

REVIEW

# Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis

Cameron Dezfulian, MD,<sup>a,b</sup> Kaveh Shojanian, MD,<sup>h</sup> Harold R. Collard, MD,<sup>j</sup>  
H. Myra Kim, ScD,<sup>f</sup> Michael A. Matthay, MD,<sup>g,h,i</sup> Sanjay Saint, MD, MPH<sup>c,d,e</sup>

<sup>a</sup>From the Critical Care Medicine Department, National Institutes of Health, Bethesda,

<sup>b</sup>Division of Pediatric Anesthesia and Critical Care Medicine, Department of Anesthesia and Critical Care Medicine, Johns Hopkins University, Baltimore;

<sup>c</sup>Veterans Administration Medical Center, Ann Arbor;

<sup>d</sup>Department of Medicine and

<sup>e</sup>Patient Safety Enhancement Program, University of Michigan Medical School and Health System, Ann Arbor;

<sup>f</sup>Center for Statistical Consultation and Research, University of Michigan, Ann Arbor;

<sup>g</sup>Division of Pulmonary and Critical Care Medicine;

<sup>h</sup>Department of Medicine, and

<sup>i</sup>Department of Anesthesia, University of California, San Francisco; and

<sup>j</sup>Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Health Sciences Center, Denver.

## KEYWORDS:

Ventilators;  
Mechanical;  
Pneumonia;  
Infection control;  
Respiratory tract  
infections;  
Meta-analysis

**Purpose:** To assess the efficacy of subglottic secretion drainage in preventing ventilator-associated pneumonia.

**Methods:** We performed a comprehensive, systematic meta-analysis of randomized trials that have compared subglottic secretion drainage with standard endotracheal tube care in mechanically ventilated patients. Studies were identified by a computerized database search, review of bibliographies, and expert consultation. Summary risk ratios or weighted mean differences with 95% confidence intervals were calculated for each outcome using a fixed-effects model.

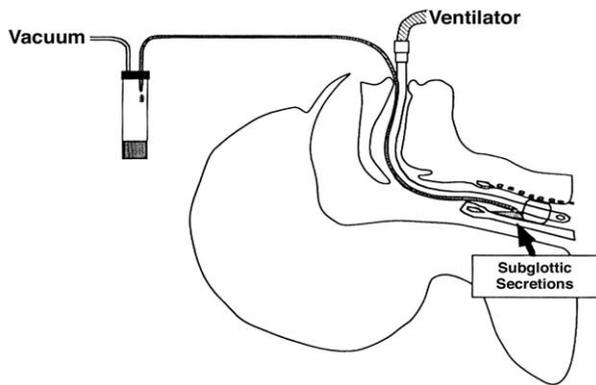
**Results:** Of 110 studies retrieved, five met the inclusion criteria and enrolled 896 patients. Subglottic secretion drainage reduced the incidence of ventilator-associated pneumonia by nearly half (risk ratio [RR] = 0.51; 95% confidence interval [CI]: 0.37 to 0.71), primarily by reducing early-onset pneumonia (pneumonia occurring within 5 to 7 days after intubation). Although significant heterogeneity was found for several endpoints, this was largely resolved by excluding a single outlying study. In the remaining four studies, which recruited patients expected to require >72 hours of mechanical ventilation, secretion drainage shortened the duration of mechanical ventilation by 2 days (95% CI: 1.7 to 2.3 days) and the length of stay in the intensive care unit by 3 days (95% CI: 2.1 to 3.9 days), and delayed the onset of pneumonia by 6.8 days (95% CI: 5.5 to 8.1 days).

**Conclusion:** Subglottic secretion drainage appears effective in preventing early-onset ventilator-associated pneumonia among patients expected to require >72 hours of mechanical ventilation.

© 2005 Elsevier Inc. All rights reserved.

Dr. Saint is supported by a Career Development Award from the Health Services Research and Development Program of the Department of Veterans Affairs, and a Patient Safety Developmental Center Grant from the Agency for Healthcare Research and Quality (P20-HS11540). Dr. Matthay is supported by National Institutes of Health Grants HL51854, HL51856, and PSOHL74005.

Requests for reprints should be addressed to: Cameron Dezfulian, MD, 10 Center Drive, Building 10, Room 7D43, Bethesda, Maryland 20892-1662. E-mail address: cdezfulian@cc.nih.gov.



