

Impact of passive humidification on clinical outcomes of mechanically ventilated patients: A meta-analysis of randomized controlled trials*

Ilias I. Siempos, MD; Konstantinos Z. Vardakas, MD; Petros Kopterides, MD; Matthew E. Falagas, MD, MSc, DSc

Objective: Previous meta-analyses reported advantages of passive (i.e., heat and moisture exchangers, or HMEs) compared with active (i.e., heated humidifiers, or HHs) humidifiers in reducing the incidence of ventilator-associated pneumonia, but they did not examine the effect of these devices on mortality, length of intensive care unit stay, and duration of mechanical ventilation. In addition, relevant data were recently published.

Design: Meta-analysis of randomized controlled trials comparing HMEs with HHs for the management of mechanically ventilated patients to determine the impact of these devices on clinical outcomes of such patients.

Methods: We searched PubMed and the Cochrane Central Register of Controlled Trials as well as reference lists from publications, with no language restrictions. We estimated pooled odds ratios (ORs) and 95% confidence intervals (CIs), using a random effects model.

Results: Thirteen randomized controlled trials, studying 2,580 patients, were included. There was no difference in incidence of

ventilator-associated pneumonia among patients managed with HMEs and HHs (OR 0.85, 95% CI 0.62–1.16). There was no difference between the compared groups regarding mortality (OR 0.98, 95% CI 0.80–1.20), length of intensive care unit stay (weighted mean differences, –0.68 days, 95% CI –3.65 to 2.30), duration of mechanical ventilation (weighted mean differences, 0.11 days, 95% CI –0.90 to 1.12), or episodes of airway occlusion (OR 2.26, 95% CI 0.55–9.28). HMEs were cheaper than HHs in each of the randomized controlled trials.

Conclusion: The available evidence does not support the preferential performance of either passive or active humidifiers in mechanical ventilation patients in terms of ventilator-associated pneumonia incidence, mortality, or morbidity. (Crit Care Med 2007; 35:2843–2851)

KEY WORDS: epidemiology; guidelines; infection control; health-care associated pneumonia

Warming and humidifying the gases delivered to patients under invasive mechanical ventilation (MV) is common practice because it prevents injury of the respiratory tract mucosa (1) and prevents ventilator-associated pneumonia (VAP). VAP, a common infection in the intensive care unit (ICU) (2), is associated with increased mortality (3), length of ICU stay, and healthcare costs (4).

Humidification of the inspired gases for the management of patients undergoing MV can be passive, performed by heat and moisture exchangers (HMEs) to allow condensation from the patient's expired air to be evaporated during inspiration, or it can be active, performed by heated humidifiers (HHs), in which the inspired gases pass across or over a heated water bath. An HME may be hydrophobic or hygroscopic (i.e., containing hygroscopic salts to improve moisture retention). An HME may also contain a filter (5) (i.e., a heat and moisture-exchanging filter). On the other hand, an HH may contain heated wire circuits to avoid formation of ventilator tubing condensate, which has been blamed for enhancing the risk for VAP development (6). It has been advocated that each of these humidification systems may have advantages in preventing VAP: HMEs by reducing contaminated condensate in the ventilator circuit, and HHs by preserving mucociliary clearance, because they can condition inspired gas to a

higher absolute humidity level than HMEs.

Although the passive operation and feasibility of HMEs have popularized their use in recent years, controversy exists about their advantage over HHs for the prevention of VAP. Indeed, in three systematic reviews (7–9), the authors stated that HMEs were associated with VAP rates that were either similar to or lower than VAP rates associated with HHs; however, these authors emphasized that the relevant evidence was inconclusive.

In 2003, Hess et al. (10) performed a meta-analysis of six randomized controlled trials (RCTs) (11–16) that compared HMEs with HHs for the management of patients undergoing MV; the combined effect from this analysis demonstrated a lower VAP incidence for the use of passive than active humidifiers. Even more recently (2005), Kola et al. (17) conducted a meta-analysis of this aspect by including eight relevant RCTs (11–16, 18, 19); these authors found a reduction in the incidence of VAP in patients managed with HMEs, particularly in

*See also p. 2875.

From Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece (IIS, KZV, PK, MEF); Critical Care Department, "Attikon" University Hospital, Athens, Greece (PK); Department of Medicine, Henry Dunant Hospital, Athens, Greece (MEF); and Department of Medicine, Tufts University School of Medicine, Boston, MA (MEF).

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: m.falagas@aibs.gr

Copyright © 2007 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/01.CCM.0000295302.67973.9A

patients ventilated for ≥ 7 days. However, the results of these two meta-analyses (10, 17) may have been affected by the large difference in outcomes in one of the included RCTs (15), a limitation clearly noted by Hess et al. (10). Also, these two meta-analyses (10, 17) did not examine the effect of the different methods of humidification on other, also important, outcomes, such as mortality, duration of mechanical ventilation, and ICU length of stay. One may agree that it is difficult to reconcile reduction in VAP risk due to an intervention with an absence of effect of the same intervention on the previously mentioned outcomes (20).

In the last few years, three additional large RCTs (21–23) on this issue have been published. Reporting conflicting results, these trials enhanced the debate about the preferential use of passive or active humidifiers. Thus, we endeavored to exploit the growing body of evidence to evaluate the comparative impact of passive (HMEs) and active (HHs) humidification on outcomes of patients undergoing MV, by performing a meta-analysis of relevant RCTs.

METHODS

Data Sources

This meta-analysis was conducted according to the guidelines from the Quality of Reporting of Meta-Analyses conference (24). To identify relevant RCTs, we systematically searched PubMed (until October 2006) and the Cochrane Central Register of Controlled Trials by using the following keywords: *pneumonia* and (*humidification* or *humidifier* or *exchangers* or *heat-and-moisture* or *heat and moisture exchangers*). The references of the initially identified RCTs were reviewed as well, although abstracts of conference proceedings were not sought.

Study Selection

Two of the authors (IIS and KZV) independently performed the literature search to locate potentially eligible reports. Only RCTs examining the role of a passive compared with an active humidifier for the management of adult patients undergoing MV and reporting on the clinical outcomes of such patients (namely VAP incidence, mortality, duration of MV or ICU length of stay) were considered for inclusion in this meta-analysis. There was no restriction on time and language of publication. RCTs reporting only on the mechanical effects of the different techniques of humidification, such as airway resistance, physiologic deadspace, and work of breathing, were not

included in the meta-analysis. In addition, we excluded reports providing information only on ventilator circuit colonization as well as those comparing two different passive or active humidifiers for the management of patients undergoing MV.

