MAJOR ARTICLE

The Influence of High-Efficiency Particulate Air Filtration on Mortality and Fungal Infection among Highly Immunosuppressed Patients: A Systematic Review

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Background. Patients with hematological malignancies who are treated with intensive chemotherapy or who receive bone marrow transplants are exposed to an increased risk of developing nosocomial fungal infections. The aim of this systematic review was to compare the effectiveness of high-efficiency particulate air (HEPA) filtration with that of non-HEPA filtration in decreasing the rates of mortality and fungal infection among patients with diagnosed hematological malignancies and neutropenia or among patients with bone marrow transplants.

Methods. Articles identified in a Medline search, guidelines, and books, as well as the bibliographies of review articles, monographs, and the articles identified by Medline, were researched. Randomized trials and observational studies comparing HEPA filtration with conventional room ventilation were selected for inclusion in the present review.

Results. Sixteen trials (9 with death as an outcome and 10 with fungal infection as an outcome) that compared HEPA filtration with non-HEPA filtration were selected for meta-analyses. We discovered no significant advantages of HEPA filtration in the prevention of death among patients with hematological malignancies with severe neutropenia in randomized controlled trials (RCTs; relative risk [RR], 0.86 [95% confidence interval {CI}, 0.65–1.14]) and in studies of a lower standard (non-RCTs; RR, 0.87 [95% CI, 0.60–1.25]).

Conclusions. The placement in protected areas of patients with hematological malignancies with severe neutropenia or patients with bone marrow transplants appears to be beneficial, but no definitive conclusion could be drawn from the data available.

Fungal infections are a major complication of severe neutropenia brought on by the treatment of hematological malignancies [1], and they are associated with high mortality rates [2, 3]. High environmental *Aspergillus* spore counts constitute a major risk for infection after inhalation of the spores [4, 5]. Therefore, patients with acute lymphocytic leukemia, acute nonlymphocytic leukemia, aplastic anemia, or cancer who are being treated with chemotherapy or are receiving bone marrow transplants (BMTs), thereby developing severe neutropenia, are often placed in rooms with high-efficiency particulate air (HEPA) filtration, with or without laminar airflow (LAF) [6]. HEPA filtration leads to a significant decrease in the number of microorganisms in the air, whereas LAF increases air change in the cleanest zone, which is why both measures are frequently combined. Krüger et al. [6], in a survey of various practices of infectious disease prevention and management during hematopoietic stem cell transplantation, found that only 16.5% of the patients receiving autologous BMTs and 5.3% of the patients receiving allogeneic BMTs did not receive special accommodation.

To be highly protected, patients are confined to a room, and persons who enter the room have to wear masks and gowns. This may be why there were some studies that reported a high frequency of mental dis-

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turbance among patients with BMTs during the course of their isolation [7, 8].

In 4 guidelines from the Centers for Disease Control and Prevention (CDC), the installation of HEPA filters according to category BIII or IB is recommended [9–12]. However, the guidelines refer to only a small number of studies and, in part, only to outbreaks. There are more studies that examine the influence of protective environment on fungal infection and mortality than are mentioned in the recommendations.

There has been a trend toward relaxing the degree of patient isolation, in the absence of definitive data to support its use [13]. Because the protective environment regimen is expensive and is a burden on patients, and because there is still no systematic review of HEPA filtration available, we conducted a systematic review to investigate whether HEPA filtration reduces the risk of death and fungal infection for patients with hematological malignancies who have severe neutropenia or for patients with bone marrow transplants.

METHODS

Literature search. The type of literature that we selected for the present review included literature on randomized trials, cohort studies, case-control studies, and nonrandomized controlled trials (non-RCTs). In these trials and studies, the effectiveness of HEPA filtration, with or without LAF, was compared with that of standard ventilation of patient hospital rooms with no air filtration, with regard to identification of decreasing rates of death and fungal infection among patients with hematological malignancies who have neutropenia due to their illness or its treatment (i.e., chemotherapy or BMTs [no stem cell transplantation]) or among patients without cancer who have BMTs (no stem cell transplantation) for other reasons. Every study included both an intervention group of patients who were treated in rooms with HEPA filtration with or without LAF and a control group of patients who were treated in patient hospital rooms with standard ventilation. Each study had to have at least 1 type of outcome enabling measurement of mortality or fungal infection.