**Figure 1** Diagram of a patient receiving subglottic secretion drainage. The patient is intubated with an endotracheal tube containing a dorsal lumen (black arrow) that opens above the cuff of the tube. This lumen can be connected to suction to remove the secretions that pool above the cuff in the subglottic space. Adapted with permission from Valles et al.<sup>18</sup>

Ventilator-associated pneumonia is a common complication of mechanical ventilation. The risk of this complication in the intensive care unit (ICU) ranges from 8% to 25%,<sup>1-3</sup> with an incidence of 5 to 10 cases per 1000 ventilator-days.<sup>2,4,5</sup> Ventilator-associated pneumonia leads to increased hospital length of stay and cost, and may have an attributable mortality of up to 27%.<sup>1,6-10</sup>

Ventilator-associated pneumonia is often divided into early-onset (developing in the first 5 to 7 days of mechanical ventilation) and late-onset (developing after 5 to 7 days of mechanical ventilation) forms. Although early-onset pneumonia is usually caused by microaspiration of bacteria colonizing the oropharynx (gram-positive cocci and *Haemophilus influenza*),<sup>1,2,11,12</sup> the relation of late-onset pneumonia to microaspiration is less clear. Late-onset pneumonia is usually caused by nosocomial organisms such as *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus*.<sup>1,2,12-14</sup>

Secretions have been demonstrated radiographically to pool above the cuff of the endotracheal tube (in the subglottic region) prior to entering the lower airways via microaspiration.<sup>15</sup> Investigators have attempted to preemptively remove these secretions with the goal of reducing microaspiration and the risk of ventilator-associated pneumonia. Subglottic secretion drainage is accomplished through use of a specially designed endotracheal tube with a separate dorsal lumen that opens directly above the endotracheal tube cuff (Figure 1).

Randomized controlled trials of subglottic secretion drainage for the prevention of ventilator-associated pneumonia have reported promising but mixed results.<sup>16-20</sup> None of these trials were adequately powered to demonstrate potential benefits in other important outcome measures, such as length of ICU or hospital stay, duration of mechanical ventilation, and mortality. We use meta-analysis to review randomized clinical trials that have evaluated the use

of subglottic secretion drainage for preventing ventilator-associated pneumonia.

## Methods

### Data sources

Two authors (CD, KS) independently searched the MEDLINE, CINAHL, EMBASE, Cochrane Library, Current Contents, and Biological Abstracts databases for relevant studies in any language from January 1966 to May 2003, using exploded Medical Subject Headings or the appropriate corresponding keywords *glottis* or *suction* or *drainage* and *respiration*, *artificial* or *ventilation*, *mechanical* and *pneumonia*. The titles and abstracts of all the articles were scanned, and potentially relevant articles and reviews were retrieved in full text. A second, larger search was performed using MEDLINE to identify any therapeutic or prevention strategies directed at ventilator-associated pneumonia as part of an earlier project<sup>21</sup> and was updated for the present review. The database searches were supplemented with a manual search of the reference lists of the retrieved original research and review articles. Authors of included articles were contacted to ensure the completeness of the search and to identify any unpublished studies.

### Study selection

Studies were included if mechanically ventilated patients were prospectively assigned randomly to some form of subglottic secretion drainage versus no drainage (control), and if the incidence of pneumonia was reported in both groups.

### Definitions and outcomes

The primary outcome of interest was the risk of ventilator-associated pneumonia reported as a proportion of all mechanically ventilated patients. Ventilator-associated pneumonia was minimally defined as the development, after intubation, of a new or progressive infiltrate on chest radiograph accompanied by another confirmatory finding of pneumonia. The additional requirements for confirmation of pneumonia varied among studies and included positive bronchoalveolar lavage culture,<sup>16</sup> positive bronchoalveolar lavage, protected specimen brush culture, or a clinical response to antibiotics,<sup>18</sup> or one of a list of findings such as clinical features of pneumonia, radiographic evidence of pulmonary abscess, histologic evidence of pneumonia, or positive blood or pleural fluid cultures.<sup>17,19,20</sup>

Other outcomes of interest were the incidence of ventilator-associated pneumonia, ICU length of stay, hospital length of stay, duration of mechanical ventilation, and time from intubation to the diagnosis of pneumonia. The bacte-

riologic cause of pneumonia was based on bronchoalveolar lavage or protected specimen brush culture<sup>18</sup> or tracheal aspirate culture.<sup>17,19,20</sup> If more than one potentially pathogenic organism was isolated from a patient with pneumonia, each organism was considered a separate cause.

## Data extraction

Two authors (CD, KS) independently abstracted data from all studies using standardized forms. Data were abstracted on study design, study setting and sample, method of subglottic secretion drainage utilized, definition of ventilator-associated pneumonia, use of other interventions that may affect the risk of ventilator-associated pneumonia (e.g., stress ulcer prophylaxis),<sup>22</sup> and the primary and secondary outcomes discussed above. Data were separated based on whether or not intention-to-treat analysis was used. Intention-to-treat data analyzed all randomized patients, whereas studies not using intention-to-treat analyses excluded patients who developed pneumonia or died, or who were extubated before 72 hours of mechanical ventilation. Disagreements between the primary abstracters were resolved by a third author (SS).