Data Extraction

Two reviewers (IIS and KZV) independently collected the following data from all eligible articles: study design, year of publication, type of ICU and study population, number of patients enrolled, severity of illness on ICU admission, type of passive or active humidification, and cultures required for confirmation of VAP diagnosis in each of the included RCTs. Data on incidence of VAP, mortality, length of ICU stay, duration of MV, episodes of airway occlusion, and cost associated with performance of these devices were also extracted from the selected articles. In addition, we individually assessed the following components: randomization, generation of random numbers, details of double-blinding procedure, information on withdrawals, and concealment of allocation to evaluate the methodological quality of each RCT according to a modified Jadad score (25). One point was awarded for the specification of each criterion; the maximum score for a study is 5.

Analyzed Outcomes and Definitions

Outcomes. The outcome measures for this meta-analysis were the incidence of VAP and the all-cause mortality during the study period (i.e., until a patient's death or ICU discharge) for the patients included in the selected RCTs. Length of ICU stay, duration of MV (until patient's death or extubation), episodes of airway occlusion (defined as those requiring an emergency reintubation), and cost associated with the use of humidification devices (calculated from the individual price of disposable equipment and the personnel time spent maintaining the equipment) were also used as outcomes for this meta-analysis.

Definition of VAP. Pneumonia was defined by clinical (fever or hypothermia, purulent tracheal secretions), laboratory (leukocytosis or leukopenia), and imaging (new and persistent infiltrate on chest radiograph) findings attributed by the authors of the RCTs to this infection. To be considered as ventilator-associated, these findings indicating pneumonia should have occurred in patients receiving MV for ≥ 48 hrs.

Data Analysis and Statistical Methods

Statistical analyses were performed using Review Manager (RevMan version 4.2.8; Copenhagen: Nordic Cochrane Center, Cochrane Collab-

oration, 2003). The heterogeneity between RCTs was assessed by using both the I^2 statistic and a chi-square test; $p < .10$ was defined to note statistical significance in the analysis of heterogeneity. Publication bias was assessed by the funnel plot method using Egger's test. Continuous outcomes were analyzed using weighted mean differences and 95% confidence intervals (CIs). Pooled odds ratios (ORs) and 95% CIs for all outcomes of this meta-analysis were calculated by using the DerSimonian-Laird random effects model (26).

RESULTS

Selected Randomized Controlled Trials

In Figure 1 we present a flow diagram describing the selection process applied to identify the pool of RCTs included in the meta-analysis. A PubMed search yielded 78 potentially relevant articles; four more reports that were not captured in this search were found through a review of the references of the retrieved articles. A search using the Cochrane Central Register of Controlled Trials did not reveal any additional relevant RCTs. Finally, 13 RCTs (11–16, 18, 19, 21–23, 27, 28) of the 82 initially located articles fulfilled the inclusion criteria for this meta-analysis.

Characteristics of the Selected Studies

In Table 1 we summarize the characteristics of the 13 RCTs (11–16, 18, 19, 21–23, 27, 28), involving 2,580 adult patients undergoing MV, included in the meta-analysis. The mean quality score of the included RCTs was 2.2 (range 1–3) and their mean sample size was 198 patients (range 56–381). In the majority of the selected RCTs, patients were eligible for inclusion if the duration of MV was >24 or 48 hrs. However, in two RCTs (23, 27) only patients undergoing MV for >5 days were enrolled. The compared groups of patients (i.e., those managed with HMEs and HHs) were similar at the time of ICU admission with respect to demographic characteristics and severity of illness in each of the RCTs included in the meta-analysis. The characteristics of humidifiers as well as the frequency of change of passive humidifiers and frequency of change of the ventilator circuit varied in the individual RCTs (Table 1).

Only in three (13, 16, 21) of the 13 (11–16, 18, 19, 21–23, 27, 28) selected

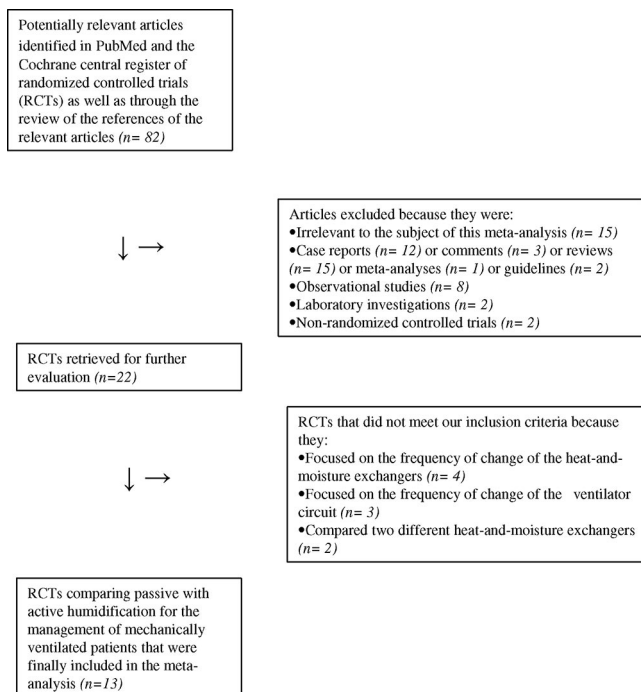


Figure 1. Flow diagram of the reviewed studies.

RCTs, risk factors for VAP (e.g., stress ulcer prophylaxis, enteral feeding, and sedation) were recorded. Patients with conditions that have been considered as contraindications for the use of passive humidifiers (such as hemoptysis, airway obstructive disease, hypothermia, requirement for high minute volume, bronchopleural fistula, and production of tenacious secretions) (5) were excluded from seven (14–16, 18, 21, 22, 28) of the RCTs included in our meta-analysis.

