Prevention of Ventilator-Associated Pneumonia Through Aspiration of Subglottic Secretions

A Systematic Review and Meta-Analysis

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Ventilator-associated pneumonia (VAP) is a subset of hospital-acquired pneumonias and is a serious, sometimes fatal, complication in patients who need mechanical ventilation. In addition, pay-for-performance initiative has placed increased emphasis on preventing nosocomial infections including VAP. Facilities may not be reimbursed for costs associated with prevalence infections. This article presents a review and meta-analysis of the prevention of VAP through the aspiration of subglottic secretion.
Keywords: Aspiration, Subglottic secretions, Ventilated-associated pneumonia

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Critically ill patients are particularly prone to infections either because of their illness, comorbidities, or invasive devices/procedure associated with their critical management. Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in critically ill patients[1] and the second most common hospital infection.[1] Pay-for-performance initiatives have placed increased emphasis on preventing nosocomial infections including VAP.[2,3]

The Pathogenesis of VAP

Ventilator-associated pneumonia is a subset of hospital-acquired pneumonias.[4] The Centers for Disease Control and Prevention's National Healthcare Safety Network defines VAP as a pneumonia that develops in patients who are intubated and ventilated at the time of or who develop a pneumonia within 48 hours of discontinuation of mechanical ventilation (MV).[5] However, some definitions consider VAP pneumonia to be a pneumonia that develops after 48 hours of mechanical ventilator with pneumonias developing prior to 48 hours to be either a preexisting pneumonia or the result of aspiration during intubation. Ventilator-associated pneumonias are further classified as being either early onset or late onset. Early-onset pneumonias that develop within the first 4 days are often caused by organisms such as *Moraxella catarrhalis*, *Haemophilus*, and *Staphylococcus pneumoniae*. Late-onset pneumonias are caused by agents such as gram-negative bacilli, *Staphylococcus aureus*,

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methicilin-resistant *S aureus*, and viruses such as influenza A, influenza B, legionnellae, yeasts, and fungi.[5]

Patients who require MV are either intubated with an endotracheal tube (ETT) or ventilated through placement of a tracheostomy. The longer a patient is intubated, the greater the likelihood of developing VAP.[6] Also, later-developing VAPs are more likely to be caused by antibiotic resistant organisms. Ventilator-associated pneumonia increases costs to payors and the health care system as a whole through increased lengths of stay in high-cost intensive care units (ICUs), increased length of hospital stay, and additional costs of antibiotic therapy.[7-10] Ventilator-associated pneumonia is a preventable complication of MV and is also associated with increased mortality and morbidity. Pneumonia rates are 6 to 21 times higher in patients receiving MV, and the risk increases by as much as 1% per ventilator day.

Several mechanisms have been cited as causative factors in the pathogenesis of bacterial pneumonia.[11,12] They include bacteremia, gastrointestinal colonization, inhalation of pathogens from the environment, and introduction of pathogens from the environment such as through suctioning, MV, or colonization of the oral cavity with VAP-associated pathogens.[13-15]

Although a frequently cited complication of MV, VAP is not inevitable.[16,17] As national focus has highlighted the significance of this problem,[18] a barrage of interventions has been proposed in consensus standards, national campaigns, and in the literature.[19-26] It is important to continually analyze existing science underlying these recommendations so that beneficial interventions may be implemented and the need for further studies may be highlighted.

Subglottic Secretion Drainage

The cuff of an ETT serves several purposes. It helps secure the tube in the correct location, helps in the delivery of appropriate tidal volumes, and aids in the prevention of aspiration of secretions from either the oral cavity and/or the stomach. However, over time, secretions can accumulate above the endotracheal cuff, and aspiration into the lungs can occur if these fluids remain in place.[27,28] Contamination of the lower respiratory tract by these secretions can cause VAP.

Aspiration or drainage of subglottic secretions is available through a specialized ETT, which has an additional lumen above the cuff. This lumen can be connected to either continuous or intermittent suction. Manufacturers recommended suction rates that vary from −20 mm Hg to around −100 to −150 mm Hg (Mallinckrodt and Nelcor, both in St Louis, Missouri).

Objective of the Review

The objective of this review was to examine the effectiveness of subglottic secretion aspiration in reducing the occurrence of VAP. The sub-objectives of this review were (1) reduction in VAP rates, (2) duration of MV, (3) mortality, (4) length of stay, and (5) length of hospital stay.

METHODS

Criteria for Considering Studies for Review

Original studies were included in this review if they focused on subglottic secretion drainage (SSD) and met the following criteria: (1) utilized a prospective design; (2) sampled human subjects, and (3) had a control group. Ultimately, other systematic reviews were identified and included in the discussion of this systematic review.

Types of Participants

Participants who served as the focus of this review were human subjects hospitalized in an ICU who were intubated and receiving MV.

Types of Interventions

Subglottic secretion drainage comprised the intervention of interest. Studies were included that implemented either intermittent or continuous SSD.

Subglottic secretion drainage comprises the intervention of interest.

Types of Outcome Measures

Dichotomous outcomes included (1) the presence or absence of ventilator pneumonia and (2) mortality. Continuous outcomes included (1) incidence of VAP per 1000 ventilator days, (2) days to onset of VAP, (3) duration of MV, (4) length of ICU stay, and (5) length of hospital stay.

Search Strategy for Identification of Studies

Medline (OVID and PubMed) 1448 to March week 1 2011; EMBASE 1980 to 2011 week 16; Medline in-process and other nonindexed citations April 26, 2100; Cochrane Database of Systematic Reviews 2005 to March 2011; EBM Reviews—ACP Journal Club 1991 to March 2011; OVID Nursing; Dissertation Abstracts; BMJ Clinical Evidence; and CINAHL 1981 to April 2011 databases were utilized to locate relevant abstracts for review. Search terms for the outcome variables included (1) *pneumonia* (prevention and outcome variables), (2) *ventilator-associated pneumonia*, and (3) *pneumonia*,

ventilator-associated. Search terms for the intervention included (1) *intracheal intubation*, (2) *endotracheal intubation*, (3) *endotracheal cuff*, (4) *endotracheal tube*, (5) *subglottic*, and (6) *glottis*. Searches were then performed using both "key word" searches and also mapping to MeSH (Medical Subject Headings) subject headings. Searches were combined using the Boolean operator "and" and then limited to clinical trials and humans. As studies were retrieved, reference lists were reviewed, and possible relevant studies obtained for review of either the abstract or full review of the article. After variables of interest were combined and limits applied, 259 articles were selected for abstract review. From this list, 38 articles were selected for full review.

