	4.43	1.41-13.98	.011
15-28	19.80	7.18-54.63	.000
29 and above	80.89	30.84-212.20	.000
Diagnosis			
Others	Ref		
With malignancy/posttrans-plantation/agranulocytosis	6.07	3.45-10.69	.000

NOTE. Sex, age, and the interaction term (diagnosis*length of stay) were excluded from the final model because *P* exceeded .05.

and an estimated annual maintenance cost of $500. The financial implications of managing IA have been well studied and documented.[31,32] The costs of treating affected patients are enormous. Besides the price of drugs, the cost of treatment includes the costs associated with prolonged hospitalization and treatment of complications, as well as with additional antifungal agents needed to compensate for primary treatment failure. Hospitalization accounts for the major share of the cost associated with preventing or treating IA.[33] Compared with patients without IA, patients with IA have an average excess duration of hospitalization of 12.3 days and an excess cost of hospitalization of $51,779.[33] Thus, the deployment of portable HEPA units is a very cost-effective strategy.

Like all hospitals, SGH undergoes constant infrastructural changes, involving numerous construction projects and renovations in close proximity to hospital wards. Construction work or renovation activities within the hospital or in surrounding areas are considered the most common (49.1%) probable or possible sources of nosocomial aspergillosis outbreaks, followed by a contaminated or defective air supply system (17%).[9,26,34] SGH did not experience any nosocomial aspergillosis outbreaks during the study period, however. This might be attributed to the stringent guidelines applied to involved agencies and the preventive measures taken in accordance with the hospital's infection control policy. The preventive measures included a formal risk assessment involving facilities directorate staff, clinical directors, and the infection control team. Construction activities around the hospital followed certain predefined guidelines aimed at ensuring a safe environment for at-risk patients (eg, heavy-duty plastic sheeting to seal off dust-generating areas, sealing of windows overlooking external building sites).[35] The protection of these vulnerable patients will depend on the acceptance and effectiveness of these measures,

Table 5. Logistic regression analysis of the impact of patient characteristics and HEPA filtration on the incidence rate of IA (including only proven and probable cases of IA)

Characteristic	aOR	95% CI	*P* value
Portable HEPA filters			
Absent	Ref		
Present	0.84	0.39-1.84	.666
Length of stay, days			
0-7	Ref		
8-14	3.11	0.78-12.48	.109
15-28	19.08	6.07-60.01	.000
29 and above	28.93	8.45-99.01	.000
Diagnosis			
Others	Ref		
With malignancy/posttrans-plantation/agranulocytosis	2.79	1.12-6.99	.028

NOTE. Sex, age, and the interaction term (diagnosis*length of stay) were excluded from the final model because *P* exceeded .05.

which will require a high level of commitment, understanding, and cooperation from all personnel involved.

The CDC has recommended the use of portable HEPA filters for the prevention of nosocomial IA under certain circumstances in hospitals meeting certain requirements. These include filtration rates in the range of 300-800 ft^3/min, the ability to recirculate all or nearly all of the room air, the ability to provide $\geq$12 air changes/hour, a filtration efficiency of 99.97 % at 0.3 microns, and verification of filter performance by appropriate particle testing. We must ensure that fresh-air requirements for the area are fulfilled and that the units are located appropriately to filter all of the room air.[34]

Other alternative strategies for creating a protective environment using mobile units that recycle and distribute treated air through a plenum over isolated zones are currently under evaluation. Instead of simply filtering the air, these units destroy airborne molds using cold-plasma reactors.[36]

Several limitations of our study must be noted. First, like any retrospective study, this study depends heavily on accurate medical records. Second, the study population included all patients admitted to the wards belonging to group I. Ideally, it should have been confined to severely immunocompromised patients, the population at high risk for IA. Because this was a retrospective study, with data extracted from an administrative database, such a clear selection of cases or adjustment for the level of immunosuppression was not feasible. Our adjustment in logistic regression by grouping patients with a malignancy, transplantation recipients, and patients with a diagnosis of agranulocytosis represented only an effort to address this issue to some extent; thus, our effect estimates are only a guide to help hospital administrators evaluate the benefits of deploying these units. Third, determining whether a case of IA was acquired inside or outside the hospital was difficult. Because there is no consensual definition of facility-acquired IA, we restricted the IA cases included by using delay criteria, in accordance with most published studies of nosocomial IA. Finally, there was no information on the antifungal prophylaxis protocol used during the study period. Any change, such as the introduction of a newer or more effective systemic antifungal, could have influenced the results. We identified no such change in the prophylaxis protocol. The wards admitted patients from different specialties, including renal medicine, hematology, cardiothoracic surgery, nephrology, medical oncology, and otolaryngology, and a change in protocol would not have been uniform across all of these.

In summary, the installation of portable HEPA filtration units in certain wards as an adjunct infection control measure resulted in a significant drop in the number cases of nosocomial IA in these wards. These portable filters are readily available, easy to install, efficient, and fairly inexpensive. Many of the newer HEPA units are fairly quiet, with sound levels $<$40 dB.[3] However, the benefits conferred by the portable units require appropriate maintenance and education of staff and patients.

Our findings support the effectiveness of portable HEPA filters in preventing IA in hospitals. The costs of widespread HEPA filtration will be more than offset by significant decreases in the rates of nosocomial infections in general and IA in particular. Studies restricted to severely immunocompromised patients, conducted over even longer periods, are needed.

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