In the majority of the RCTs (11, 14–16, 18, 19, 22, 23, 27, 28) included in this meta-analysis, the presence of VAP was suspected by clinical, laboratory, and imaging findings, and it was confirmed by tracheal aspirates cultures. However, in one RCT (12) tracheal aspirates cultures were not required for the diagnosis of VAP, while in the remaining two RCTs (13, 21) VAP had to be confirmed by quantitative cultures of invasive respiratory specimens (i.e., protected brush or catheter specimen, or bronchoalveolar lavage) or by positive blood culture with the same microorganism isolated from blood and sputum specimens.

Incidence of Ventilator-Associated Pneumonia

In Table 2 we depict the outcomes studied in our study. Data regarding incidence of VAP in patients receiving

MV were reported in 12 (11–16, 18, 19, 21–23, 28) of the 13 RCTs included in the meta-analysis. There was no heterogeneity among the identified comparisons ($p = .13$, $I^2 = 0.33$, 95% CI 0–0.66). Publication bias was not detected (Egger's test $p = .69$). There was no difference in the incidence of VAP between patients managed with HMEs and those managed with HHs (OR 0.85, 95% CI 0.62–1.16, 2,341 patients). The ORs for VAP incidence in the individual RCTs, as well as the pooled OR, are presented in Figure 2.

Subgroup Analyses. A subgroup analysis was performed by including only the five RCTs (14, 16, 21–23) in which the used HH contained heated wire circuits. This analysis showed no difference in the development of VAP between patients undergoing MV managed with HMEs and those managed with HHs with heated wire circuits (OR 1.16, 95% CI 0.73–1.84, 1,267 patients). The subgroup analysis of the seven RCTs (11–13, 15, 18, 19, 28) in which heated circuits were not employed demonstrated that use of an HME was associated with fewer episodes of VAP than use of HHs without heated circuits (OR 0.61, 95% CI 0.42–0.90, 1,073 patients). Another subgroup analysis was carried out by including only the RCTs in which the mean duration of MV was >7 days (11–13, 15, 19, 21–23, 28); no differ-

ence was found in the incidence of VAP between patients managed with HMEs and HHs (OR 0.81, 95% CI 0.54–1.21, 1,812 patients). Finally, in three (21–23) of the seven (11–13, 15, 19, 21–23, 28) RCTs in which the mean duration of MV was >7 days, the used HHs contained heated wire circuits. Analysis of these three (21–23) RCTs revealed no difference between patients managed with passive and active humidifiers regarding the incidence of VAP (OR 1.32, 95% CI 0.65–2.68, 870 patients).

All-Cause Mortality

Eleven (11–13, 16, 18, 19, 21–23, 28) of the 13 RCTs included in the meta-analysis provided information regarding all-cause mortality. Ten (11–13, 18, 19, 21–23, 28) of these 11 RCTs reported data on ICU mortality, while the remaining RCT (16) reported on hospital (instead of ICU) mortality. Heterogeneity was not found among the comparisons ($p = .56$, $I^2 = 0$, 95% CI 0–0.64); in addition, publication bias was not detected (Egger's test $p = .88$). Use of HMEs was not associated with fewer deaths when compared with HHs (OR 0.98, 95% CI 0.80–1.20, 2,104 patients, Fig. 3).

There was no difference in mortality rate between the compared humidification systems in the RCTs in which HHs contained heated wire circuits (OR 0.90, 95% CI 0.69–1.18, 1,164 patients, data from four RCTs) (16, 21–23) or did not contain heated wire circuits (OR = 1.04, 95% CI 0.70–1.54, 1,158 patients, data from six RCTs) (11–13, 18, 19, 28).

Length of ICU Stay

Data regarding the length of ICU stay were available for six (12, 15, 16, 21, 22, 28) of the 13 RCTs included in this meta-analysis. There was no difference between HME and HH groups regarding this outcome (weighted mean differences, –0.68 days of ICU stay; 95% CI –3.65 to 2.30, 1,291 patients).

Duration of Mechanical Ventilation

All the RCTs (11–16, 18, 19, 21–23, 27, 28) included in the meta-analysis reported on the duration of MV. No difference was found between the compared groups with regard to this outcome (weighted mean differences, 0.11 days of MV; 95% CI –0.90 to 1.12, 2,397 patients).

Table 1. Main characteristics of the randomized controlled trials included in the meta-analysis (comparison of passive versus active humidification)

First Author (Reference No.)	Study Design/Year of Publication	Study Quality Score ^a	Type of ICU/Study Population	Exclusion Criteria Include Potential Contraindications for Passive Humidifier Use	No. of Patients Enrolled
Lorente (23)	SC RCT/2006	3	Medical-surgical/patients (18 yrs) requiring MV >5 days	No	120
Boots (22)	SC RCT/2006	2	General/patients requiring MV >48 hrs	Yes: airway hemorrhage, asthma, airway burns	381
Lacherade (21)	MC RCT/2005	3	Medical, surgical, neurosurgical/patients requiring MV >48 hrs	Yes: NA	369
Memish (19)	SC RCT/2001	2	Medical-surgical/patients (>18 yrs) requiring MV >48 hrs	No	243
Kollef (16)	SC RCT/1998	3	Medical-surgical/patients (>18 yrs) requiring MV	Yes: airway hemorrhage	322
Boots (18)	SC RCT/1997	1	General/patients (>18 yrs) requiring MV >48 hrs	Yes: airway hemorrhage, asthma, airway burns	116
Kirton (15)	SC RCT/1997	3	Trauma/patients (>15 yrs) requiring MV	Yes: requirement for high minute volume	280
Hurni (28)	SC RCT/1997	2	Medical/patients (>18 yrs) requiring MV >48 hrs	Yes: hypothermia	237
Branson (14)	SC RCT/1996	3	Medical-surgical/patients (18 yrs) requiring MV >24 hrs	Yes: airway hemorrhage, tenacious secretions, hypothermia	103
Dreyfuss (13)	SC RCT/1996	2	Medical/patients (>18 yrs) requiring MV >48 hrs	No	164
Roustan (12)	SC RCT/1996	1	General/patients requiring MV	No	116
Misset (27)	SC RCT/1991	2	Medical-surgical/patients requiring MV ≥5 days	No	56
Martin (11)	SC RCT/1990	1	General/patients requiring MV >24 hrs	No	73

ICU, intensive care unit; VAP, ventilator-associated pneumonia; SC, single center; RCT, randomized controlled trial; MV, mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation; HME, heat and moisture exchanger; HH, heated humidifier; HMEF, heat and moisture-exchanging filter; MC, multicenter; SAPS, Simplified Acute Physiology score; NA, not available/applicable; ISS, Injury Severity score.