## Statistical analysis

A risk ratio with 95% confidence intervals comparing the drainage-treated group with control subjects was calculated for the following outcomes: risk of ventilator-associated pneumonia, mortality, and risk of gram-positive cocci or *H. influenzae* causing ventilator-associated pneumonia (as a surrogate for early-onset pneumonia) versus all other causes. Incidence rate ratios were calculated for the outcome of incidence of ventilator-associated pneumonia, defined as cases per 1000 ventilator-days. The summary risk ratio for the pooled studies was then calculated using both fixed- and random-effects models.<sup>23</sup> A summary risk ratio of <1 reflects a decreased risk of the outcome occurring in the subglottic secretion drainage group compared with the control group. For continuous variables, nonstandardized mean differences between treatment and control groups were calculated, and using the standard deviations provided by the studies, these mean differences were weighted by their inverse variances.<sup>23</sup> The weighted mean differences were then pooled across studies to derive summary mean differences for each continuous variable. A negative summary mean difference indicates that the outcome was of shorter duration in the drainage group compared with the control group. Statistical heterogeneity was assessed for each summary measure using the chi-squared test where  $P \leq 0.05$  was considered indicative of statistical heterogeneity. Statistical analyses were performed using STATA 7.0 (College Station, Texas).<sup>24,25</sup> In calculating each endpoint, intention-to-treat data was used preferentially when available. We were unsuccessful in obtaining intention-to-treat data from the corresponding authors of studies that did not publish these data.

## Sensitivity analyses

Prior to data analysis, several sensitivity analyses were planned. The first excluded the trial by Kollef et al<sup>17</sup> because the patient sample (post-cardiac surgery patients only) and the inclusion criteria (patients were enrolled at the time of intubation for their surgery) differed substantially from the other studies in which patients who were expected to require >72 hours of mechanical ventilation were recruited. The additional sensitivity analyses used either only intention-to-treat data or only non-intention-to-treat data.

## Results

### Study selection

The MEDLINE search retrieved 110 citations, of which five met our inclusion criteria (Table 1). A total of 896 patients were evaluated in these five trials; four of these studies were in English and one was in Chinese. We excluded one study<sup>26</sup> that evaluated the technique of subglottic secretion drainage in 10 patients with tracheostomies because of lack of a control group. The remaining 104 citations fell into one or more of the following exclusionary categories: noninterventional studies characterizing the epidemiology of ventilator-associated pneumonia (n = 25 studies), studies focused on the diagnosis of ventilator-associated pneumonia (n = 20), investigations of techniques other than subglottic secretion drainage for preventing ventilator-associated pneumonia (n = 19), studies focused on patients not receiving mechanical ventilation (n = 7), case reports (n = 6), investigations in animals only (n = 5), and review articles or editorials (n = 25). Keyword searches of the CINAHL, EMBASE, Cochrane Library, Current Contents, and Biological Abstracts databases; hand searches of article bibliographies; and expert consultation identified no additional studies.

Randomization was achieved using a card from a sealed envelope in two studies<sup>18,19</sup> and patients' year of birth in one study.<sup>17</sup> Two studies<sup>16,20</sup> did not report the actual method by which patients were randomized. Only one study blinded the ultimate outcome assessor.<sup>17</sup> Two other studies blinded the radiologists who were reading the chest radiographs.<sup>18,19</sup> One study did not report the brand of endotracheal tubes used.<sup>20</sup> In the remaining four studies,<sup>16-19</sup> subglottic secretion drainage was accomplished using the Hi-Lo Evac endotracheal tube (Tyco Healthcare/Mallinckrodt, St. Louis, Missouri). In three studies,<sup>16-18</sup> control subjects were also intubated with the Hi-Lo Evac endotracheal tube but the dorsal lumen was not used. Three of the studies were performed in combined medical-surgical ICUs,<sup>16,18,19</sup> one in a surgical ICU,<sup>20</sup> and one in a cardiothoracic ICU.<sup>17</sup> Four studies targeted patients who were expected to be mechanically ventilated for >72 hours.<sup>16,18-20</sup> The fifth study<sup>17</sup> recruited cardiac surgery patients whose duration of mechanical ventilation (mean, 1.5 days) was shorter than