A Medline search of the literature published from 1 January 1966 through 30 June 2005 was performed. One or more of the following search terms were used: "LAF," "laminar airflow," "HEPA," "high-efficiency particulate," and "protect* environment" (where "*" denoted a wild card). The term or terms were then combined with ⩾1 of the following search terms: "BMT," "marrow transplant*" (where "*" denoted a wild card), and "chemotherapy." In addition, we searched for guidelines [9–12], related sections of books [14–16], and bibliographies of review articles, monographs, and articles identified in our initial search of the literature. We also established personal contact with experts in the field.

Literature selection. All the references that were identified were initially selected on the basis of their titles and/or abstracts. Full reports from potentially relevant publications were obtained and checked for eligibility for inclusion in the review. Decisions about whether to include trials were based on the completeness of the trials. Only randomized controlled trials (RCTs), non-RCTs, cohort studies, and case-control studies were considered. Because of differences in study design, RCTs were analyzed separately, and the results of observational studies and non-RCTs were dealt with in other analyses [17, 18]. In some of the studies, additional prevention measures were investigated, because these studies were 3- and 4-arm studies. Studies were only considered for inclusion if the HEPA (intervention) and non-HEPA (control) groups had similar additional intervention measures.

On the basis of outcome and study design, the studies that were identified were categorized into 4 groups, as follows: (1) RCTs with death due to all causes as an outcome; (2) RCTs with fungal infection (invasive aspergillosis and non-*Candida* fungal infection were among the infections considered to be fungal infection) as an outcome; (3) non-RCTs with death due to all causes as an outcome; and (4) non-RCTs with fungal infection as an outcome. Because of the 2 different outcomes assessed, it was decided to perform 2 meta-analyses for each study design. If a study assessed both outcomes, then it was included in 2 meta-analyses.

Data collection and analysis. Two investigators assessed the methodology used in each trial individually and then extracted the information required. Differences in the data extracted were resolved together by the investigators. From each study, we extracted source details (authors, country and city where the study was performed, and year of publication), study information (design and outcome[s] assessed), patient information (number of patients evaluated, diagnosis received, therapy received, and age), intervention (type of protected area and additional intervention used), duration of follow-up, time in the protected area, and outcome (fungal infection and/or death).

The random-effects method was used to derive a summary estimate, as implemented in Stata software (version 7.0; Stata) [19]. Protective effects (with 95% confidence intervals [CIs] and heterogeneity testing) were calculated.

RESULTS

Literature search. Figure 1 shows the route of identification of relevant articles. Of a preliminary total of 923 articles identified by a Medline search and an additional 25 articles identified by a hand search, only 64 were retained after the titles and abstracts were read, and then only 16 were retained after the full articles were evaluated. Although the 923 articles were identified through an extensive search strategy, the majority of articles focused on topics other than air filtration and patients with neutropenia. The 48 studies that were excluded were mainly

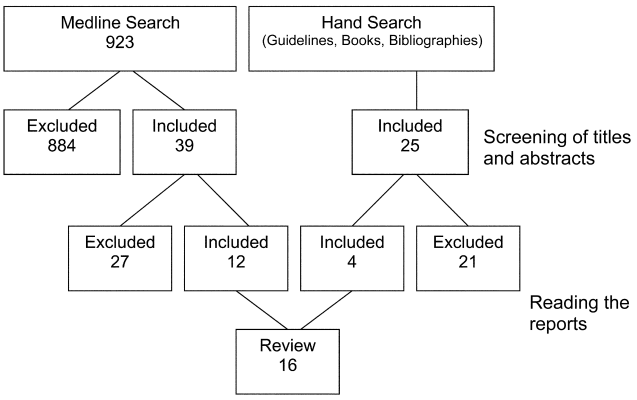

Figure 1. Route of references collected from Medline, guidelines, books, and bibliographies

nonsystematic reviews, descriptions of outbreaks, and studies that dealt with the problem on a technical level. Appropriate numerical data or figures were missing from some studies.

An advantage for the use of air filtration was suggested by one study that did address our question and criteria but did not contain valid data [20]. The other study of a similar nature suggested no advantage [21].

There are 2 additional important reasons for the exclusion of preselected articles. First, some studies that examine the influence of air filtration on fungal infection and death among immunosuppressed patients contain contradictions between the text and a figure [20] or a figure and a table (see [21] for a contradiction regarding death as an outcome). Because the studies in question were older, we decided not to ask their authors for clarification, and we therefore did not consider the studies for inclusion in the review. Second, 2 research centers (Seattle and Houston) in the United States were the main sources of the discussion of the use of air filtration for immunosuppressed patients in the 1970s and 1980s. There were 5 studies (31%) from Seattle alone in our meta-analyses. However, because there were patients who were included in >1 study, one study was of no use in the meta-analysis (i.e., the patients in the study of Freireich et al. [22] were a subgroup of the patients in the study of Rodriguez et al. [23], and, therefore, the study of Freireich et al. [22] was excluded). Another study was only partially useful, because the patients who had aplastic anemia diagnosed in the study of Buckner et al. [24] were a subgroup of the patients in the study of Storb et al. [25].