^aAccording to a modified Jadad score; ^baccording to the authors.

Episodes of Airway Occlusion

Data on the episodes of airway occlusion requiring an emergency reintubation were provided in 11 RCTs (11–16, 18, 21, 22, 27, 28). Heterogeneity ($p = .11$, $I^2 = 0.49$, 95% CI 0–0.64) and publication bias (Egger's test $p = .62$) were not detected. Use of HMEs was not associated with more episodes of occlusion when compared with HHs (OR 2.26, 95% CI 0.55–9.28, 2,049 patients). However, one RCT (11) was terminated after the death of a patient in the HME group that was associated with complete occlusion of the endotracheal tube.

Cost

Only six (13–16, 18, 22) of the 13 selected RCTs reported on the cost asso-

ciated with the use of humidification devices. In each of these six RCTs, the cost associated with the use of HMEs was lower than the cost of HHs (data shown in Table 2).

DISCUSSION

The purpose of this meta-analysis was to evaluate the comparative impact of passive and active humidification on various clinically important outcomes in patients undergoing MV. The findings of this study suggest that there is no difference between patients managed with HMEs and those managed with HHs with regard to the incidence of VAP, mortality rate, ICU length of stay, duration of MV, and episodes of airway occlusion. One

may postulate that these findings are predictable as there is no relationship between the different modes of humidification and the cause of VAP.

Our results provide further support for the guidelines for the management of adults with hospital-acquired, ventilator-associated pneumonia and healthcare-associated pneumonia published in 2005 by the American Thoracic Society and the Infectious Diseases Society of America (29). In these guidelines, the authors concluded that HMEs cannot be regarded as a VAP prevention tool, because they have not been found to consistently reduce the incidence of VAP (29). On the other hand, the Canadian Critical Care Trials Group and the Canadian Critical Care Society in their published clinical

Table 1.—Continued

Severity of Illness on ICU Admission, mean \pm SD	Passive Humidifier/Frequency of Change of Passive Humidifier	Active Humidifier	Frequency of Change of the Ventilator Circuit	Cultures Required for Confirmation of VAP Diagnosis
APACHE II, 18.1 \pm 2.4 vs. 18.7 \pm 2.3	HME/every 48 hrs	HH with heated wire circuits	No routine change ^b	Tracheal aspirates
APACHE II, 20 vs. 19 or 20	HMEF (hygroscopic)/every 24 hrs	HH with heated wire circuits in both inspiratory and expiratory circuit limbs or in inspiratory limb only	Every new patient	Tracheal aspirates
SAPS II, 45.4 \pm 18.4 vs. 49.3 \pm 19.2	HMEF (hygroscopic)/every 48 hours	HH with heated wire circuits	Every new patient	Quantitative cultures of invasive respiratory specimens
APACHE II, 20.8 \pm 9.4 vs. 20.6 \pm 8.1	HME (hygroscopic)/NA	HH	NA	Tracheal aspirates
APACHE II, 17.0 \pm 6.9 vs. 18.2 \pm 6.3	HME (hygroscopic)/every week	HH with heated wire circuits	Every new patient	Tracheal aspirates
APACHE II, 19 vs. 18	HMEF (hygroscopic)/every 24 hrs	HH	HMEF group, every 2 days; HH group, every 2 or 4 days	Tracheal aspirates
ISS, 22 \pm 10 vs. 20 \pm 10	HMEF (hygrophobic)/every 24 hrs	HH	Every 7 days	Tracheal aspirates
SAPS, 12.9 \pm 5.1 vs. 12.8 \pm 5.0	HMEF (hygroscopic)/every 24 hrs	HH	HMEF group, every week; HH group, every 48 hrs	Tracheal aspirates
SAPS, 9 \pm 3 vs. 8 \pm 4	HME (hygroscopic)/every 24 hrs	HH with heated wire circuits	Every 7 days	Tracheal aspirates
SAPS, 16.0 \pm 4.9 vs. 16.4 \pm 5.3	HME (hygroscopic)/every 24 hrs	HH	Every new patient	Quantitative cultures of invasive respiratory specimens
SAPS, 11.5 \pm 4.9 vs. 11.5 \pm 4.8	HME (hygrophobic)/every 24 hrs	HH	NA	None
SAPS, 14 \pm 4 vs. 13 \pm 5	HME (hygrophobic)/every 24 hrs	HH	Every 8 days	NA
NA	HME (hygrophobic)/every 24 hrs	HH	Three times weekly	Tracheal aspirates

guidelines regarding the evidence-based clinical practice for the prevention of VAP (2004) advocated the use of HMEs, primarily on the basis of cost issues; however, these groups mentioned that only a slightly decreased incidence of VAP may be associated with the use of HMEs as opposed to HHs (30). Finally, in the most recent guidelines (2003) for preventing healthcare-associated pneumonia published by the Centers for Disease Control and Prevention (31) as well as those by the European Task Force on VAP (published in 2001) (32), the authors concluded that no recommendation can be established for the preferential use of either HMEs or HHs to prevent pneumonia in patients undergoing MV.

The findings of this meta-analysis are also supported by those of a recent large study (33) that was not designed as an RCT. Kranabetter et al. (33) compared the incidence of VAP in patients using

HMEs with a historical group using HHs and found no difference among the compared groups regarding this outcome. However, Kranabetter et al. (33) reported that in the subgroup of patients requiring MV for >2 days, use of HMEs was associated with lower VAP incidence compared with HHs.

On the other hand, the results of the present study contradict those of two previously published meta-analyses (10, 17) on the same issue. The inclusion of three recently published, relevant, large RCTs (21–23) involving 870 patients presumably explains this contradistinction. In all of these RCTs (21–23), the used HHs contained heated wire circuits. In a subgroup analysis that we performed, we found no difference in the development of VAP between patients managed with HMEs and HHs with heated wire circuits; in contrast, use of HMEs was found to be associated with fewer episodes of VAP than use of HHs

without heated circuits. Thus, it seems plausible that the inclusion of patients managed with HHs with heated wire circuits in our analysis may abrogate the advantage of HMEs over HHs demonstrated in the previous meta-analyses (10, 17).