Web of Science Citations was searched for articles that had cited the studies listed in Table 1. The most frequently cited studies and representative number of studies were Valles et al[40] (254), Mahul et al[37] (157), and Kollef[32] (108). Abstracts of the 688 articles that cited studies listed in Table 1 were also reviewed for inclusion in this review.

Sixteen articles, which included original studies (n = 12) and reviews (n = 4), were included in this systematic review. Three studies were written in Chinese and were translated by S.H.L., a doctorally prepared nurse with a critical care background and experience conducting systematic reviews.

Data Collection and Analysis

SELECTION OF STUDIES

Two authors independently searched the literature to locate studies. Studies were included if they examined SSD.

DATA EXTRACTION AND MANAGEMENT

Two reviewers independently extracted data pertaining to outcome variables with no difference in data extraction noted.

Two reviewers independently appraised the studies and extracted data pertaining to outcome variables.

ASSESSMENT OF METHODOLOGY

Two reviewers (A.R.L. and J.S.) independently assessed studies for methodologic quality using a standardized checklist. When reviewing studies, we addressed representativeness of the sample. It was considered desirable when investigators recruited subjects sequentially and also provided data that reflected how subjects were similar or different from the accessible population. As VAP prevention practices have changed throughout the last decade and because the development of science has occurred in an international setting, we reviewed the description of clinical care in order to clearly identify and describe the standard of care for this patient group.[43-45] Specifically, we looked for standard care measures such as head-of-bed elevation, routine oral care protocols, use of a standardized weaning protocol, maintenance of endotracheal cuff pressure between 20 and 25 cm H_2O or 20 and 30 cm H_2O,[46,47] and stress ulcer prophylaxis.[48] In an ideal world, each study would have used the same criteria for screening for the suspicion of and then confirming the presence of VAP.[49] However, the international settings utilized similar but different criteria; we included only the randomized studies that used a prospectively identified criteria and that utilized prospectively identified standardized screening and diagnostic tools that were uniformly applied to both the experimental and control groups.[50-52]

Across studies, 3 components were utilized in establishing the diagnosis of VAP. The first component addressed systemic signs of infection such as fever, tachycardia, and leukocytosis. The second component addressed chest x-rays, whereas the third component examined bacteriologic evidence of pulmonary infection based on culture results.[53,54] When reviewing studies, we looked for the use of standardized criteria in determining suspicion of VAP. Serial x-rays were preferred to a single x-ray, and it was preferable if the radiologist was blinded to group assignment when evaluating the x-rays.[49]

Although tracheal secretions are easily obtained through endotracheal suctioning, the results often are contaminated by upper respiratory tract pathogens. Bronchoalveolar lavage or protected brush specimen with either calibrated loop or serial dilution techniques for microbiologic evaluation was considered to be the most desirable measures for confirmation of VAP.[55,56] Although the visibility of the specialized ETT made it impossible to blind investigators and clinicians to group assignment, we did evaluate whether the radiologists who read chest x-rays and the microbiologists who analyzed the laboratory specimens were blinded to group assignment.

Disagreements regarding study quality were resolved through discussion or through consultation with a third party. In an attempt to avoid either a too restrictive or too lenient approach to inclusion in this systematic review, we reviewed and abstracted data from each study prior to discussing the results (Tables 1 and 2). Agreement among the review group was reached in determining which studies to include in the final review.

TABLE 1 Characteristic of Studies Abstracted and Reviewed

Study Author and Design	Setting and Accessible Population	Intervention (I) and Control (C)	Determination of VAP	Findings	Comments
Bo et al[29] RCT Included	Surgical ICU in Shanghai. Excluded were oral surgery patients and those with pneumonia at study entry.	I = SSD with continuous aspiration of secretions. C = conventional ETT	VAP diagnosed based on quantitative cultures obtained by PBS.	The same organisms were isolated in subglottic secretions and the lower respiratory tract in 61% (14/23) patients with VAP.	All of the subjects received stress ulcer prophylaxis and had an NG tube in place.
Bouza et al[30] RCT Included	ICU in a 1750 bed hospital in Madrid, Spain. The sample was drawn from 1101 patients who had major heart surgery between May 2004 and July 2006	I = SSD with continuous aspiration of secretions with a negative pressure maintained between 100 and 150 mm Hg. C = conventional endotracheal tube	The CDC definition was used to screen for VAP. Patients with a clinical pulmonary infection score >6 were also considered to have pneumonia. VAP was confirmed by the isolating of ≥1 bacterial counts with aspirates obtained from either endotracheal aspiration or telescopic brush sampling of respiratory secretions.	No complications in the SSD group were observed. Antibiotic burden was significantly reduced with a calculated savings of approximately 21,000€. The extra cost of acquiring SSD tubes was approximately 2800€.	Following informed consent procedures 714 patients undergoing MHS were randomized by drawing a card from a sealed envelope. Of the initial group, 85 patients were mechanically ventilated ≥48 h after undergoing surgery. This subgroup was included in this meta-analysis. All patients received stress ulcer prophylaxis with pantoprazole.
Girou et al[31] RCT Excluded	10-Bed ICU in a French University Hospital ICU patients expected to be mechanically ventilated >5 d were eligible for inclusion.	I = semirecumbent and SSD (N = 8) C = supine and conventional ETT (N = 10)	Oropharyngeal and tracheal secretions were sampled and cultured daily from day 1 to 10, extubation, or death.	After day 1 of mechanical ventilation, 75% of the SSD and 80% of the control group patients were colonized in the trachea. There was no significant difference in daily tracheal and oropharyngeal bacteria counts between the 2 groups. Thus, SSD did not modify the level of oropharyngeal and tracheal colonization.	All patients received sucrafate, which may have affected colonization Among the 5 patients extubated in the suctioning group, 2 (40%) developed laryngeal edema immediately after extubation. The frequency of oral care was not reported.
Kollef et al[32] RCT	Subjects were drawn from the cardiothoracic ICU at Barnes Jewish Hospital in St Louis, Missouri; 343 cardiac surgery patients who required MV were included in the study.	I = SSD with continuous low intermittent suction <20 mm Hg	The American College of Chest Physicians criteria were used to screen for VAP. A clinical diagnosis of VAP was utilized that was not based on bronchoscopically obtained cultures of the lower respiratory tract.	Episodes of VAP occurred statistically later among the SSD group by 2.7 days.	Birth years were used to assign patients to groups. Patients in this study were intubated for a relatively brief period as compared with other studies.