Literature selection. Six RCTs [24–29] and 3 non-RCTs [23, 30, 31] were considered for 2 meta-analyses with death as the outcome. The meta-analyses included 774 and 231 patients, respectively. Four RCTs [21, 24, 27, 32] and 6 non-RCTs [23, 33–37] were suitable for 2 meta-analyses with fungal infection as the outcome; the meta-analyses included 238 and 759 patients, respectively. Three of the studies [23, 24, 27] included both death and fungal infection as outcomes.

Table 1, which presents data from RCTs, and table 2, which presents data from non-RCTs, provide an overview of the basic features of the included studies that were heterogeneous with regard to various parameters. The publication dates of the studies span 28 years (from 1973 to 2001). The participants in the trials were patients with different kinds of acute leukemia and aplastic anemia, as well as patients who had received an unspecified BMT. In the trials, patient treatment consisted of chemotherapy (6 trials [37.5%]) [21, 23, 26, 27, 32, 37] and allogeneic and autologous BMT (9 trials [56.3%]) [24, 25, 28–31, 33–35]. In one trial, patient treatment consisted of both chemotherapy and allogeneic and autologous BMT [36]. Follow-up duration and additional measures differed partially. Time in a protected area was mentioned in only 6 studies (37.5%) [21, 24, 25, 27, 32, 33]. In 5 of these 6 studies, the time in a protected area was 50 days; in the other study [32], this time was 29 days. One study investigated mainly children [31], whereas the other studies investigated mainly adults. In the study of Rhame et al. [34], the protected area was established through in-room HEPA units, and, in the study of Oren et al. [37], the protected area was established through the use of HEPA filtration without LAF. All other protected areas were provided with HEPA filtration with LAF. In no study was the sample size calculated.

In the study of Rodriguez et al. [23], patients were only randomized to a protected environment when a unit was available. If all the units were occupied, patients were treated in rooms without HEPA filtration. Because of this severe methodological flaw in randomization, this study was considered to be a non-RCT. Some of the patients included in the study of Navari et al. [33] were not randomized. This study was also counted as a non-RCT. Of the remaining 6 non-RCTs, 5 were cohort studies, and the study of Schmeiser et al. [30] was an interventional trial.

In some studies, only subgroups of patients were considered for the meta-analyses, because comparison of protected and nonprotected areas was possible only for the subgroups considered (table 1 and table 2). In the study of Yates et al. [26], information about death as an outcome in relation to a protected environment was available solely for 1 subgroup of the patients included. These data were used in the meta-analysis. In the study of Buckner et al. [24], which had death as an outcome, only patients with acute leukemia were considered for inclusion, because the more extensive study of Storb et al. [25] included patients with aplastic anemia.

Data analysis. Table 3 shows results of the single trials and the pooled relative risks (RRs) for studies with death as the outcome. The mortality rates in the 9 studies varied between 8% and 86%. Five of 9 studies suggested a decrease in the mortality rate. Four of 6 RCTs showed some advantage associated with the use of HEPA filtration with LAF (pooled RR, 0.86 [95% CI, 0.65–1.14]).

Table 1. Characteristics of 8 randomized controlled trials included in the meta-analyses.

Authors, year of publication [reference]	Location	Outcome	Clinical condition(s) of participants	Therapy received	Portion of participants considered[a]	Follow-up duration	Additional therapy received
Levine et al., 1973 [27]	Bethesda, MD	Fungal infection and death	Acute leukemia	Chemotherapy	Patients in 2 of 3 study arms	50 days	Topical or orificial antiseptics and antibiotics
Yates et al., 1973 [26]	Buffalo, NY	Death	Acute myeloid leukemia	Chemotherapy	A portion of the patients evaluated	Not mentioned	Partial gut sterilization
Schimpff et al., 1975 [21]	Baltimore, MD	Fungal infection	Acute myeloid leukemia	Chemotherapy	Patients in 2 of 3 study arms	120 days	Oral nonabsorbable antibiotics
Buckner et al., 1978 [24][b]	Seattle, WA	Fungal infection and death	Aplastic anemia plus acute leukemia; acute leukemia only	BMT	For fungal infection as the outcome, all participants; for death as the outcome, a portion of the participants	6 months to 4 years	Oral nonabsorbable antibiotics[c]
Lohner et al., 1979 [32]	Brussels, Belgium	Fungal infection	Acute leukemia, agranulocytosis, lymphosarcoma	Chemotherapy	All	Not mentioned	Oral nonabsorbable antibiotics
Storb et al., 1983 [25]	Seattle, WA	Death	Aplastic anemia	BMT	All	16 months to 11 years	Oral nonabsorbable antibiotics[c]
Petersen et al., 1987 [29]	Seattle, WA	Death	All diseases that make BMT necessary	BMT	All	100 days	Prophylactic systemic antibiotics
Petersen et al., 1988 [28]	Seattle, WA	Death	All diseases that make BMT necessary	BMT	Patients in 2 of 4 study arms	30 days	Prophylactic systemic antibiotics or nonabsorbable antibiotics

