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Review Article

Assessment of microbiological air quality in hemato-oncology units and its relationship with the occurrence of invasive fungal infections: an integrative review

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ABSTRACT

Worldwide aging of the human population has promoted an increase in the incidence of neoplasia, including hematological cancers, which render patients particularly vulnerable to invasive fungal infections. For this reason, air filtration in hemato-oncology units has been recommended. However, scarce literature has assessed the impact of microbiological air quality on the occurrence of fungal infections in this population. We performed an integrative review of studies in the MEDLINE database that were published between January 1980 and October 2012, using the following combinations of keywords: air × quality × HEPA, air × quality × hematology, and airborne fungal infections. The search yielded only 13 articles, suggesting that high-efficiency filtering of the ambient air in hemato-oncology units can prevent the incidence of invasive fungal infections. However, no randomized clinical trial was found to confirm this suggestion. Currently, there is no consensus about the maximum allowable count of fungi in the air, which complicates filtration monitoring, including filter maintenance and replacement, and needs to be addressed in future studies.

Keywords: Airborne fungal infections. Invasive aspergillosis. High-efficiency particulate air filter. Hematology. Bone marrow transplantation.

INTRODUCTION

The expansion of the elderly population is a worldwide phenomenon that is also occurring in Brazil, and with this expansion comes an increased incidence of neoplasia[1]. Cancer is now a major public health problem in Brazil and many other parts of the world. It is estimated that in this country, 1 in 3 women and 1 in 2 men will develop cancer during their lifetime[2].

Medullary neoplasias, particularly acute myeloid leukemia, are rarely diagnosed before age 40 but exhibit an exponential increase in incidence with age. The molecular and cellular mechanisms associated with this age-related increase remain poorly understood[3]. Hematopoietic stem cell transplantation has been a widely used alternative in the treatment of leukemias[4]. However, it is important to note that both the period of neutropenia prior to the grafting of these cells and chemotherapy-induced neutropenia involve intense immunosuppression of these patients, making these individuals susceptible to various infections that affect treatment outcomes[5]. Invasive fungal infections, particularly aspergillosis, are common in these patients and have high morbidity and mortality rates in immunocompromised patients[6].

In this context, the microbiological air quality in oncological units is important, particularly in the prevention of fungal infections. The Centers for Disease Control and Prevention recommends air filtration using high-efficiency particulate air (HEPA) filters[7]. The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)[8] also recommends that places designated as a *protective environment* be separated from the rest of the hospital and have a heating, ventilation, and air conditioning system with a HEPA filter that completes at least 12 full exchanges of air per hour[8].

The minimum acceptable limits for fungal growth in these units remain controversial. The SEIMC sets a limit of 0.5 CFU/m³ in the air of *protective environment* areas. This limit entails the detection of no more than one colony of filamentous fungi within a 2-m³ sample of air. This recommendation is justified by evidence that concentrations as low as 1 CFU/m³ can cause infection in high-risk patients. However, it has also been suggested that studies be conducted at individual centers to first determine the normal concentrations and then detect significant increases[8].

Given that this topic is scarcely discussed and controversial in the literature and that there is no consensus on the safety limits

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for air filtration, this study aimed to review the literature on air quality and its association with fungal infections in hemato-oncology patients.

GENERAL OBJECTIVE

To review the literature on air quality and its association with fungal infections in hemato-oncology patients.

SPECIFIC OBJECTIVES

1) To identify the impact of air filtration on the incidence of invasive aspergillosis in patients with hemato-oncological cancers during restructuring periods. 2) To identify the impact of air filtration on the routine incidence of invasive aspergillosis in patients with hemato-oncological cancers outside of restructuring periods. 3) To identify the maximum fungal concentration in HEPA-filtered air above which there would be a correlation between the fungal concentration and an increased incidence of aspergillosis.

METHODS

This study is an integrative review of the literature, which is an approach that can make research results more accessible, reduce certain barriers to the use of scientific knowledge, and enable a reader to gain access to various surveys conducted in a single study[9]. The main question in this integrative review was *What scientific knowledge is there regarding air quality and its association with fungal infections in hemato-oncology patients*?

This survey was conducted using the MEDLINE database and the following combinations of keywords: air × quality × HEPA, air × quality × hematology, and airborne fungal infections. The inclusion criteria established in this selection were the availability of full-text articles published between January 1990 and October 2012 in English or Portuguese that were primary studies focused on air quality and its association with fungal infections in adult hemato-oncology patients. Articles that discussed air filtration in operating rooms, patients with cystic fibrosis or asthma, or air quality in kindergartens and homes were excluded.