(continues)

TABLE 1 Characteristic of Studies Abstracted and Reviewed, continued

Study Author and Design	Setting and Accessible Population	Intervention (I) and Control (C)	Determination of VAP	Findings	Comments
Excluded		C = SSD without suction			No complications related to SSD were observed in the intervention group. Outcomes assessor was blinded to group assignment
Lacherade et al[33] RCT Included	Subjects were drawn from 4 medical/surgical ICUs in France	I = SSD (Hi-Lo Evac) suctioned manually with a 10-mL syringe with an intended frequency of 1 suction per hour. C = Hi-Lo Evac ETT without aspiration	Clinical suspicion of VAP was based on the presence of a recent and persistent infiltrate on chest x-ray and at least 2 of the following: fever greater than 38.3°C or hypothermia of less than 36°C, white blood cell count greater than 10.10/L or less than 4.10/L, and purulent tracheal secretions. Confirmation of VAP required a positive quantitative culture of either a protected telescoping catheter sample or BAL. Cultures were considered positive if the catheter sample or BAL grew at least 10^3 or at least 10^4 colony-forming units/mL, respectively, of at least 1 microorganism.	Of the cases of VAP, 2 of 169 cases in the experimental group and 10 of 164 cases in the control group occurred within 5 days. Late-onset VAP that occurred after 5 days was 23 of 126 cases in the experimental group and 32 of 97 cases in the control group.	Analysis included 9 control group and 8 SSD group patients who required MV for <48 h. Routine care measures included oral rather than nasal route of intubation of tracheal and gastric tubes, enteral delivery of nutritional support, ETT cuff pressures between 20 and 30 cm H_2O, and semirecumbent body position. No selective digestion decontamination was used. Within the first 48 h of MV 9 SSD and 15 control group patients developed pneumonia. These subjects were included in the analysis.
Liu et al[34] Excluded	Sixty subjects aged ≥60 y who were expected to require mechanical ventilation for >48 h were recruited from an ICU in Shanghai, China	I = SSD (continuous subglottic secretion drainage), semirecumbent position, and mosapride citrate C = Standard endotracheal tube	VAP diagnostic criteria as described by Bergmans et al[35] were followed. Early VAP was considered a VAP that occurred within 5 d of endotracheal intubation with mechanical ventilation, whereas late VAP was that which occurred after 5 d	Incidence of VAP the intervention group was lower than that in control group	SSD was 1 of a 3-part bundle of interventions that was compared with standard care, which included a standard endotracheal tube. Thus, it was not possible to determine the contribution of each of the 3 elements of the intervention in preventing VAP.

(continues)

TABLE 1 Characteristic of Studies Abstracted and Reviewed, continued

Study Author and Design	Setting and Accessible Population	Intervention (I) and Control (C)	Determination of VAP	Findings	Comments
Lorente et al[36]	The setting for this study was a 24-bed medical-surgical ICU in a 650-bed tertiary hospital in Tenerife, Spain. Subjects were recruited between March 1, 2006, and October 31, 2006.	I = SSD (Seal-Guard [Covidien, Boulder, Colorado] EVAC Endotracheal tube or Seal Guard tracheostomy), which has a polyurethane cuff. Intermittent secretion drainage every 1 h with a 10-mL syringe	The diagnosis of pneumonia was considered when all of the following criteria were present: new onset of purulent bronchial sputum; body temperature >38°C or <35.5°C; white blood cell count >10,000 or <4000/μL; chest radiograph showing new or progressive infiltrates; and significant quantitative culture of respiratory secretions by tracheal aspirate (>10^6 colony-forming units/mL)	Poisson regression analysis showed a higher incidence density of VAP in the control group than in the experimental group. The investigators found a lower incidence of both early- and late-onset VAP.	Standard care for both groups included no routine change of ventilator circuits; tracheal suction by an open system as needed; semirecumbent body position every 4 h; intracuff pressure of 25 cm of H_2O which was verified every 4 h; NG tube; continuous enteric nutrition; stress ulcer prophylaxis with ranitidine; oral care with chlorhexidine every 8 h; and no selective digestive decontamination
RCT					The procedures for the confirmation of the diagnosis of VAP were not described in detail.
Included		C = Hi-Lo ETT that does not incorporate a separate dorsal lumen for subglottic secretion drainage	The confirmation of diagnosis was made by an expert panel blinded to treatment assignment.		Pneumonia was considered to be VAP when it was diagnosed during mechanical ventilation and was not present at the time mechanical ventilator was established. The investigators did not consider a pneumonia that developed within the first 48 h to be an existing pneumonia.
Mahul et al[37] Factorial design	The sample was drawn from 415 admissions to an ICU in France.	I = SSD (70) 34 received aluminum hydroxide, and 36 received sucrafate. SGS was performed hourly with a 10-mL syringe.	A new and persistent infiltrate on CXR occurring after 2 d of intubation was considered as nosocomial pneumonia. Diagnosis was confirmed with aerobic microorganisms on BAL of ≥10.5 colony-forming units/mL	The incidence of VAP was 50% lower in the SGS group (13%) as compared with the no-SGS group (29.1%). Also, the days to onset of VAP were 16.2 in the SGS group and 8.3 in the control group.	
Included		C = Regular ETT (75), 38 received aluminum hydroxide, and 37 received sucrafate			