The use of HHs has been associated with formation of ventilator tubing condensate that predisposes to VAP, according to several investigators (6, 7). In detail, the presence of tubing condensate has been blamed for allowing the bacteria that typically colonized the ventilator circuits to thrive (5). There is also the risk of spilling contaminated condensate accumulated in the tubing into the patient's respiratory tract while turning the patient or raising the bed rail (5, 21). However, new generations of HHs include heated ventilator circuits, which markedly reduce the formation of condensate; thus, the aforementioned unfavorable events are less likely to occur (4). Indeed,

Table 2. Outcome data of the randomized controlled trials included in the meta-analysis (comparison of passive vs. active humidification)

First Author (Reference No.)	Primary		Secondary			
	Incidence of VAP, n/N (%)	All-Cause ICU Mortality, n/N (%)	ICU Length of Stay, Days, mean ± SD	Duration of MV, Days, mean ± SD	Episodes of Airway Occlusion Requiring Reintubation, n/N (%)	Cost, \$ per Patient per Day
Lorente (23)	21/53 (40) vs. 8/51 (16)	13/53 (25) vs. 12/51 (24)	NA	19.5 ± 16.4 vs. 20.8 ± 17.1	NA	NA
Boots (22)	24/190 (13) vs. 23/191 (12) ^e	29/190 (15) vs. 34/191 (23) ^e	11.4 vs. 14.5 or 13.0	10.5 vs. 13.2 or 12.3	0/190 (0) vs. 0/191 (0) ^e	8.6 vs. 8.9 or 9.6 (AUS)
Lacherade (21)	47/185 (25) vs. 53/184 (29)	60/185 (32) vs. 63/184 (34)	21.4 ± 20.8 vs. 25.3 ± 30.1	13.5 ± 16.3 vs. 14.9 ± 15.1	1/185 (0.5) vs. 5/184 (3)	NA
Memish (19)	14/123 (11) vs. 19/120 (16)	40/123 (33) vs. 30/120 (25)	NA	8.5 ± 10.5 vs. 10.1 ± 9.3	NA	A cost reduction of about 43% could be achieved by using HMEs ^b
Kollef (16)	15/163 (9) vs. 15/147 (10)	40/163 (25) vs. 39/147 (27) ^c	5.7 ± 5.7 vs. 5.3 ± 5.5	4.6 ± 5.8 vs. 3.7 ± 4.1	0/163 (0) vs. 0/147 (0)	15.9 vs. 38.3 (US) ^d
Boots (18)	14/75 (19) vs. 7/41 (17)	13/75 (17) vs. 4/41 (10)	NA	5.2 or 7.6 vs. 6.3 ^e	0/75 (0) vs. 0/41 (0)	6.7 vs. 8.2 (AUS)
Kirton (15)	9/140 (6) vs. 22/140 (16)	NA	1156 vs. 1343	20.4 ± 15.3 vs. 16.3 ± 13.7	1/140 (0.7) vs. 0/140 (0)	17.5 vs. 27.8 (US) ^d
Hurni (28)	5/59 (9) vs. 7/56 (13)	17/59 (29) vs. 19/56 (34)	11.1 ± 7.7 vs. 13.8 ± 13.0	7.6 ± 6.5 vs. 7.8 ± 5.8	0/59 (0) vs. 1/56 (2) ^f	NA
Branson (14)	3/49 (6) vs. 3/54 (6)	NA	NA	4.5 ± 3.9 vs. 4.1 ± 3.2	0/49 (0) vs. 0/54 (0) ^f	4.7 vs. 8.9 (US)
Dreyfuss (13)	6/61 (10) vs. 8/70 (11)	17/61 (28) vs. 12/70 (17) ^g	NA	10.0 ± 8.6 vs. 12.5 ± 14.2	1/61 (2) vs. 0/70 (0)	5 vs. 11 (US)
Roustan (12)	5/55 (9) vs. 9/61 (15)	10/55 (18) vs. 15/61 (25)	13.9 ± 16.6 vs. 9.3 ± 10.2	10.9 ± 14.5 vs. 8.2 ± 11.9	9/55 (16) vs. 0/61 (0) ^f	NA
Misset (27)	NA	13/30 (44) vs. 16/26 (62)	NA	12 ± 7 vs. 11 ± 6	4/30 (13) vs. 2/26 (8)	NA
Martin (11)	2/31 (7) vs. 8/42 (19)	7/31 (22) vs. 11/42 (26) ^h	NA	9.7 ± 10.0 vs. 13.5 ± 10.0	6/31 (19) vs. 0/42 (0) ^f	NA

VAP, ventilator-associated pneumonia; ICU, intensive care unit; MV, mechanical ventilation; NA, not available/applicable; HME, heat and moisture exchanger. ^aPatients managed with a heated humidifier (regardless of the existence of the heater wire in both inspiratory and expiratory circuit or in the inspiratory limb only) were added; ^baccording to the authors; ^cthe hospital mortality rate (rather than ICU mortality rate) was provided by this randomized controlled trial (RCT); ^donly the cost per patient (not the cost per patient per day) was provided in this RCT; ^emedian of the parameter measured rather than mean (±SD) was reported in this RCT; ^fin these RCTs, airway occlusion was defined as the inability to pass a suction catheter (10 gauge external diameter) via the endotracheal tube; ^gthe mortality during mechanical ventilation or within 48 hrs of weaning (rather than ICU mortality) was provided by this RCT; ^hthe mortality during controlled mechanical ventilation (rather than ICU mortality) was provided by this RCT.

the subgroup analysis of the RCTs (14, 16, 21–23) in which HHs contained heated wire circuits revealed no difference between patients managed with HMEs and HHs regarding VAP incidence or mortality. This was also the case for the subgroup analysis of the three RCTs (21–23) in which the used HH contained heated wire circuits and the mean duration of MV was >7 days. Unfortunately, the scarcity of relevant data did not allow us to perform a subgroup analysis by including only patients managed with HMEs or HHs with heated wire circuits and ventilated for >7 days. On the other hand, the use of HHs without heated circuits was associated with more episodes of VAP than HMEs, based on the findings of a subanalysis of seven RCTs (11–13, 15, 18, 19, 28).