NOTE. BMT, bone marrow transplantation.

[a] For inclusion in the meta-analyses.

[b] When death was the study outcome, we considered only patients with acute leukemia, because the other patients were included in the study of Storb et al. [25], which was published 5 years after the study of Buckner et al. [24].

[c] Received only by patients in the intervention group.

Table 2. Characteristic of 8 nonrandomized controlled trials included in the meta-analyses.

Authors, year of publication [reference]	Location	Outcome	Clinical condition(s) of participants	Therapy received	Portion of study participants considered[a]	Follow-up duration	Additional therapy received
Rodriguez et al., 1978 [23][b]	Houston, TX	Fungal infection and death	Acute leukemia	Chemotherapy	All	10 months to 4 years	Oral antibiotics and systemic antibiotics
Navari et al., 1984 [33][c]	Seattle, WA	Fungal infection	Aplastic anemia	BMT	Patients in 2 of 3 study arms	100 days	None
Rhame et al., 1984 [34]	Minneapolis, MN	Fungal infection	All diseases that make BMT necessary	BMT	All	Not mentioned	Oral nonabsorbable antibiotics[d]
Sherertz et al., 1987 [35]	Gainesville, FL	Fungal infection	All diseases that make BMT necessary	BMT	All	>50 days	None
Schmeiser et al., 1988 [30][e]	Ulm, Germany	Death	All diseases that make BMT necessary	BMT	All	Not mentioned	Total decontamination
Gamillscheg et al., 1991 [31]	Graz, Austria	Death	Aplastic and sideroblastic anemia; hematological and solid malignancies	BMT	All	10 months to 12 years	Total decontamination
Withington et al., 1998 [36]	Christchurch, New Zealand	Fungal infection	All diseases that make BMT necessary	BMT and chemotherapy	Patients from 2 of 3 study periods	Not mentioned	Prophylactic intranasal amphotericin (selective)
Oren et al., 2001 [37]	Haifa, Israel	Fungal infection	AML and ALL	Chemotherapy	Patients in 2 of 3 study arms from 1 of 3 periods	Not mentioned	None

NOTE. ALL, acute lymphatic leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplantation.

[a] For inclusion in the meta-analyses.

[b] Patients were only randomized to be placed in a protected environment when a unit was available. If all units were occupied, patients were placed in hospital rooms with standard ventilation. Hence, this study was counted as a nonrandomized controlled trial.

[c] Some of the patients who were included in the study were not randomized.

[d] Received only by patients in the intervention group.

[e] The study is an interventional trial.

Table 3. Results of meta-analyses of studies with death as the outcome.

Authors, year of publication [reference]	Patients in rooms with HEPA/LAF ventilation, no.		Patients in rooms with no ventilation system, no.		Total patients, no.	RR (95% CI)	Mortality rate, %		
	Who died	Who survived	Who died	Who survived			With HEPA/LAF ventilation	Without ventilation	Overall
RCTs with death as the outcome									
Yates et al., 1973 [26]	11	24	17	35	87	0.96 (0.51–1.78)	31	33	32
Levine et al., 1973 [27]	1	21	9	29	60	0.19 (0.03–1.42)	5	24	17
Buckner et al., 1978 [24]	23	6	25	2	56	0.86 (0.69–1.06)	79	93	86
Storb et al., 1983 [25]	5	34	28	63	130	0.42 (0.17–1.00)	13	31	25
Petersen et al., 1987 [29]	13	36	12	38	99	1.11 (0.56–2.18)	27	24	25
Petersen et al., 1988 [28]	13	128	15	186	342	1.24 (0.61–2.51)	9	7	8
All	66	249	106	353	774	0.86[a] (0.65–1.14)	21	23	22
Non-RCTs with death as the outcome									
Rodriguez et al., 1978 [24]	39	24	69	13	145	0.74 (0.59–0.91)	62	84	74
Schmeiser et al., 1988 [30]	1	25	0	15	41	1.78 (0.08–41.1)	4	0	2
Gamillscheg et al., 1991 [31]	16	9	11	9	45	1.16 (0.71–1.91)	64	55	60
All	56	58	80	37	231	0.87[a] (0.60–1.25)	49	68	59