(continues)

TABLE 1 Characteristic of Studies Abstracted and Reviewed, continued

Study Author and Design	Setting and Accessible Population	Intervention (I) and Control (C)	Determination of VAP	Findings	Comments
Pneumatikos et al[38] Excluded	14-Bed general ICU in a university hospital in Greece	I = Hi-Lo Evac ETT with continuous infusion of a suspension of 3 nonabsorbable antibiotics (polymyxin, tobramycin, amphotericin) C = Placebo infusion through a Hi-Lo Evac ETT	VAP suspected in the presence of new and persistent pulmonary infiltrates in addition to: temperature of greater than 38.3°C, white blood cell count of greater than 12,000/μL or less than 4000/μL; and purulent tracheal secretions. Suspected VAP was confirmed by a quantitative culture of secretions in a protected specimen collected by a double catheter either blind or bronchoscopically. The diagnosis of VAP was made by a chest physician, radiologist, and a physician experienced in infectious diseases who was blinded to group assignment. The team decided on the presence or absence of VAP.	No patients with negative bronchial secretion cultures developed VAP. Ventilator-associated pneumonia developed in 16% of the patients receiving selective decontamination of the subglottic area and 51% of the patients who received the placebo.	Gastric and tracheal secretions were obtained after intubation and every 4 days thereafter. All patients had a nasogastric tube in place and if possible were placed in a semirecumbent position at a 30- to 45-degree angle.
Smulders et al[39] RCT Included	12-Bed general ICU in Amsterdam, the Netherlands The sample was drawn from 150 patients admitted to the ICU who were expected to receive MV >72 h.	I = SSD intermittent 20-s intervals, 8-s duration, 100–mm Hg suction C = standard ETT	VAP was diagnosed based on a new or progressive radiographic evidence for cavitation or histologic evidence of pneumonia, or positive blood culture finding without other sources.		All patients received stress ulcer prophylaxis with sucrafate. All subjects were orally intubated. A radiologist who was blinded to group assignment interpreted all CXRs.
Valles et al[40]	Subjects were recruited from an ICU in Spain. Those eligible for inclusion were those who were expected to be intubated at least 72 h.	I = SSD C = SSD endotracheal tube but did not receive aspiration of subglottic secretions.	VAP suspected after 72 h of MV if temperature >38.3°C, WBC >12,000/μL or <4000/μL, purulent secretions, new or persistent infiltrate.	Use of SSD reduced the incidence of VAP by 43.4%.	Intracuff pressures were monitored every 4 h and kept >20 mm Hg

(continues)

TABLE 1 Characteristic of Studies Abstracted and Reviewed, continued

Study Author and Design	Setting and Accessible Population	Intervention (I) and Control (C)	Determination of VAP	Findings	Comments
RCT	190 Patients were recruited between 1990 and 1993, with 153 completing the study.		Diagnosis confirmed by positive protected bush specimen containing ≥103 colony-forming units/mL, BAL ≥104 colony-forming units/mL, or good response to antibiotic agents.		All patients received stress ulcer prophylaxis.
Included		C = SSD endotracheal tube but did not receive aspiration of subglottic secretions.	Based on clinical presentation. X-ray showing lung infiltration. At least 2 symptoms: body temperature greater than 38.3°C, white blood cell count greater than 12.0×10^9/L or less than 4.0×10^9/L. Discharge culture positive. Determination of VAP was determined using the simplified version of the clinical pulmonary infection score (≥5).	The morbidity of VAP in the SSD group was 25%, and that for the control group was 46.5% ($P = .032$), and the length of time before the onset of VAP in these groups was 7.3 ± 4.2 days and 5.1 ± 3 days, respectively ($P = .10$). In the SSD group, the volume of the subglottic secretions aspirated the first day was significantly less than that in patients without VAP ($P = .006$). The morbidity of VAP in patients who failed early aspiration (the volume of secretions first aspirated ≤ 20 mL) was significantly higher than that in patients in whom the aspiration was effective ($P < .01$).	Chest x-rays were interpreted by a radiologist who was blinded to group assignment. At time of analysis, the investigators did analyze data to examine the impact of antibiotic treatment at time of randomization on incidence of VAP.
Yang et al[41] RCT	Patients mechanically ventilated in an ICU between October 2004 and April 2006 were randomized to groups.	I = SSD continuous aspiration of subglottic secretions C = No aspiration of subglottic secretions			There was a significant increase in the percentage of gram-positive cocci from the lower respiratory tracts in the control group ($P = .004$).
Zheng et al[42] RCT	From January 2005 to June 2006, patients with an expected duration of mechanical ventilation for more than 48 hours and age older than 18 years were enrolled and randomized to groups.	I = SSD C = standard endotracheal tube	The National Nosocomial Infection Surveillance System diagnostic criteria for VAP were followed.	Compared with the control group, the incidence of VAP was significantly lower (30% vs 51.6%, $P < .05$), and the duration of mechanical ventilation was 7.9 ± 2.6 versus 10.4 ± 2.6 days.	

Abbreviations: BAL, bronchoalveolar lavage; C, control; CSGS, continuous subglottic suctioning; CXR, chest x-ray; ETT, endotracheal tube; I, intervention; ICU, intensive care unit; €, euro; NG, nasogastric; PBS, pulmonary bronchial suction; CDC, Centers for Disease Control and Prevention; MHS, major hear surgery; MV, mechanical ventilator; RCT, randomized clinical trial; SGS, subglottic secretion suctioning; SSD, subglottic secretion drainage; VAP, ventilator-associated pneumonia; WBC, white blood count.