**Table 1** Characteristics of included trials

First Author (Reference)	Setting and Patients	Definition of Ventilator-Associated Pneumonia	Exclusion Criteria	Method of Subglottic Secretion Drainage	Stress Ulcer Prophylaxis	Other Interventions
Mahul <sup>16</sup>	Medical-surgical ICU patients expected to require >72 hours of mechanical ventilation	Positive bronchoalveolar lavage culture required	Gastrointestinal bleeding; risk of reintubation; intubated before ICU; tracheostomy	Hourly aspiration with syringe	Randomized to aluminum hydroxide or sucralfate	Antibiotics (not reported); endotracheal tube cuff pressure check every 8 hours
Valles <sup>18</sup>	Medical-surgical ICU patients expected to require >72 hours of mechanical ventilation	Clinical features confirmed with bronchoscopically obtained cultures or response to antibiotics	Intubated prior to arriving at the emergency department or ICU; tracheostomy	Continuous wall suction	All patients received sucralfate	Antibiotics (64% drainage, 58% control); endotracheal tube cuff pressure check every 8 hours
Kollef <sup>17</sup>	Cardiothoracic ICU patients mechanically ventilated after cardiac surgery	Clinical features; positive tracheal, blood, or pleural cultures; radiographic abscess; or positive histology	Intubated before ICU; transfer from outside hospital	Low intermittent wall suction	73% of control and 75% of drainage patients received stress ulcer prophylaxis (no specific drug data)	Antibiotics (99% drainage, 98% control); head elevated (99% drainage, 95% control); circuit change mimized
Bo <sup>20</sup>	Surgical ICU patients expected to require >72 hours of mechanical ventilation	Clinical features or positive blood/pleural cultures or radiographic abscess or positive histology	Intubated at outside hospital; high-risk surgery or trauma; pre-existing infection	Continuous wall suction	All patients received histamine-2 receptor blocker or proton pump inhibitor	Antibiotics (29% drainage, 36% control)
Smulders <sup>19</sup>	Medical-surgical ICU patients expected to require >72 hours of mechanical ventilation	Clinical features or positive blood/pleural cultures or radiographic abscess, or positive histology	None reported	High intermittent wall suction	All patients received sucralfate	Antibiotics (48% drainage, 51% control); endotracheal tube cuff check every 4 hours

ICU = intensive care unit; drainage = subglottic secretion drainage group.

that in the other studies. The method of subglottic secretion drainage was intermittent wall suction in two studies,<sup>17,19</sup> continuous wall suction in two others,<sup>18,20</sup> and hourly syringe suction in one.<sup>16</sup>

The use of additional interventions believed to reduce the risk of ventilator-associated pneumonia<sup>3</sup> varied across the five studies. Although all studies used some form of stress ulcer prophylaxis, the actual medication choice varied. Only one study<sup>17</sup> routinely employed semirecumbent positioning of the patients, with this intervention distributed approximately equally between the drainage and control groups. The frequency of systemic antimicrobial therapy use varied among studies, but within any given study was similar between the drainage and control groups. The definition of ventilator-associated pneumonia was identical and based mostly on clinical and radiographic criteria in three studies.<sup>17,19,20</sup> In the remaining two studies,<sup>16,18</sup> bacteriologic cultures obtained using bronchoscopy were part of the definition of ventilator-associated pneumonia.

### Effects of subglottic secretion drainage

When summarized by meta-analysis Table 2; Figures 2 and 3, the use of subglottic secretion drainage reduced the risk of ventilator-associated pneumonia by about half (summary risk ratio [RR] = 0.51; 95% confidence interval [CI]: 0.37 to 0.71). There was a similar reduction in the incidence of ventilator-associated pneumonia (summary rate ratio = 0.57; 95% CI: 0.33 to 0.97). Patients who received subglottic secretion drainage, compared with those who received standard endotracheal tube care, developed pneumonia 3.1 days later (95% CI: 2.7 to 3.4 days) and had a reduced risk of early-onset pneumonia based on bacteriologic etiology (summary RR = 0.38; 95% CI: 0.16 to 0.88). Further, patients receiving subglottic secretion drainage required 1.8 fewer days of mechanical ventilation (95% CI: 1.5 to 2.1 days) and had a 1.4-day shorter ICU stay (95% CI: 0.8 to 2.1 days). Hospital length of stay and mortality were not significantly different between the two groups. The use of a random-effects model in summarizing this data did not yield substantially different results.

### Sensitivity analyses

The effects of subglottic secretion drainage on several outcomes were significantly different among the studies summarized, specifically for the duration of mechanical ventilation (heterogeneity  $P = 0.004$ ), length of ICU stay (heterogeneity  $P < 0.001$ ), and time to onset of pneumonia (heterogeneity  $P < 0.001$ ) Figures 2 and 3. These differences were no longer apparent (all heterogeneity  $P \geq 0.40$ ) after excluding the study by Kollef et al.<sup>17</sup> In the remaining four studies, all of which recruited patients expected to require >72 hours of mechanical ventilation, subglottic secretion drainage reduced the risk of pneumonia by half (summary RR = 0.50; 95% CI: 0.35 to 0.71). Patients receiving subglottic secretion drainage in these four studies required 2 fewer days of mechanical ventilation