NOTE. CI, confidence interval; HEPA, high-efficiency particulate air; LAF, laminar airflow; non-RCT, nonrandomized controlled trial; RCT, randomized controlled trial; RR, relative risk.

[a] Pooled RR determined by the DerSimonian and Laird method.

The results for fungal infection as the outcome are shown in table 4. The rate of fungal infection was 2%–18%. Three of the RCTs reported no fungal infection among patients in the intervention group. Most (9 of 10) studies pointed to a decrease in the rate of fungal infection in association with the use of HEPA filtration or LAF. In 1 of the 4 RCTs with fungal infection as the outcome, an increased risk was noted (pooled RR, 0.57 [95% CI, 0.13–2.53]).

Forrest plots of the 6 RCTs that had death as an outcome and the 4 RCTs that had fungal infection as an outcome are shown in figure 2; the corresponding funnel plots are shown in figure 3. The funnel plots show no publication bias for death as an outcome, but they show a huge bias for fungal infection as an outcome.

All meta-analyses were calculated using the random-effects method, because the clinical heterogeneity of the studies suggests that the effect differs with each study. However, the test for statistical heterogeneity was not significant for any of the 4 meta-analyses ($P > .05$).

DISCUSSION

Of the 923 articles identified by a systematic search of the literature, only 16 were useful for analysis.

Rates of fungal infection and death. All the meta-analyses indicated a decrease in the rates of death or fungal infection in protected areas, but the result was significant only for non-RCTs for which fungal infection was an outcome. The statistical homogeneity was considerable (the results of tests of heterogeneity of the meta-analyses were all not significant). Even if all studies—RCTs and non-RCTs—with death as an outcome are included in one analysis, the result of the test of heterogeneity is not statistically significant ($P = .27$).

The huge differences in rates of infection and death between the studies are, in part, a consequence of study design, but there is, in fact, no satisfactory explanation. Only 3 of 10 studies with fungal infection as an outcome already had fungal infection noted in the intervention group. That would mean that all fungal infections that occurred during hospitalization were acquired in the hospital. This is unlikely, because the sinuses of the patients could have been colonized before admission to the hospital.

The funnel plot of the 4 RCTs with fungal infection as an outcome revealed publication bias. Studies that showed a small effect and no influence of ventilation on fungal infection are missing.

Heterogeneity of the studies. Although there is only little overall statistical heterogeneity in the results, the clinical heterogeneity is huge. We considered different kinds of studies. The patients in the trials had different underlying diseases, and their treatment programs were variable. Fungal infection as an outcome is the least common denominator for a range of outcome definitions. During the 28-year period during which the publications appeared (from 1973 to 2001), much with regard to study design, treatment, and technical equipment had, of course, changed. It is difficult to combine data from studies conducted during such a long period. Because only the 2 newest

Table 4. Results of meta-analyses of studies with fungal infection as the outcome.

Authors, year of publication [reference]	Patients in rooms with HEPA/LAF ventilation, no.		Patients in rooms with no ventilation system, no.		Total patients, no.	RR (95% CI)	Fungal infection rate, %		
	With fungal infection	Without fungal infection	With fungal infection	Without fungal infection			With HEPA/LAF ventilation	Without ventilation	Overall
RCTs with fungal infection as the outcome									
Levine et al., 1973 [27]	0	22	3	35	60	0.24 (0.013–4.48)	0	8	5
Schimff et al., 1975 [21]	0	24	1	18	43	0.27 (0.011–6.20)	0	5	2
Buckner et al., 1978 [24]	0	46	3	41	90	0.14 (0.0073–2.57)	0	7	3
Lohner et al., 1979 [32]	5	19	2	19	45	2.19 (0.47–10.1)	21	10	16
All	5	111	9	113	238	0.57[a] (0.13–2.53)	4	7	6
Non-RCTs with fungal infection as the outcome									
Rodriguez et al., 1978 [23]	3	60	9	73	145	0.43 (0.12–1.54)	5	11	8
Navari et al., 1984 [33]	0	36	1	30	67	0.29 (0.012–6.83)	0	3	1
Rhame et al., 1984 [34]	9	158	12	55	234	0.30 (0.13–0.68)	5	18	9
Sherertz et al., 1987 [35]	0	39	14	74	127	0.077 (0.0047–1.25)	0	16	11
Withington et al., 1998 [36]	0	51	1	63	115	0.41 (0.017–10.0)	0	2	1
Oren et al., 2001 [37]	0	26	13	32	71	0.063 (0.0039–1.02)	0	29	18
All	12	370	50	327	759	0.29[a] (0.15–0.54)	3	13	8