TABLE 2 ICU Impact of Subglottic Secretion Drainage on Ventilator-Associated Pneumonia Outcomes

Study	Sample Size (n)	VAP	Mortality	Incidence of VAP per 1000 Ventilator Days	Days to Onset of VAP	Mean Duration of MV	Length of ICU Stay	Length of Hospital Stay
Bo et al[29]	SSD, 35	8			14.8 ± 8			
	Control, 33	15			6.4 ± 4			
Bouza et al[30]	SSD, 45	12	20	31.5				
	Control, 40	19	21	51.6				
Girou et al[31]	SSD, 8	5						
	Control, 10	6						
Kollef et al[32]	SSD, 160	8	6	34.3	5.6 ± 2.3	1.5 ± 3.3	3.7 ± 4.6	11 ± 11.2
	Control, 183	13	8	43.2	2.9 ± 1.2	1.9 ± 5.1	3.2 ± 4.5	12.4 ± 14.2
Lacherade et al[33]	SSD, 169	25	80	17.0	10.5 ± 11.12			
	Control, 164	42	84	34.0	7.2 ± 5.30			
Liu et al[34]	SSD, 41	4						
	Control, 45	9						
Lorente et al[36]	SSD, 140	11	26	7.5	10.5 ± 11.12	10.5 ± 15.91	14.1 ± 17.91	
	Control, 140	31	32	19.9	7.2 ± 5.3	11.0 ± 15.19	15.5 ± 19.93	
Mahul et al[37]	SSD, 70	9	11		16.2 ± 11			
	Control, 75	21	16		8.3 ± 5			
Pneumatikos et al[38]	SSD, 31	5	5	12.4				
	Control, 30	16	7	36.44				
Smulders et al[39]	SSD, 49	2	9	6.4		7.9 ± 9.7	11.9 ± 8.8	32.1 ± 25.1
	Control, 56	10	10	21.3		7.1 ± 3.4	14.2 ± 11.1	32.8 ± 31.6
Valles et al[40]	SSD, 76	14	30	19.6	12 ± 7.1	11 ± 1	19 ± 4	
	Control, 77	25	28	39.6	5.9 ± 2.1	13 ± 1	22 ± 2	
Yang et al[41]	SSD, 48	12	32		7.3 ± 4.2	8.1 ± 7.5		
	Control, 43	20	29		5.1 ± 3.0	8.4 ± 6.0		
Zheng et al[42]	SSD, 30	9	8		6.5 ± 1.3	7.9 ± 2.5	9.3 ± 2.9	
	Control, 31	16	12		5.5 ± 0.6	10.4 ± 0.9	12.3 ± 5.7	

Abbreviations: ICU, intensive care unit; MV, mechanical ventilation; SSD, subglottic secretion drainage; VAP, ventilator-associated pneumonia.

EXCLUDED STUDIES

The study by Girou and colleagues[31] was excluded because patients were randomized to either semirecumbent position and continuous SSD or prone position and standard ETT. Because the influence of head-of-bed elevation could not be separated from the effectiveness of SSD in reducing VAP, this study was excluded from the meta-analysis of pooled results.

Liu and colleagues[34] utilized SSD as one of a 3-part "bundle" of interventions, which was compared with standard care that included a standard ETT. Because of the intervention with a bundle rather than a direct causal comparison between an ETT that did and did not use SSD, this study was not included in the meta-analysis of findings.

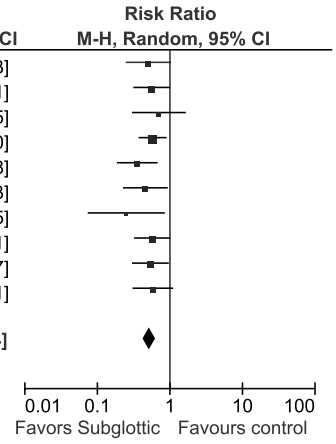
Pneumatikos and colleagues[38] intubated patients with an ETT capable of SSD (Hi-Lo Evac, Boulder, Colorado; Mallinckrodt, St Louis, Missouri). The continuous infusion of a suspension of polymyxin, tobramycin, and amphotericin B. The control group received

TABLE 3 Effectiveness of Subglottic Drainage on Reducing the Incidence of Ventilator-Associated Pneumonia

A

Study or Subgroup	Subglottic Drainage Events	Subglottic Drainage Total	No Subglottic Drainage Events	No Subglottic Drainage Total	Weight	Risk Ratio M-H, Random, 95% CI
Bo	8	35	15	33	7.9%	0.50 [0.25, 1.03]
Bouza	12	45	19	40	11.9%	0.56 [0.31, 1.01]
Kollef	8	160	13	183	5.5%	0.70 [0.30, 1.65]
Lacherade	25	169	42	164	20.3%	0.58 [0.37, 0.90]
Lorente	11	140	31	140	9.7%	0.35 [0.19, 0.68]
Mahul	9	70	21	75	8.0%	0.46 [0.23, 0.93]
Smulders	3	75	12	75	2.7%	0.25 [0.07, 0.85]
Valles	14	76	25	77	12.4%	0.57 [0.32, 1.01]
Yang	12	48	20	43	11.8%	0.54 [0.30, 0.97]
Zheng	9	30	16	31	9.8%	0.58 [0.31, 1.11]
Total (95% CI)		**848**		**861**	**100.0%**	**0.52 [0.43, 0.64]**
Total events	111		214			

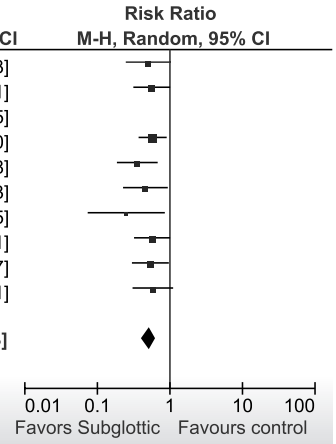
Heterogeneity: Tau² = 0.00; Chi² = 3.86, df = 9 (P = 0.92); I² = 0%
Test for overall effect: Z = 6.34 (P < 0.00001)