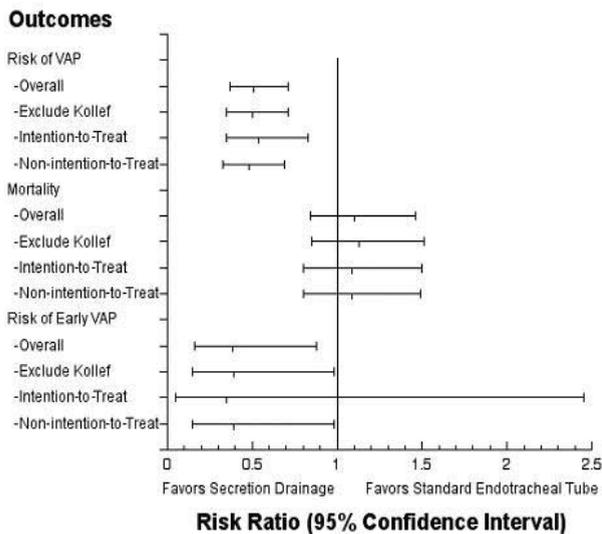
**Table 2** Summary of results of included trials\*

First Author (Reference)	Frequency of Pneumonia		Mortality		ICU Length of Stay (days)		Hospital Length of Stay (days)		Ventilation Duration (days)		Time to Pneumonia (days)	
	Secretion Drainage	Control	Secretion Drainage	Control	Secretion Drainage	Control	Secretion Drainage	Control	Secretion Drainage	Control	Secretion Drainage	Control
	n/N (%)											
Mahul <sup>16</sup>	9/70 (13)†	21/75 (28)	17/70 (24)	16/75 (21)	19 ± 4	22 ± 2	11 ± 1	13 ± 1	16.2 ± 11†	8.3 ± 5		
Valles <sup>18</sup>	16/95 (17)	25/95 (26)	39/95 (41)	35/90 (37)	3.7 ± 4.6	3.2 ± 4.5	1.5 ± 3.3	1.9 ± 5.1	12 ± 7†	6 ± 2		
Kollef <sup>17</sup>	8/160 (5)	15/183 (8)	6/160 (4)	8/183 (4)	9.3 ± 7.4	12.3 ± 3.6	26.8 ± 23.3	28.3 ± 28.2	65.6 ± 2.3†	32.9 ± 1.2		
Bo <sup>20</sup>	8/35 (23)†	15/33 (45)	12/75 (16)	10/75 (13)	5.8 ± 4.4	7.1 ± 5.4	14 ± 8†					
Smulders <sup>19</sup>	3/75 (4)	12/75 (16)										

ICU = intensive care unit.

\*For each outcome in the overall meta-analysis, data derived by intention-to-treat analysis were used preferentially.

†The result in the subglottic secretion drainage group was significantly different ( $P \leq 0.05$ ) from the control group for this outcome measure.



**Figure 2** Summary risk ratios for the overall meta-analysis and sensitivity analyses. Risk ratios are presented as point estimates with error bars signifying the 95% confidence intervals. A summary risk ratio <1 favors the use of subglottic secretion drainage for the outcome displayed. The results of the overall meta-analysis for each outcome appear first, followed by each of the three sensitivity analyses for that outcome. The sensitivity analyses are the exclusion of the data from the Kollef et al<sup>17</sup> study ("Exclude Kollef"), the analysis of only intention-to-treat data, and the analysis of only non-intention-to-treat data. ICU = intensive care unit; VAP = ventilator-associated pneumonia.

(95% CI: 1.7 to 2.3 days) and had their ICU stays shortened by an average of 3 days (95% CI: 2.1 to 3.9 days). When pneumonia occurred in these patients, it was on average 6.8 days later (95% CI: 5.5 to 8.1 days) and less likely to be caused by organisms that typically characterize early-onset ventilator-associated pneumonia (summary RR = 0.39; 95% CI: 0.15 to 0.98). Analysis using only non-intention-to-treat data yielded very similar results. When only intention-to-treat data were summarized, nearly half of patients were extubated, died, or developed pneumonia prior to 72 hours. In this sensitivity analysis, subglottic secretion drainage significantly decreased only the risk of ventilator-associated pneumonia (summary RR = 0.54; 95% CI: 0.35 to 0.83) and prolonged the time to onset of pneumonia by 2.7 days (95% CI: 2.3 to 3.1 days).