To collect the data, we used an instrument that allowed: 1) the identification of publications (title of the article and journal, main author, year of publication, and study sites); 2) the characterization of publications regarding the evaluation criteria in the studies (type of filter used); and 3) the characterization of methodological characteristics (type of study, study objectives, results, limitations, and conclusions).

RESULTS AND DISCUSSION

The final sample consisted of 13 articles. **Figure 1** describes the inclusion process, as recommended by the PRISMA flowchart[10].

Regarding the characterization of the studies' year of publication, **Figure 2** shows that the studies were first published in 1998; since 2009, no further studies have been published on this topic. We also observed that the distribution was homogeneous in the number of articles published, and no single year was divergent.

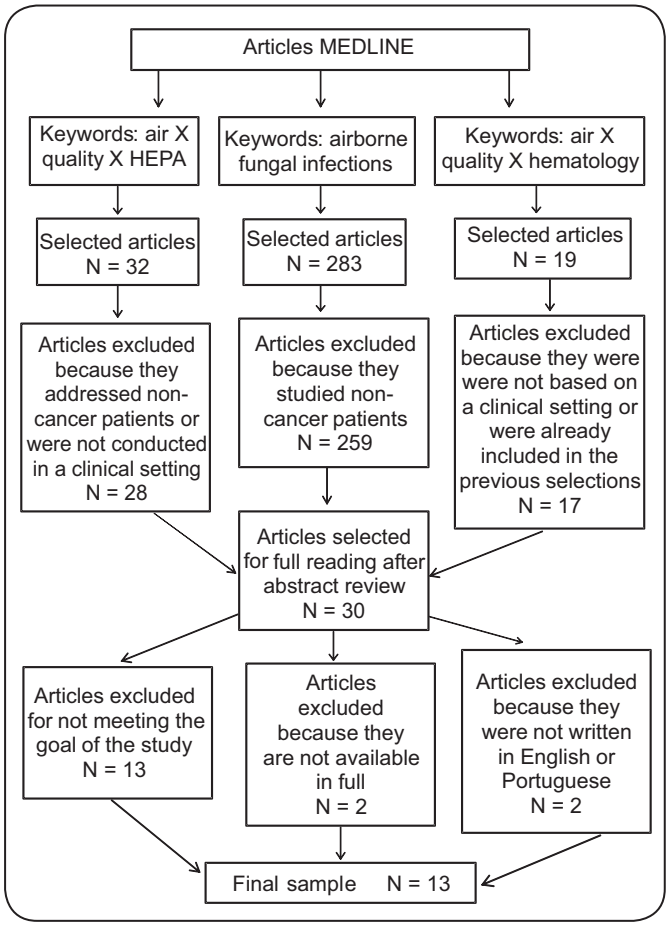

FIGURE 1 - Inclusion process for articles in the review. HEPA: high-efficiency particulate air.

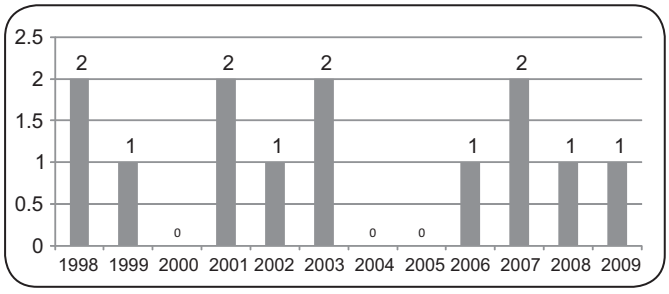

FIGURE 2 - Number of included articles in the review according to the year of publication.

An analysis of the articles enabled grouping according to the following subthemes: 1) effectiveness of HEPA filters in preventing invasive fungal infections in hemato-oncology patients during non-restructuring periods; 2) effectiveness of HEPA filters in preventing invasive fungal infections in hemato-oncology patients during restructuring periods; and 3) efficacy of HEPA filters in reducing the fungal concentration in the air in hemato-oncology units, without addressing patient outcomes.

Effectiveness of HEPA filters in preventing invasive fungal infections in hemato-oncology patients during non-restructuring periods: This subtheme included six studies[11-16], five[11-15] of which

showed a benefit for air filtration via reduced CFU values and a subsequent reduction in the number of fungal infections and/or decreased patient mortality after transplantation. However, Hospenthal et al.[16] questioned the impact of HEPA filters on the prevention of invasive aspergillosis. **Table 1** presents the core findings of these studies.

Effectiveness of HEPA filters in preventing invasive fungal infections in hemato-oncology patients during restructuring periods:

TABLE 1 - Results of studies evaluating the effectiveness of HEPA filters in preventing invasive fungal infections in hemato-oncology patients during non-restructuring periods.