The increased risk of airway occlusion when a passive humidifier is used was an

issue of considerable concern. Earlier studies in which purely hydrophobic HMEs were used demonstrated a higher rate of endotracheal occlusion for HMEs compared with HHs (11, 12, 34, 35); two (11, 12) of these studies were included in our meta-analysis. Moreover, a meta-analysis by Hess (36) reported a greater risk of airway occlusion with passive than with active humidifiers (relative risk 3.84, 95% CI 1.92–7.69). Based on such observations it has been recommended that clinicians avoid using HMEs in patients at high risk of airway occlusion (namely, patients with hemoptysis or tenacious secretions) (5, 10, 30); indeed, this was common practice in the more recently published RCTs included in our meta-analysis (14, 16, 18, 21–23). However, the new generations of HMEs that exhibit hygroscopic properties have proven to be safer than hydrophobic HMEs (35, 37,

38). Thus, several experts strongly advise that HMEs can be safely used in patients with chronic obstructive pulmonary disease who have copious and tenacious secretions or patients with high minute ventilation (39–42). Finally, it seems that the performance of hygroscopic HMEs as well as the avoidance of their use in patients with hemoptysis almost abrogated the risk for airway occlusion.

Several experts stated that HMEs should be considered primarily a cost-saving method of providing humidification to patients undergoing MV (43), an opinion supported by the findings of this meta-analysis. On the other hand, the association of passive humidification with lower expenses and with savings in care providers' time will depend in large part on the frequency of replacement of these devices (21). Indeed, guidelines do not recommend changing the HMEs less fre-

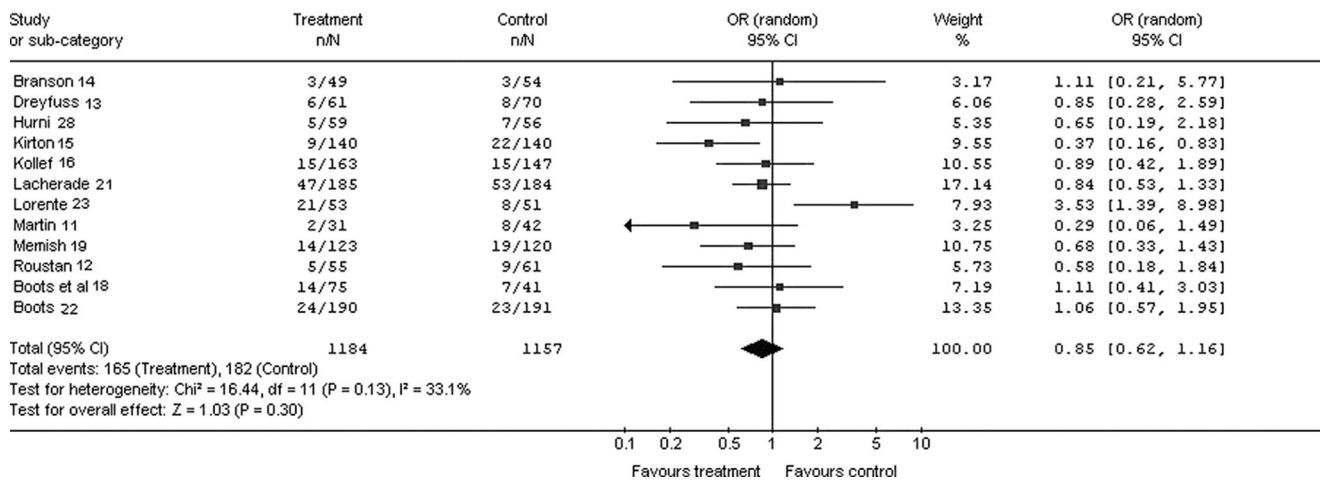


Figure 2. Odds ratios (OR) of incidence of ventilator-associated pneumonia for the individual randomized controlled trials comparing heat and moisture exchangers (treatment) and heated humidifiers (control) for the humidification of patients undergoing mechanical ventilation and the pooled analysis. Vertical line, “no difference” point between the two regimens; squares, odds ratios (the size of each square denotes the proportion of information given by each trial); diamond, pooled odds ratios for all randomized controlled trials; horizontal lines, 95% confidence intervals (CI).

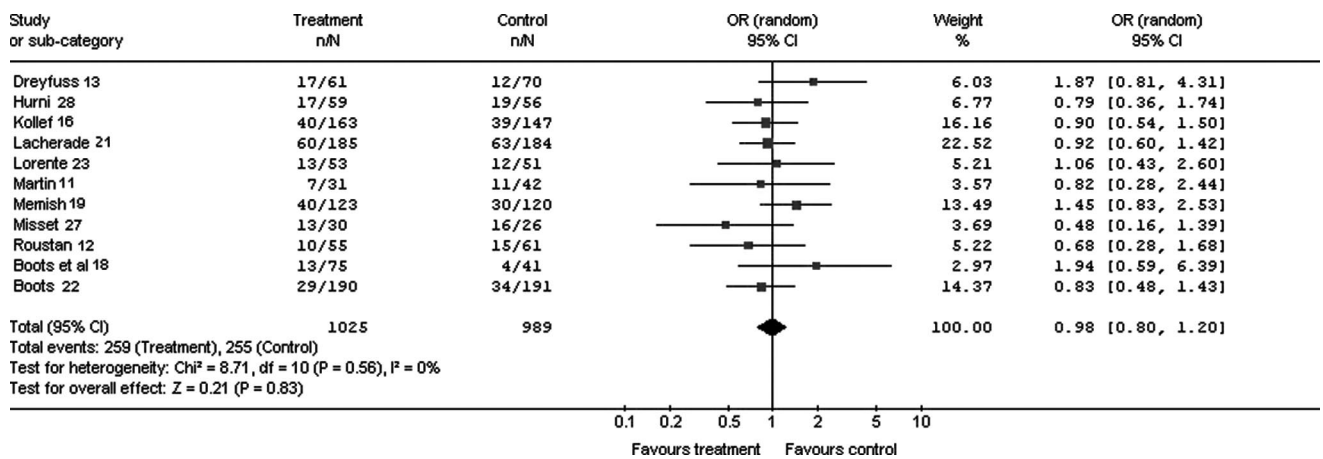


Figure 3. Odds ratios (OR) of all-cause mortality for the individual randomized controlled trials comparing heat and moisture exchangers (treatment) and heated humidifiers (control) for the humidification of patients undergoing mechanical ventilation and the pooled analysis. Vertical line, “no difference” point between the two regimens; squares, odds ratios (the size of each square denotes the proportion of information given by each trial); diamond, pooled odds ratios for all randomized controlled trials; horizontal lines, 95% confidence intervals (CI).

quently than every 48 hrs (30, 31), based on the evidence from relevant RCTs (44–47). In addition, the frequency of ventilator circuit change should also be considered when assessed the cost-effectiveness of the different humidification systems. Indeed, the relevant guidelines strongly discourage the replacement of ventilator circuits regardless of the kind of humidifier used (30, 31). However, even in the three RCTs (13, 16, 22) in which circuits were not changed, HMEs were more cost-effective than HHs.