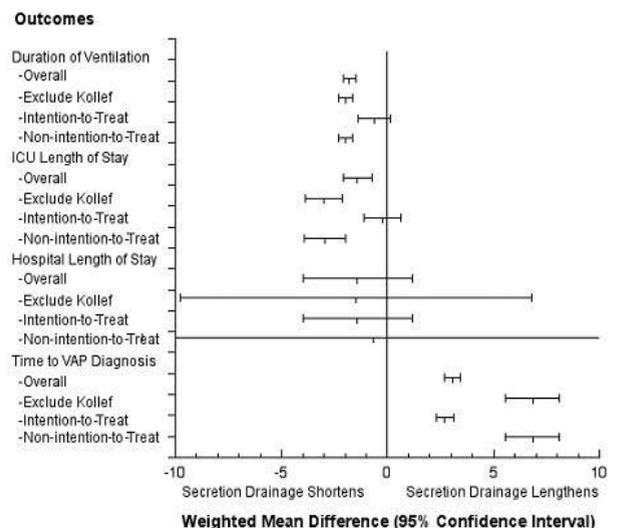
## Discussion

We found that the use of subglottic secretion drainage in mechanically ventilated patients reduces the risk of ventilator-associated pneumonia by nearly 50%. Additionally, subglottic secretion drainage results in marked reductions in the duration of mechanical ventilation and ICU stay. In sensitivity analyses, the benefits of subglottic secretion drainage were most substantial when this technique was applied to patients expected to be mechanically ventilated for >72 hours. In this patient group, additional benefits included a nearly 2-day reduc-

tion in the duration of mechanical ventilation and a 3-day reduction in the length of ICU stay. Supporting our findings, Heyland et al<sup>10</sup> calculated an almost 3-day increase in length of ICU stay attributable to ventilator-associated pneumonia caused by organisms other than *Pseudomonas*, *Stenotrophomonas*, *Acinetobacter*, and methicillin-resistant *S. aureus* but found no increase in mortality due to early-onset pneumonia.

Subglottic secretion drainage appears to reduce primarily early-onset ventilator-associated pneumonia.<sup>2</sup> It is not clear why it may not prevent late-onset pneumonia. *P. aeruginosa* and other gram-negative bacilli, common causes of late-onset ventilator-associated pneumonia, can colonize the trachea (and, presumably from there, the lower airways) without first appearing in the oropharyngeal or subglottic secretions,<sup>16,27,28</sup> possibly through adhesion to endotracheal tube biofilms.<sup>29-31</sup> Thus, subglottic secretion drainage may be ineffective in preventing late-onset ventilator-associated pneumonia because microaspiration may be less relevant to the pathogenesis of pneumonia with these organisms.

Drainage of subglottic secretions appears to be far less effective in patients requiring <72 hours of mechanical ventilation, likely because the accumulation of contaminated subglottic secretions and their subsequent microaspiration requires several days to occur. The diminished benefit in patients requiring short-term mechanical ventilation is supported by Kollef et al's study of postoperative patients,<sup>17</sup> in which the mean duration of mechanical ventilation was less than 2 days.



**Figure 3** Summary weighted mean differences for the overall meta-analysis and sensitivity analyses. Mean differences are presented as point estimates with error bars signifying the 95% confidence intervals. A weighted mean difference <0 signifies that subglottic secretion drainage reduces the duration, measured in days, for the outcome of interest. The results of the overall meta-analysis for each outcome appear first, followed by each of the three sensitivity analyses for that outcome. The sensitivity analyses are the exclusion of the data from the Kollef et al<sup>17</sup> study ("Exclude Kollef"), the analysis of only intention-to-treat data, and the analysis of only non-intention-to-treat data. ICU = intensive care unit; VAP = ventilator-associated pneumonia.

This study failed to show a difference in any outcome except time to pneumonia onset. The vast majority of patients intubated for elective cardiac surgery are extubated within 72 hours.<sup>32</sup> Therefore, average-risk patients who are mechanically ventilated for routine surgical procedures are unlikely to benefit from subglottic secretion drainage.

When faced with a newly intubated patient, how does a clinician predict the need for more than 72 hours of mechanical ventilation? A retrospective study found that clinical variables were approximately 60% accurate in accounting for variation in the duration of mechanical ventilation in general medical and surgical ICU patients.<sup>33</sup> Two studies in our analysis reported both intention-to-treat and non-intention-to-treat data; their accuracy of predicting the need for >72 hours of mechanical ventilation was 70%<sup>19</sup> and 80%.<sup>18</sup> Thus, ICU physicians appear fairly accurate in predicting the need for prolonged mechanical ventilation.

Subglottic secretion drainage appears cost-effective in patients expected to require prolonged mechanical ventilation. Despite the additional cost of \$14 per endotracheal tube, a formal economic evaluation by Shorr and colleagues demonstrated a savings of \$4992 per case of pneumonia averted, or \$1872 saved per mechanically ventilated patient.<sup>34</sup> Using our results to adjust this study's estimated cost of ventilator-associated pneumonia, we found a slightly lower yet marked cost savings of \$3535 per case of pneumonia. Formal economic evaluation is required to confirm these estimates.

There are few complications related to subglottic secretion drainage. No complications were reported in any of the studies in our analysis. Plugging of the specialized lumen through which secretions are aspirated has been anecdotally reported (Marin Kollef, MD, oral and written communication, October 2003). This complication causes the specialized endotracheal tube to function like a standard tube and has had no adverse effect on patients.