Authors and year	Study population	Methods	Core results	Conclusions
Araújo et al., 2008[11]	221 hemato-oncology patients	Quasi-experimental study (before and after HEPA filter implementation)	Air fungal counts (from 22-278 to 7 CFU/m³) and fungal infections (from 6.6% to 4.9%) decreased after renovation and HEPA filter installation	HEPA filters were effective in reducing both the fungal concentration in the air and the incidence of fungal infections
Bénet et al., 2007[12]	356 intensive-care hemato-oncology patients	Quasi-experimental study (before and after HEPA filter implementation)	Invasive aspergillosis incidence decreased from 13.2% to 1.6% after HEPA filter installation	HEPA filters were effective in reducing the incidence of fungal infections
Hahn et al., 2002[13]	91 hemato-oncology patients with a baseline low risk of fungal infection	Outbreak investigation with a quasi-experimental intervention (before and after HEPA filter implementation)	During the outbreak, the *Aspergillus* air count was >150 CFU/m³. After HEPA filter installation, the count decreased to <4 CFU/m³, which controlled the outbreak	HEPA filters were effective in reducing both the fungal concentration in the air and the incidence of fungal infections
Alberti et al., 2001[14]	Bone marrow transplantation unit and two hematology wards	Retrospective cohort study comparing rooms with HEPA filters with rooms with conventional filters (less effective than HEPA filters)	Of all air samples, 1.1% were positive for *Aspergillus* spp. in rooms equipped with HEPA filters, whereas 6.7-9.4% were positive in rooms with conventional filters. The authors detected a correlation between air contamination and invasive aspergillosis	HEPA filters were effective in reducing the fungal concentration in the air, which was correlated with a reduction in the incidence of invasive aspergillosis
Passweg et al., 1998[15]	5,065 patients with leukemia who underwent allogeneic bone marrow transplantation	Quasi-experimental study (before and after HEPA filter implementation)	Post-transplantation mortality risk due to fungal infections was significantly lower after HEPA filter installation	HEPA filters were effective in reducing the incidence of fungal infections and in improving survival after transplantation
Hospenthal et al., 1998[16]	Oncology unit with HEPA filters	Prospective cohort study analyzing the incidence of invasive fungal infections among rooms with variable concentrations of conidia	The average fungal concentration was 1.8 CFU/m³ for *Aspergillus* spp., but individual samples reached concentrations as high as 11.6 CFU/m³. There were six cases of invasive aspergillosis during the study period	There was no association between the concentration of conidia and cases of invasive aspergillosis

HEPA: high-efficiency particulate air; CFU/m³: colony-forming units per cubic meter.

This theme included three studies[17-19] demonstrating that HEPA filters effectively reduced the fungal concentration in the air, thus possibly preventing cases of invasive fungal infections during restructuring periods. **Table 2** presents the main findings of these studies.

Efficacy of HEPA filters in reducing the fungal concentration in the air in hemato-oncology units, without addressing patient outcomes: This theme included four studies[20-23] that evaluated the efficacy of HEPA filters in reducing the fungal concentration in the air in hemato-oncology units but did not address patient outcomes. Two of the studies found that HEPA filter performance was no better than regular air filtration[20,21]. Another study found that HEPA filters effectively reduced the fungal concentration in the air but that water systems could be a source of *Aspergillus* spp., which are not completely eliminated by air filtration[22]. Finally, Cornet et al.[23] reported that HEPA filters did not effectively prevent air contamination by fungi during a construction period, unless combined with laminar airflow[23]. **Table 3** presents the core findings of these studies.

CONCLUSIONS

Scientific observations evaluating the microbiological air quality in hemato-oncology units and the relationship between air quality and the incidence of invasive fungal infections in patients admitted to these units are relatively scarce. Compounding this lack of data, we found no randomized controlled trials evaluating the effectiveness of the cited preventive measures, which was likely due to the serious ethical restrictions associated with such trials.

Taken together, the available studies suggest that there is a certain clinical benefit associated with the treatment of ambient air in hemato-oncology units using HEPA filters and positive pressure. However, the studies were subject to selection bias because most of the studies analyzed non-randomized patients,

TABLE 2 - Results of studies evaluating the effectiveness of HEPA filters in preventing invasive fungal infections in hemato-oncology patients during restructuring periods.