B

Study or Subgroup	Subglottic Drainage Events	Subglottic Drainage Total	No Subglottic Drainage Events	No Subglottic Drainage Total	Weight	Risk Ratio M-H, Random, 95% CI
Bo	8	35	15	33	8.4%	0.50 [0.25, 1.03]
Bouza	12	45	19	40	12.6%	0.56 [0.31, 1.01]
Kollef	8	160	13	183	0.0%	0.70 [0.30, 1.65]
Lacherade	25	169	42	164	21.5%	0.58 [0.37, 0.90]
Lorente	11	140	31	140	10.2%	0.35 [0.19, 0.68]
Mahul	9	70	21	75	8.5%	0.46 [0.23, 0.93]
Smulders	3	75	12	75	2.9%	0.25 [0.07, 0.85]
Valles	14	76	25	77	13.1%	0.57 [0.32, 1.01]
Yang	12	48	20	43	12.5%	0.54 [0.30, 0.97]
Zheng	9	30	16	31	10.3%	0.58 [0.31, 1.11]
Total (95% CI)		**688**		**678**	**100.0%**	**0.51 [0.42, 0.63]**
Total events	103		201			

Heterogeneity: Tau² = 0.00; Chi² = 3.38, df = 8 (P = 0.91); I² = 0%
Test for overall effect: Z = 6.33 (P < 0.00001)



a continuous infusion of a placebo. Because this study focused on the decontamination of the subglottic area rather than the SSD, this study was excluded.

RESULTS

The summary and appraisal of studies are presented in Table 1. Table 2 contains summary data of the outcomes variables. The pooled analyses across studies are graphically represented in Tables 3 to 8. The center vertical line indicates that the estimated effects are the same for both the interventions and control groups and is often called the line of no difference. Values to the left of the center line favor SSD and those to the right favor the control. The diamond on the lower aspect of the graph near the horizontal line represents pooled values.[57]

The Effectiveness of Subglottic Secretion Aspiration in Reducing VAP Rates

Across the studies, there were 848 cases in the experimental group and 861 in the controlled group. The pooled results examining the effectiveness of SSD in reducing the incidence of VAP demonstrated a 52% reduction (risk ratio, 0.52; 95% confidence interval, 0.43-0.64) in rates (Table 3).[58]

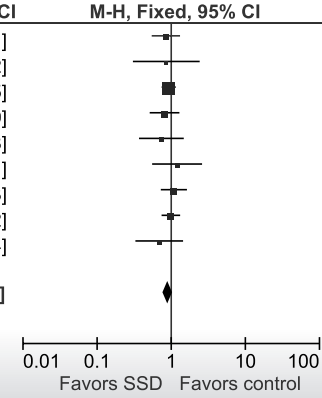
The Effectiveness of Subglottic Secretion Aspiration in Reducing the Duration of MV

Both Bouza and colleagues[30] and Lacherade and colleagues[33] reported median rather than days' duration of mechanical ventilation. Median durations of ventilation rates in the experimental groups were 3 and 8 days, and

TABLE 4 Effect of Subglottic Drainage on Mortality Rates

Study or Subgroup	Subglottic Drainage Events	Subglottic Drainage Total	No Subglottic Drainage Events	No Subglottic Drainage Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bouza	20	45	21	40	9.2%	0.85 [0.55, 1.31]
Kollef	6	160	8	183	3.1%	0.86 [0.30, 2.42]
Lacherade	80	169	84	164	35.1%	0.92 [0.74, 1.15]
Lorente	26	140	32	140	13.2%	0.81 [0.51, 1.29]
Mahul	11	70	16	75	6.4%	0.74 [0.37, 1.48]
Smulders	12	75	10	75	4.1%	1.20 [0.55, 2.61]
Valles	30	76	28	77	11.5%	1.09 [0.72, 1.63]
Yang	32	48	29	43	12.6%	0.99 [0.74, 1.32]
Zheng	8	30	12	31	4.9%	0.69 [0.33, 1.44]
Total (95% CI)		**813**		**828**	**100.0%**	**0.91 [0.80, 1.05]**
Total events	225		240			

Heterogeneity: Chi² = 2.76, df = 8 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)



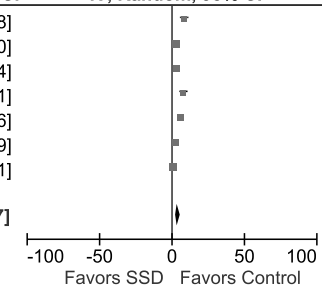
those for the control group were 7 and 7 days, respectively. When pooled, the results across studies that examined the impact of subglottic secretion drainage on days of mechanical ventilation were $\chi^2 = 14.73$, $df = 5$ ($P < .01$), $I^2 = 66\%$ (Table 6). An assumption of a systematic review is that the effect of the treatment being studied across patients is the same. This can be examined visually when all studies consistently demonstrate similar findings (favors either treatment or control). Consistency of treatment effect can also be examined by tests of heterogeneity with a low P value, indicating differences in underlying effects across studies. Thus, the $P < .0001$ would indicate the need for caution in interpreting the findings. The I^2 statistic is an estimate of

TABLE 5 Effectiveness of Subglottic Drainage on Increasing Days of Ventilator-Associated Pneumonia

A

Study or Subgroup	Subglottic Drainage Mean	SD	Total	No Subglottic Drainage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bo	14.8	8	35	6.4	4	33	10.2%	8.40 [5.42, 11.38]
Kollef	5.6	2.3	160	2.9	1.2	183	18.0%	2.70 [2.30, 3.10]
Lorente	10.5	11.12	140	7.2	5.3	140	13.3%	3.30 [1.26, 5.34]
Mahul	16.2	11	70	8.3	5	75	10.7%	7.90 [5.09, 10.71]
Valles	12	7.1	76	5.9	2.1	77	14.7%	6.10 [4.44, 7.76]
Yang	7.3	4.2	48	5.1	3	43	15.3%	2.20 [0.71, 3.69]
Zheng	6.5	1.3	30	5.5	0.6	31	17.8%	1.00 [0.49, 1.51]
Total (95% CI)			**559**			**582**	**100.0%**	**4.04 [2.60, 5.47]**

Heterogeneity: Tau² = 2.94; Chi² = 80.96, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 5.52 (P < 0.00001)