NOTE. CI, confidence interval; HEPA, high-efficiency particulate air; LAF, laminar airflow; non-RCT, nonrandomized controlled trial; RCT, randomized controlled trial; RR, relative risk.

[a] Pooled RR, determined by the DerSimonian and Laird method.

studies [36, 37] provide definitions of nosocomial aspergillosis, it now becomes clear why we cannot provide information regarding its definition.

In 4 studies [23–25, 31], the duration of follow-up for the different patients was between months and years, with the authors having set specific dates for follow-up analyses. The long follow-up times explain why, for 3 of these studies [23, 24, 31], mortality rates were 60%–86%. Because 2 of the 3 studies in the analysis were non-RCTs with death as an outcome, the mean mortality rate in non-RCTs was high (59%).

In the cohort study of Gamillscheg et al. [31], which had a historical control group, it was not considered appropriate to set a fixed date for follow-up analysis for all patients. It is more surprising that the control group with a much longer follow-up (2–12 years, compared with 10 months to 2 years of follow-up in the intervention group) had a lower mortality rate (55% vs. 64%).

Two important explanations for this heterogeneity in the mortality rate are probably the duration and severity of neutropenia. Only a small number of the studies mentioned the severity and duration of neutropenia, although immunosuppression was the constant underlying theme in all the studies.

In 3 studies, decontamination (with oral nonabsorbable antibiotics) was part of the intervention. A meta-analysis conducted by Cruciani et al. [38] indicated that routine gut decontamination was not effective in preventing infection-related death; we may, therefore, assume that the reduction in mortality and/or fungal infection was the result of isolation and not decontamination.

In 2 of the 16 studies, only HEPA filtration, without LAF, was used [34, 37]. Environmental studies [4, 39] showed differences between LAF and HEPA filtration. The reduction in the number of fungal infections in these 2 studies did not differ from that noted in other non-RCTs with fungal infection as an outcome.

Limitations of all the studies. Another important point is that none of the studies was blinded. In each study, the medical team, as well as the patients, were aware of whether or not the patients were situated in a protected area. No studies involved the appropriate control subjects, who should have been situated in rooms with air conditioning but without HEPA filters. Of course, in these trials, the benefit of freedom of movement for the patients, which supports well-being, would be lost.

The only existing information about ventilation concerns HEPA filtration with or without LAF. However, of course, problems like pressure, location of filters (terminal HEPA), and protection of individual rooms only or protection of the whole unit are of concern.

Other studies. Two multicenter studies supported the benefit of a protected environment [40, 41]. Fischer et al. [40] an-

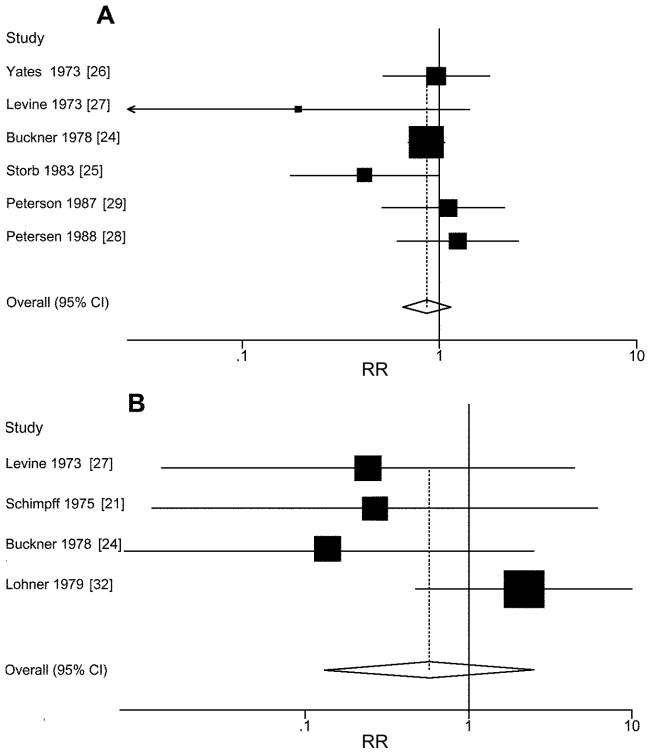

Figure 2. Forrest plot of relative risks (RRs) and 95% confidence intervals (CIs) for mortality *(A)* in 6 randomized controlled trials (RCTs) of air filtration and for fungal infection *(B)* in 4 RCTs of air filtration.