Authors and year	Study population	Methods	Main results	Conclusions
Nihtinen et al., 2007[17]	55 patients treated in a HEPA filter-equipped ward during a construction period	Prospective cohort study analyzing both the fungal concentration in the air and the incidence of invasive fungal infections	Despite an increase in the fungal concentration in the air outside of the ward (1-31 CFU/m^3), 31 of 33 air samples collected inside patients' rooms were negative for fungi. There were no new cases of invasive fungal infections during the construction period	HEPA filters were effective in reducing the fungal concentration in the air during a period of construction, thus preventing fungal infections
Kruger et al., 2003[18]	28 patients treated during construction and 652 patients treated outside of the construction period in a HEPA filter-equipped ward	Quasi-experimental design analyzing air contamination and the incidence of fungal infections before, during, and after a period of construction	Air samples yielded *Aspergillus* at a concentration of 0-2 CFU/m^3 before construction, 0-5 CFU/m^3 during construction, and 0 CFU/m^3 after construction. The incidence of invasive aspergillosis was similar between the three periods	HEPA filters provided effective protection against invasive aspergillosis, despite construction
Oren et al., 2001[19]	111 high-risk patients treated before and after HEPA filter installation	Outbreak investigation during a construction period, with a quasi-experimental intervention	The average air concentration of *Aspergillus* was 15 CFU/m^3 in the non-filtered period and 0.18 CFU/m^3 in the filtered period. The incidence of invasive aspergillosis was 50% before HEPA filters and chemoprophylaxis, 43% after amphotericin B prophylaxis, and 0% after HEPA filter implementation and continuing chemoprophylaxis	In a construction period, HEPA filters were more effective than amphotericin B in protecting patients against invasive aspergillosis.

HEPA: high-efficiency particulate air; CFU/m^3: colony-forming units per cubic meter.

TABLE 3 - Results of studies evaluating air filtration and performing a mycological analysis of the air in hemato-oncology units, without analyzing patients.

Authors and year	Study population	Methods	Main results	Conclusions
Crimi et al., 2009[20]	Two hematology units, only one of which was equipped with HEPA filters	Cross-sectional study addressing air contamination and its relationship with air filtration	No fungi were found in air samples, but bacteria were isolated from the air samples from the non-filtered unit	Both units performed equivalently regarding air contamination by fungi.
Crimi et al., 2006[21]	Two hematology units; one had central HEPA filters, and the other had a peripherally located HEPA filter	Cross-sectional study addressing air contamination and its relationship with the type of air filtration	The bacterial load in the air was higher in the central HEPA-filtered area, but no significant differences were observed in fungal load between the two areas	Both units performed equivalently regarding air contamination by fungi.
Anaissie et al., 2003[22]	Two hematology units with HEPA filters over a three-year period.	Observational study addressing air contamination by fungi and fungal sources. Samples for mycological culture from the air, environmental surfaces, and water systems were collected	The *Aspergillus* spp. air concentration in the bathrooms (2.95 CFU/m^3) was superior to that observed in patient rooms (0.78 CFU/m^3) and corridors (0.61 CFU/m^3)	HEPA filters were effective in reducing the fungal concentration in the air, but water systems can be a source of *Aspergillus* spp., which are not completely eliminated by air filtration
Cornet 1999[23]	Three hematology units equipped with HEPA filters alone (unit A1) or with HEPA filters and laminar airflow (unit A2) or a non-filtered area (unit B)	Prospective cohort study analyzing the concentration of fungi prior to, during, and after a period of construction in the three units	Overall, a major increase in fungal concentration was detected in air samples collected during a construction period from units A1 and B, but not from unit A2, which had no air cultures that were positive for *Aspergillus* spp. Fungal infections were not assessed	HEPA filters alone were not effective in preventing air contamination by fungi during a construction period but were effective when combined with laminar airflow

HEPA: high-efficiency particulate air; CFU/m^3: colony-forming units per cubic meter.

and several of the investigations were performed in specific restructuring situations. Moreover, invasive fungal infection is an outcome related to many other risk factors, including the following: the degree of immunosuppression induced by either a hematologic disease and/or its treatment; comorbidities, including previous pulmonary diseases; the use of anti-fungal prophylaxis; and the microbiological quality of the tap water in the units. Thus, from a scientific perspective, one cannot be sure that the benefits observed in the cited studies were strictly related to air filtration.

It is important to highlight that HEPA filter installation alone is likely insufficient to guard against infection; proper maintenance must also be performed. If any preventive benefit is actually associated with the use of this type of system, this benefit will likely occur only when the equipment is operated according to the manufacturer's recommendations, using unsaturated filters. Larger doubts remain regarding the maximum allowable count of fungi in the air because levels vary widely between studies. This lack of consensus makes it difficult to estimate a cutoff above which we can establish a direct association with the incidence of fungal infections. We believe that this issue should be addressed by future studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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