B

Study or Subgroup	Subglottic Drainage Mean	SD	Total	No Subglottic Drainage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bo	14.8	8	35	6.4	4	33	14.7%	8.40 [5.42, 11.38]
Kollef	5.6	2.3	160	2.9	1.2	183	0.0%	2.70 [2.30, 3.10]
Lorente	10.5	11.12	140	7.2	5.3	140	16.6%	3.30 [1.26, 5.34]
Mahul	16.2	11	70	8.3	5	75	15.1%	7.90 [5.09, 10.71]
Valles	12	7.1	76	5.9	2.1	77	17.3%	6.10 [4.44, 7.76]
Yang	7.3	4.2	48	5.1	3	43	17.6%	2.20 [0.71, 3.69]
Zheng	6.5	1.3	30	5.5	0.6	31	18.7%	1.00 [0.49, 1.51]
Total (95% CI)			**399**			**399**	**100.0%**	**4.61 [2.16, 7.05]**

Heterogeneity: Tau² = 8.27; Chi² = 74.09, df = 5 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.69 (P = 0.0002)

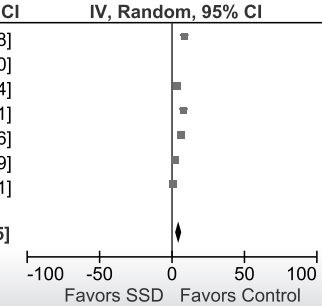
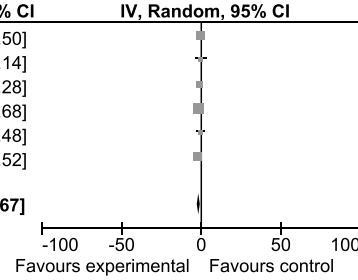


TABLE 6 Effectiveness of Subglottic Drainage on Duration of Mechanical Ventilation

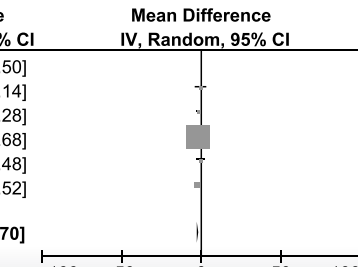
Study or Subgroup	Subglottic Drainage Mean	SD	Total	No Subglottic Drainage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kollef	1.5	3.3	160	1.9	5.1	183	22.8%	-0.40 [-1.30, 0.50]
Lorente	10.5	15.91	140	11	15.19	140	4.2%	-0.50 [-4.14, 3.14]
Smulders	5.8	4.4	75	7.1	5.4	75	14.3%	-1.30 [-2.88, 0.28]
Valles	11	1	76	13	1	77	30.6%	-2.00 [-2.32, -1.68]
Yang	8.1	7.5	48	8.4	6	43	6.6%	-0.30 [-3.08, 2.48]
Zheng	7.9	2.6	30	10.4	0.9	31	21.6%	-2.50 [-3.48, -1.52]
Total (95% CI)			**529**			**549**	**100.0%**	**-1.47 [-2.27, -0.67]**

Heterogeneity: Tau² = 0.52; Chi² = 14.73, df = 5 (P = 0.01); I² = 66%
Test for overall effect: Z = 3.60 (P = 0.0003)



Study or Subgroup	Subglottic Drainage Mean	SD	Total	No Subglottic Drainage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kollef	1.5	3.3	160	1.9	5.1	183	0.0%	-0.40 [-1.30, 0.50]
Lorente	10.5	15.91	140	11	15.19	140	0.6%	-0.50 [-4.14, 3.14]
Smulders	5.8	4.4	75	7.1	5.4	75	3.5%	-1.30 [-2.88, 0.28]
Valles	11	1	76	13	1	77	85.8%	-2.00 [-2.32, -1.68]
Yang	8.1	7.5	48	8.4	6	43	1.1%	-0.30 [-3.08, 2.48]
Zheng	7.9	2.6	30	10.4	0.9	31	8.9%	-2.50 [-3.48, -1.52]
Total (95% CI)			**369**			**366**	**100.0%**	**-1.99 [-2.29, -1.70]**

Heterogeneity: Tau² = 0.00; Chi² = 3.84, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 13.29 (P < 0.00001)

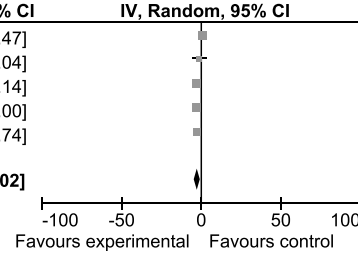


variability across studies, with an I^2 greater than 0.5 indicating large variability. In this study, the I^2 of 66% precludes confidence in the pooled analysis of study findings *because of* high levels of heterogeneity across studies. When the study by Kollef et al[32] was removed, the I^2 dropped to 0 with $z = 13.29$, $P < .00001$, indicating a

TABLE 7 Effectiveness of Subglottic Drainage on Length of Intensive Care Unit Stay

Study or Subgroup	Subglottic Drainage Mean	SD	Total	No Subglottic Drainage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kollef	3.7	4.6	160	3.2	4.5	183	24.4%	0.50 [-0.47, 1.47]
Lorente	14.1	17.91	140	15.5	19.93	140	11.0%	-1.40 [-5.84, 3.04]
Smulders	9.3	7.4	75	12.3	3.6	75	21.0%	-3.00 [-4.86, -1.14]
Valles	19	4	76	22	2	77	24.3%	-3.00 [-4.00, -2.00]
Zheng	9.3	2.9	30	12.3	5.7	31	19.2%	-3.00 [-5.26, -0.74]
Total (95% CI)			**481**			**506**	**100.0%**	**-1.97 [-3.91, -0.02]**

Heterogeneity: Tau² = 3.79; Chi² = 29.22, df = 4 (P < 0.00001); I² = 86%
Test for overall effect: Z = 1.98 (P = 0.05)