This study must be viewed in the context of its potential shortcomings. First, the value of any meta-analysis in the field of VAP prevention is inevitably limited by the fact that the populations studied as well as the criteria used for the definition

of VAP were not identical in the included RCTs. For instance, it may be postulated that the variability in the use of microbiological diagnosis of VAP among the selected RCTs might affect the results of the meta-analysis. Indeed, in only two (13, 21) of the 13 selected RCTs was diagnosis of VAP quantitative, which has been found to increase specificity compared with clinical diagnosis (29). However, in each of these two RCTs (13, 21), there was no difference between the different methods of humidification regarding VAP incidence, a result in line with the findings of this meta-analysis. This was also the case for the subgroup analysis we performed after excluding the two RCTs (11, 14) that enrolled patients requiring MV for <48 hrs.

Second, one may support that there were differences between the HMEs used regarding brand, type, and frequency of change. However, evidence from RCTs suggests that there is no difference in VAP incidence between an HME and a heat and moisture-exchanging filter (48), between hydrophobic and hygroscopic HMEs (49), or between different types of hygroscopic agents used in the HME (50). Third, the fact that several of the selected RCTs excluded patients with conditions considered by their authors as potential contraindications for HME use (Table 2) should be kept in mind when interpreting the results of this meta-analysis; it might be hard to conclude that the two modes of humidification are totally equal if a group of patients can only be managed

with one of them. Finally, routine care (e.g., use of weaning protocols that presumably affect duration of MV and, thereby, incidence of VAP) as well as co-interventions for VAP prevention in the selected RCTs, as displayed in Table 1, may be not identical. This fact may call into question the validity of the results of this meta-analysis. In an attempt to address this limitation, we used a conservative statistical random effects model to pool the available data.

CONCLUSIONS

This meta-analysis adds support to the relevant guidelines published recently by the American Thoracic Society and the Infectious Diseases Society of America as well as those by the Centers for Disease Control and Prevention, which conclude that the preferential use of either passive or active humidifiers for the prevention of VAP in patients undergoing MV should not be supported. In other words, it seems that none of the humidifiers studied should be regarded as the gold standard in terms of gas conditioning during MV. However, HMEs could be considered a cost-saving method of providing humidification to patients undergoing MV who have no contraindications (namely hypothermia, hemoptysis, and bronchopleural fistula).

REFERENCES

- Williams R, Rankin N, Smith T, et al: Relationship between the humidity and temperature of inspired gases and the function of the airway mucosa. *Crit Care Med* 1996; 24:1920-1929
- National Nosocomial Infections Surveillance (NNIS) system report: Data summary from January 1992 through June 2003, issued August 2003. *Am J Infect Control* 2003; 31:481-498
- Heyland DK, Cook DJ, Griffith L, et al: The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. *Am J Respir Crit Care Med* 1999; 159:1249-1256
- Chastre J, Fagon JY: Ventilator-associated pneumonia: State of the art. *Am J Respir Crit Care Med* 2002; 165:867-903
- Branson RD: The ventilator circuit and ventilator-associated pneumonia. *Respir Care* 2005; 50:774-785
- Craven DE, Goularte TA, Make BJ: Contaminated condensate in mechanical ventilator circuits: A risk factor for nosocomial pneumonia? *Am Rev Respir Dis* 1984; 129:625-628
- Cook D, De Jonghe B, Brochard L, et al: Influence of airway management on ventilator-associated pneumonia: Evidence from randomized trials. *JAMA* 1998; 279:781-787
- Bench S: Humidification in the long-term ventilated patient: A systematic review. *Intensive Crit Care Nurs* 2003; 19:75
- Collard HR, Saint S, Matthay MA: Prevention of ventilator-associated pneumonia: An evidence-based systematic review. *Ann Intern Med* 2003; 138:494-501
- Hess DR, Kallstrom TJ, Mottram CD, et al: American Association for Respiratory Care. Care of the ventilator circuit and its relation to ventilator associated pneumonia. *Respir Care* 2003; 48:869-879
- Martin C, Perrin G, Gevaudan MJ, et al: Heat and moisture exchangers and vaporizing humidifiers in the intensive care unit. *Chest* 1990; 97:144-149
- Roustan JP, Kienlen J, Aubas S, et al: Comparison of hydrophobic heat and moisture exchangers with heated humidifier during prolonged mechanical ventilation. *Intensive Care Med* 1992; 18:97-100
- Dreyfuss D, Djedaini K, Gros I, et al: Mechanical ventilation with heated humidifiers or heat and moisture exchangers: Effects on patient colonization and incidence of nosocomial pneumonia. *Am J Respir Crit Care Med* 1995; 151:986-992
- Branson RD, Davis K Jr, Brown R, et al: Comparison of three humidification techniques during mechanical ventilation: Patient selection, cost, and infection considerations. *Respir Care* 1996; 41:809-816
- Kirton OC, De Haven B, Morgan J, et al: A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: Rates of ventilator-associated early-onset (community-acquired) or late onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. *Chest* 1997; 112:1055-1059
- Kollef MH, Shapiro SD, Boyd V, et al: A randomized clinical trial comparing an extended use hygroscopic condenser humidifier with heated-water humidification in mechanically ventilated patients. *Chest* 1998; 113:759-767
- Kola A, Eckmanns T, Gastmeier P: Efficacy of heat and moisture exchangers in preventing ventilator-associated pneumonia: Meta-analysis of randomized controlled trials. *Intensive Care Med* 2005; 31:5-11
- Boots RJ, Howe S, George N, et al: Clinical utility of hygroscopic heat and moisture exchangers in intensive care patients. *Crit Care Med* 1997; 25:1707-1712
- Memish ZA, Oni GA, Djazmati W, et al: A randomized trial to compare the effects of a heat and moisture exchanger with a heated humidifying system on the occurrence rate of ventilator-associated pneumonia. *Am J Infect Control* 2001; 29:301-305
- Craven DE, Duncan RA: Preventing ventilator-associated pneumonia: Tiptoeing through a minefield. *Am J Respir Crit Care Med* 2006; 173:1297-1298
- Lacherade JC, Auburtin M, Cerf C, et al: Impact of humidification systems on ventilator associated pneumonia: A randomized multicenter trial. *Am J Respir Crit Care Med* 2005; 172:1276-1282
- Boots RJ, George N, Faoagali JL, et al: Double-heater-wire circuits and heat-and-moisture exchangers and the risk of ventilator-associated pneumonia. *Crit Care Med* 2006; 34:687-693
- Lorente L, Lecuona M, Jimenez A, et al: Ventilator-associated pneumonia using a heated humidifier or a heat and moisture exchanger: A randomized controlled trial. *Crit Care* 2006; 10:R116
- Moher D, Cook DJ, Eastwood S, et al, for the QUOROM group: Improving the quality of reports of meta-analyses of randomized controlled trials: The QUOROM statement. *Lancet* 1999; 354:1896-1900
- Moher D, Jones A, Cook DJ, et al: Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; 352:609-613
- DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7:177-88
- Misset B, Escudier B, Rivara D, et al: Heat and moisture exchanger vs heated humidifier during long term mechanical ventilation: A prospective randomized study. *Chest* 1991; 100:160-163
- Hurni JM, Feihl F, Lazor R, et al: Safety of combined heat and moisture exchanger filters in long-term mechanical ventilation. *Chest* 1997; 111:686-691
- The American Thoracic Society and the Infectious Diseases Society of America Guideline Committee: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171:388-416
- Dodek P, Keenan S, Cook D, et al: Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med* 2004; 141:305-313
- Tablan OC, Anderson LJ, Besser R, et al: Guidelines for preventing health-care-associated pneumonia, 2003: Recommendations of the CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Morb Mortal Wkly Rep* 2004; 53:1-36
- Torres A, Carlet J, the European Task Force on Ventilator Associated Pneumonia: Ventilator-associated pneumonia. *Eur Respir J* 2001; 17:1034-1045
- Kranabetter R, Leier M, Kammermeier D, et al: The effects of active and passive humidification on ventilation associated nosocomial pneumonia. *Anaesthetist* 2004; 53:29-35
- Cohen IL, Weinberg PF, Fein IA, et al: Endotracheal tube occlusion associated with the use of heat and moisture exchangers in the intensive care unit. *Crit Care Med* 1988; 16:277-279
- Villafane MC, Cinaella G, Lofaso F, et al: Gradual reduction on endotracheal tube diameter during mechanical ventilation via dif-