alyzed 183 patients from 15 European health care centers who had severe combined immunodeficiency and who had received BMTs. The RR for cumulative 2-year survival in a protected environment was 0.51 (95% CI, 0.37–0.69). This was a very specific group of patients who were not comparable to other patients who had also received BMT. Passweg et al. [41] analyzed 5065 patients (from 222 research teams) with leukemia who received BMT. The RR of survival after 1 year was 0.85 (95% CI, 0.78–0.92). This RR is similar to our results. Because of the large number of patients included in the study, the result is significant. It is not, however, possible to reproduce the allocation of the patients in the different centers, although this is an important factor for the outcome.

The epidemiological profile of *Aspergillus* infection in patients undergoing BMT at the Fred Hutchinson Cancer Research Center (Seattle, WA) between 1980 and 1987 and between 1987 and 1993 was analyzed in 2 retrospective cohort studies [42, 43]. During the first study period, the risk of *Aspergillus* infection was not significantly altered by methods of infection prevention, including the provision of a protective environment [42]. During the second study period, Wald et al. [43] analyzed the RR of infection for patients within 40 days after transplantation was performed. Transplantations performed outside protected environments were associated with a significantly increased risk of aspergillosis.

Existing guidelines. In 4 CDC guidelines, the installation of HEPA filters according to categories BIII or IB is recommended for immunosuppressed patients. These 4 guidelines present different categories for the use of HEPA filtration, although most of the references provided in the guidelines do not allow these conclusions. The recommendation in guidelines from 2000 for the prevention of opportunistic infections among hematopoietic stem cell transplant recipients [10] refers to 3 references [9, 34, 44] (table 5), with only one reference presenting data that provide evidence of a reduction in risk occurring in association with the use of special ventilation.

In the Healthcare Infection Control Practices Advisory Committee's 1997 guidelines for preventing nosocomial pneumonia, only staff education is included in category IA to prevent nosocomial aspergillosis [9]. This shows that definitive scientific studies are not available for any other measures. The guideline

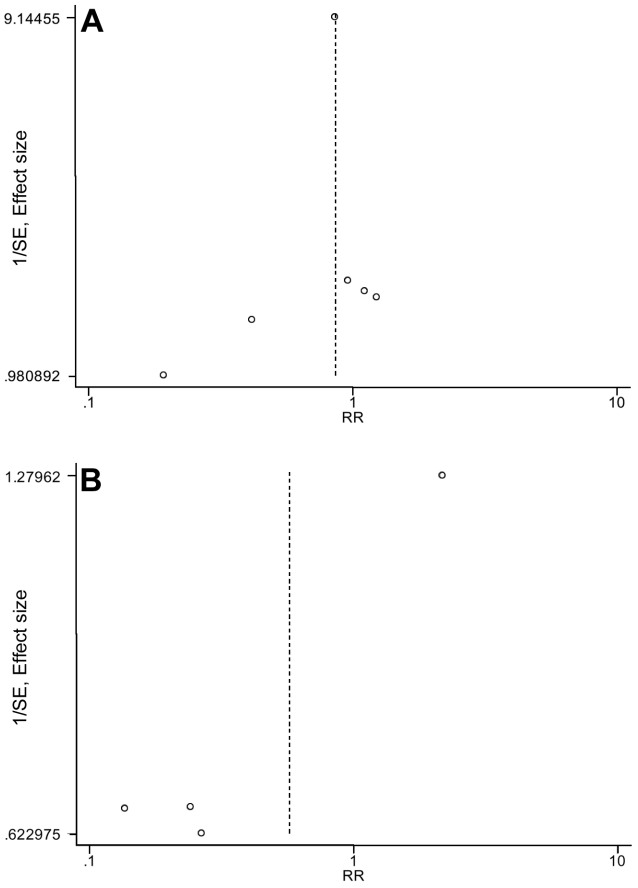

Figure 3. Funnel plot of precision (1/SE) against relative risk (RR) for mortality *(A)* in 6 randomized controlled trials (RCTs) of air filtration and for invasive fungal infection *(B)* in 4 RCTs of air filtration [17, 18]. Note: Panel *A* shows no publication bias, because the study with the biggest effect is shown exactly on the line of the overall RR, and because the smaller studies are symmetrical around the overall RR (symmetrical plot). Panel *B* shows an asymmetrical plot (publication bias); small studies have an RR of <1, and the study with the biggest effect has an RR of >1 (overall RR, slightly <1).