Our study should be interpreted in the context of its limitations. First, all meta-analyses have the potential to omit relevant studies, thereby failing to incorporate all the existing data into the summary endpoints. We performed a thorough database search, which included studies not limited to the English language but also one that necessitated translation from Chinese. We also performed a manual screening of references from original research and review articles, as well as communicated with the study authors in an attempt to identify all published and unpublished studies.

Second, the quality of the included studies is an important consideration. There are a number of checklists and scales for quality assessment of randomized controlled trials, although no one is unanimously accepted.<sup>35,36</sup> Jadad and coworkers have designed and validated a three-item scale for measuring the likelihood of bias in randomized trials.<sup>37</sup> Applying this scale in a nonblinded fashion to the studies in our meta-analysis reveals that they are all of moderate quality (scores of 2 to 4 on a scale of 0 to 5). The most important potential contributor to bias in the included studies is that only one study blinded the outcome

assessor to the presence or absence of subglottic secretion drainage.<sup>17</sup>

Third, clinical and statistical heterogeneity among studies may complicate the summation of data.<sup>15</sup> There was significant statistical heterogeneity in several secondary outcome measures evaluated. This was not surprising since one study recruited a substantially different patient sample that remained ventilated for a far shorter duration.<sup>17</sup> As recommended by Thompson et al,<sup>15</sup> we attempted to resolve heterogeneity using sensitivity analysis. Indeed, a sensitivity analysis based on a priori considerations removed most of this heterogeneity. The most important source of clinical heterogeneity among the five studies was the different definitions of ventilator-associated pneumonia. Although all five studies required the presence of an infiltrate on chest radiograph, two confirmed the diagnosis primarily on the basis of cultures obtained by bronchoscopy,<sup>16,18</sup> whereas the remaining three used nonbronchoscopic criteria.<sup>17,19,20</sup> In defining the bacteriologic cause of ventilator-associated pneumonia, only one study used culture results obtained by bronchoscopy,<sup>18</sup> whereas three used tracheal aspirates<sup>17,19,20</sup> and one did not report bacteriologic results.<sup>16</sup> This heterogeneity cannot be resolved by meta-analysis and must be accepted as an important limitation. Additional differences included the use of different methods of subglottic secretion drainage and differences in an intensive care unit setting (medical-surgical vs. cardiothoracic vs. surgical). We know of no data to suggest that the method of subglottic secretion drainage is important so long as the secretions are effectively removed prior to their entry into the lower airways. Further, although some studies recruited different patient samples, each was internally controlled and randomized, and each found at least a trend towards the same outcome benefits. This suggests that the benefit of subglottic secretion drainage may be generalized across a fairly broad group of ICU patients.

Limitations notwithstanding, subglottic secretion drainage appears to be an effective method to prevent ventilator-associated pneumonia, shorten the duration of mechanical ventilation, and shorten the length of ICU stay among patients expected to require mechanical ventilation for more than 72 hours.

## Acknowledgment

We are indebted to Wei Ming Sun, MD, PhD, Department of Internal Medicine, University of Michigan, for assistance with translation of the study by Bo et al<sup>20</sup> into English. We thank Marin Kollef, MD, Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine; Jordi Vallés, MD, Intensive Care and Microbiology Departments, Hospital de Sabadell, Barcelona, Spain; and Andrew F. Shorr, MD, MPH, Walter Reed Army Medical Center for responding to our requests for more information. Additionally, Dr. Shorr reviewed our extrapolation of his economic analysis. We thank Jonathan J. Deeks, MSc, for his advice in using STATA 7.0.