- ferent humidification devices. *Anesthesiology* 1996; 85:1341–1349
36. Hess DR: And now for the rest of the story. *Respir Care* 2002; 47:696–699
 37. Boyer A, Thiery G, Lasry S, et al: Long-term mechanical ventilation with hygroscopic heat and moisture exchangers used for 48 hours: A prospective clinical hygrometric and bacteriologic study. *Crit Care Med* 2003; 31:823–829
 38. Thiery G, Boyer A, Lasry S, et al: Heat and moisture exchangers in mechanically ventilated intensive care unit patients: A plea for an independent assessment of their performance. *Crit Care Med* 2003; 31:699–704
 39. Ricard JD, Le Miere E, Markowicz P, et al: Efficiency and safety of mechanical ventilation with a heat and moisture exchanger changed only once a week. *Am J Respir Crit Care Med* 2000; 161:104–109
 40. Markowicz P, Ricard JD, Dreyfuss D, et al: Safety, efficacy and cost effectiveness of mechanical ventilation with humidifying filters changed every 48 hours: A prospective, randomized study. *Crit Care Med* 2000; 28:665–671
 41. Ricard JD: Humidification. *In: Principles and Practice of Mechanical ventilation*. Tobin MJ (Ed). New York, McGraw-Hill, 2006, pp 1109–1120
 42. Ricard JD, Boyer A, Dreyfuss D: The effect of humidification on the incidence of ventilator-associated pneumonia. *Respir Care Clin* 2006; 12:263–273
 43. Kollef MH: The prevention of ventilator-associated pneumonia. *N Engl J Med* 1999; 340:627–634
 44. Djedaini K, Billiard M, Mier L, et al: Changing heat and moisture exchangers every 48 hours rather than 24 hours does not affect their efficacy and the incidence of nosocomial pneumonia. *Am J Respir Crit Care Med* 1995; 152:1562–1569
 45. Boisson C, Viviand X, Arnaud S, et al: Changing a hydrophobic heat and moisture exchanger after 48 hours rather than 24 hours: A clinical and microbiological evaluation. *Intensive Care Med* 1999; 25:1237–1243
 46. Thomachot L, Leone M, Razzouk K, et al: Randomized clinical trial of extended use of a hydrophobic condenser humidifier: 1 vs. 7 days. *Crit Care Med* 2002; 30:232–237
 47. Davis K Jr, Evans SL, Campbell RS, et al: Prolonged use of heat and moisture exchangers does not affect device efficiency or frequency rate of nosocomial pneumonia. *Crit Care Med* 2000; 28:1412–1418
 48. Thomachot L, Viviand X, Arnaud S, et al: Comparing two heat and moisture exchangers, one hydrophobic and one hygroscopic, on humidifying efficacy and the rate of nosocomial pneumonia. *Chest* 1998; 114:1383–1389
 49. Davis K Jr, Evans SL, Campbell RS, et al: Heat-moisture exchangers and risk of nosocomial pneumonia. *Infect Control Hosp Epidemiol* 2000; 21:618
 50. Thomachot L, Vialet R, Arnaud S, et al: Do the components of heat and moisture exchanger filters affect their humidifying efficacy and the incidence of nosocomial pneumonia? *Crit Care Med* 1999; 27:923–928