Table 5. Different guidelines of the Centers for Disease Control and Prevention (CDC) that recommend the installation of high-efficiency particulate air (HEPA) filters, categories of use, and the content of references included in the guidelines.

CDC guidelines	Category of HEPA filter use	References in guidelines and their content
Guidelines for the prevention of opportunistic infections in recipients of hematopoietic stem cell transplants [10]	BIII[a]	Guidelines for prevention of nosocomial pneumonia [9] Rhame et al. [34] were considered in the present review Opal et al. [44] conducted a study during hospital renovation
Guidelines for preventing nosocomial pneumonia [9]	IB[b]	Studies by Buckner et al. [24] and Sherertz et al. [35] were considered in the present review Murray et al. [45] and Streifel et al. [46] focused on technical data regarding the use of ventilation for controlling microbes Opal et al. [44] and Barnes et al. [47] conducted studies during hospital renovation Neither McWhinney et al. [48] nor Rogers [49] showed a reduction in mortality or fungal infection as a result of use of HEPA filtration
Guidelines for preventing health care–associated pneumonia [11]	IB[b]	Guidelines for environmental infection control in health care facilities [12] Studies by Sherertz et al. [35] and Oren et al. [37] were considered in the present review Thio et al. [50] conducted an investigation of an outbreak of invasive aspergillosis Rice et al. [51] focused on technical data regarding the use of ventilation for controlling microbes
Guidelines for environmental infection control in health care facilities [12]	IB[b] and IC[c]	2001 guidelines for the prevention of nosocomial pneumonia [9] 2001 guidelines for the design and construction of hospital and health care facilities [52] Siegler et al. [53] contributed a book section Studies by Buckner et al. [24] and Sherertz et al. [35] were considered in the present review Arnow et al. [54], Breton et al. [55], Guarro et al. [56], Burton et al. [57], Kyriakides et al. [58], McWhinney et al. [48], and Rhame [59] did not show a reduction in mortality or fungal infection resulting from the use of HEPA filtration Weems et al. [60], Barnes et al. [47], and Overberger et al. [61] conducted studies during hospital renovation Murray et al. [45] and Streifel et al. [46] focused on technical data regarding the use of ventilation for controlling microbes

NOTE. HEPA, high-efficiency particulate air.

[a] B: Strong or moderate evidence for efficacy, but only limited clinical benefit; generally recommended. III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

[b] IB: Strongly recommended for implementation and supported by certain experimental, clinical, or epidemiological studies and a strong theoretical rationale.

[c] IC: Required by state or federal regulation, or representing an established association standard.

refers to 8 references [24, 35, 44–49], with only 2 providing evidence that there is a reduction.

The 2004 guidelines for preventing health care–associated pneumonia [11] refer to 5 references, with 2 providing evidence that there is a reduction. The 2003 guidelines for environmental infection control in health care facilities refer to 17 references [9, 24, 35, 45–48, 52–61], including 2 studies that provide evidence in favor of the installation of HEPA filters.

Conclusion. Many experts recommend the general housing of patients in hospital rooms with HEPA filtration, although this approach is expensive. Even if it is feasible for the highest-risk patient groups for a limited period, it cannot be applied for all patients who are at risk for longer periods.

Therefore, the objective of this study was to deliver and present a systematic overview of data on the prevention of fungal infection and death by use of appropriate ventilation systems. In 1984, Armstrong stated, "The only place for protected environments today appears to be in a limited number of centers where carefully studies should be conducted" [62, p. 689]. Research scientists have rather missed the chance for conducting such studies. Only 2 additional RCTs have been performed since this statement appeared; both RCTs revealed no benefit of installing a protected environment. Because most centers now have special rooms for patients with neutropenia, a multicenter double-blinded RCT is not practicable, from the ethical viewpoint.

The results of these meta-analyses suggest that patients with hematological malignancies with severe neutropenia or patients with bone marrow transplants receive some benefit if they are placed in a protected environment. Nevertheless, the evidence is still somewhat ambiguous. Even if it does seem to be beneficial to place in protected areas patients with hematological malignancies and severe neutropenia or patients with bone marrow transplants, at present, no final conclusion can be drawn from the data available.

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