## References

1. Chastre J, Fagon JY: Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 165:867–903, 2002
2. George DL, Falk PS, Wunderink RG, et al: Epidemiology of ventilator-acquired pneumonia based on protected bronchoscopic sampling. *Am J Respir Crit Care Med* 158:1839–1847, 1998
3. Collard HR, Saint S, Matthay MA: Prevention of ventilator-associated pneumonia: an evidence-based systematic review. *Ann Intern Med* 138:494–501, 2003
4. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1990–May 1999, issued June 1999. *Am J Infect Control* 1999;27:520–532.
5. Centers for Disease Control and Prevention. Monitoring hospital-acquired infections to promote patient safety—United States, 1990–1999. *MMWR Morb Mortal Wkly Rep* 49:149–153, 2000
6. Cook DJ, Griffith LE, Walter SD, et al: The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care* 5:368–375, 2001
7. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C: Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 94:281–288, 1993
8. Fagon JY, Chastre J, Vuagnat A, Trouillet JL, Novara A, Gibert C: Nosocomial pneumonia and mortality among patients in intensive care units. *JAMA* 275:866–869, 1996
9. Bercault N, Boulain T: Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit: a prospective case-control study. *Crit Care Med* 29:2303–2309, 2001
10. Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun-Buisson C: 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* 159:1249–1256, 1999
11. Kingston GW, Phang PT, Leathley MJ: Increased incidence of nosocomial pneumonia in mechanically ventilated patients with subclinical aspiration. *Am J Surg* 161:589–592, 1991
12. Rello J, Torres A: Microbial causes of ventilator-associated pneumonia. *Semin Respir Infect* 11:24–31, 1996
13. American Thoracic Society. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. *Am J Respir Crit Care Med* 153:1711–1725, 1996
14. Torres A, Carlet J: Ventilator-associated pneumonia. European Task Force on ventilator-associated pneumonia. *Eur Respir J* 17:1034–1045, 2001
15. Greene R, Thompson S, Jantsch HS, et al: Detection of pooled secretions above endotracheal-tube cuffs: value of plain radiographs in sheep cadavers and patients. *AJR Am J Roentgenol* 163:1333–1337, 1994
16. Mahul P, Auboyer C, Jospe R, et al: Prevention of nosocomial pneumonia in intubated patients: respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. *Intens Care Med* 18:20–25, 1992
17. Kollef MH, Skubas NJ, Sundt TM: A randomized clinical trial of continuous aspiration of subglottic secretions in cardiac surgery patients. *Chest* 116:1339–1346, 1999
18. Valles J, Artigas A, Rello J, et al: Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. *Ann Intern Med* 122:179–186, 1995
19. Smulders K, van der Hoeven H, Weers-Pothoff I, Vandenbroucke-Grauls C: A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. *Chest* 121:858–862, 2002
20. Bo H, He L, Qu J: Influence of the subglottic secretion drainage on the morbidity of ventilator associated pneumonia in mechanically ventilated patients [in Chinese]. *Zhonghua Jie He He Hu Xi Za Zhi* 23:472–474, 2000
21. Collard H, Saint S: Prevention of ventilator-associated pneumonia. In: Shojania K, Duncan B, McDonald K, et al, eds. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices* Rockville, Maryland: Agency for Healthcare Research and Quality; 2001:185–203. Evidence Report/Technology Assessment No. 43. AHRQ Publication No. 01-E058.
22. Messori A, Trippoli S, Vaiani M, Gorini M, Corrado A: Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 321:1103–1106, 2000
23. Petitti D: *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis* 2nd ed. New York, New York: Oxford University Press; 2000
24. Sharp S, Sterne J: sbe16: meta-analysis. *Stata Technical Bulletin* 38:9–14, 1997
25. Bradburn M, Deeks J, Altman D: sbe24: Metan—an alternative meta-analysis command. *Stata Technical Bulletin* 44:4–15, 1998
26. Stuttman R, Weidemann D, Doehn M: What is the benefit of subglottic suction? *Anaesthetist* 36:87–90, 1987
27. Niederman MS, Mantovani R, Schoch P, Papas J, Fein AM: Patterns and routes of tracheobronchial colonization in mechanically ventilated patients. The role of nutritional status in colonization of the lower airway by *Pseudomonas* species. *Chest* 95:155–161, 1989
28. Schwartz SN, Dowling JN, Benkovic C, DeQuittner-Buchanan M, Prostko T, Yee RB: Sources of gram-negative bacilli colonizing the tracheae of intubated patients. *J Infect Dis* 138:227–231, 1978
29. Bo H, He L, Qu J: Observation of biofilms inside tracheal tubes by electron microscopy and the relationship between biofilms and VAP [in Chinese]. *Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih* 23:300–302, 2000
30. Cai S, Zhang J, Qian G: Correlation of endotracheal tube biofilm and recurrent ventilator-associated pneumonia with *Pseudomonas aeruginosa* [in Chinese]. *Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih* 24:339–341, 2001
31. Olson ME, Harmon BG, Kollef MH: Silver-coated endotracheal tubes associated with reduced bacterial burden in the lungs of mechanically ventilated dogs. *Chest* 121:863–870, 2002
32. Branca P, McGaw P, Light R: Factors associated with prolonged mechanical ventilation following coronary artery bypass surgery. *Chest* 119:537–546, 2001
33. Seneff MG, Zimmerman JE, Knaus WA, Wagner DP, Draper EA: Predicting the duration of mechanical ventilation. The importance of disease and patient characteristics. *Chest* 110:469–479, 1996
34. Shorr AF, O'Malley PG: Continuous subglottic suctioning for the prevention of ventilator-associated pneumonia: potential economic implications. *Chest* 119:228–235, 2001
35. Moher D, Jadad AR, Tugwell P: Assessing the quality of randomized controlled trials. Current issues and future directions. *Int J Technol Assess Health Care* 12:195–208, 1996
36. Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S: Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials* 16:62–73, 1995
37. Jadad AR, Moore RA, Carroll D, et al: Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 17:1–12, 1996