Study or Subgroup	Subglottic Drainage Mean	SD	Total	No Subglottic Drainage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kollef	3.7	4.6	160	3.2	4.5	183	0.0%	0.50 [-0.47, 1.47]
Lorente	14.1	17.91	140	15.5	19.93	140	3.3%	-1.40 [-5.84, 3.04]
Smulders	9.3	7.4	75	12.3	3.6	75	18.9%	-3.00 [-4.86, -1.14]
Valles	19	4	76	22	2	77	65.0%	-3.00 [-4.00, -2.00]
Zheng	9.3	2.9	30	12.3	5.7	31	12.8%	-3.00 [-5.26, -0.74]
Total (95% CI)			**321**			**323**	**100.0%**	**-2.95 [-3.76, -2.14]**

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 7.14 (P < 0.00001)

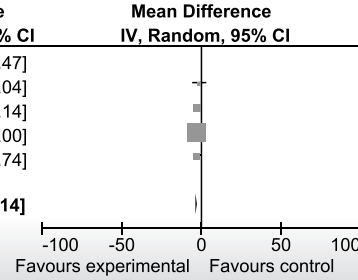
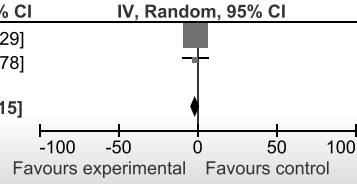


TABLE 8 Effectiveness of Subglottic Drainage on Length of Hospital Stay

Study or Subgroup	Subglottic Drainage Mean	SD	Total	No Subglottic Drainage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kollef	11	11.2	160	12.4	14.2	183	90.4%	-1.40 [-4.09, 1.29]
Smulders	26.8	23.3	75	28.3	28.2	75	9.6%	-1.50 [-9.78, 6.78]
Total (95% CI)			**235**			**258**	**100.0%**	**-1.41 [-3.97, 1.15]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)



shorter duration of mechanical ventilation by a mean of 1.99 days in the group who received subglottic secretion drainage.

An assumption of a systematic review is that the effect of the treatment being studied across patients is the same.

The Effectiveness of Subglottic Secretion Aspiration in Reducing Mortality

Eight hundred thirteen intervention cases and 828 control cases were pooled to examine the impact on mortality. Across studies the tests of heterogeneity were $\chi^2 = 2.76$, $df = 8$ ($P = .95$), $I^2 = 0$. The overall effect was $z = 1.13$ ($P = .26$), risk ratio = 0.93 (confidence interval, 0.81-1.06), indicating no significant difference in mortality rates between patients who did and did not receive subglottic secretion drainage (Table 4).

The Effectiveness of Subglottic Secretion Aspiration in Reducing the Length of ICU Stay

Tests for heterogeneity were $\chi^2 = 29.22$; $df = 4$, $P = .0001$, $I^2 = 0.86$, demonstrating that significant heterogeneity across studies would impact the reliability of pooled analysis. The test for overall effect was $z = 4.82$ ($P < .01$) (Table 7). When the study by Kollef and colleagues[32] was removed, the $I^2 = 0$ with $z = 7.14$, $P < .00001$, which indicated adequate homogeneity for pooling of study results. The mean length of ICU stay was 2.95 days shorter than that in the group that received subglottic drainage.

The Effectiveness of Subglottic Secretion Aspiration in Increasing Days to Onset of VAP

When the studies were pooled, analysis demonstrated significantly delayed onset of developing VAP in the SSD group. However, pooled tests of heterogeneity indicated significant variability across studies.[34] Consistency of treatment effect can be examined by tests of heterogeneity with a low P value, indicating differences in underlying effects across studies. Thus, $P < .0001$ would indicate differences in underlying-effect studies and require caution in interpreting the results. The I^2 statistic is an estimate of variability across studies with an I^2 precluding confidence in the pooled analysis of the findings because of high levels of heterogeneity across studies. Even though there was a statistically significant difference between the 2 groups, heterogeneity across studies would prohibit confidence in pooled findings. Even though there was a statistically significant difference between the 2 groups in the study of Kollef and colleagues[32] included in the analysis (Table 5), heterogeneity across studies would prohibit confidence in the pooled findings.

The Effectiveness of Subglottic Secretion Aspiration in Reducing the Length of Hospital Stay

The tests for heterogeneity were χ^2 0.00, $df = 1$, $P = .98$, $I^2 = 0$, indicating the results could be pooled. Test for overall effect $z = 1.08$, $P = .28$ (Table 8). The results of the analysis indicate no significant difference in length of hospital stay between the treatment and control groups.

Benefits and Harms

Although there were reports of airway complications attributed to intervention with an ETT that included SSD, complication rates were not routinely reported across studies. Types and rates of complications when intubated with any type of ETT could be used as an outcome variable in future studies.[59]

Potential Bias in the Review

As no efforts were made to locate either studies with negative results or unpublished studies, this systematic review may be at risk of publication bias.[60] The older studies were more likely to use intermittent SSD, whereas more recent studies utilized continuous aspiration, which is congruent with the manufacturer's recommendations. We included studies that utilized both intermittent and continuous SSD. As our expertise in the use of technology increases, recommendations for device use may change over time.

Consideration for Future Studies

Standard practices in the care of the critically ill change rapidly. It was most helpful when investigators included a description of standard-care practices for both groups whether it was the presence of a heeding tube, head-of-bed

elevation, or ETT cuff pressure and monitoring. The CONSORT guidelines provide a helpful framework for standardizing the information collected and reported in clinical studies.[61]

Although the "bundled" approach to reducing infections has been nationally embraced, there is still a need for randomized trials that examine the effectiveness of individual interventions.[62] By varying a single intervention at a time, causal relationships can be established. An ETT with SSD could be compared with ETTs with an ultrathin cuff membrane.[63] Investigators can contribute to the body of critical care knowledge by examining the effectiveness of this device as well as comparing ETTs with SSD to silver-coated ETTs while using consistent methods of screening in verifying the presence of VAP. The need at this time is to examine which of the specialized tubes is most effective in method comparison studies rather than to compare specialized ETTs to standard tubes.[64-66] In addition, there is the continuing need for systematic reviews focusing on an economic analysis of the cost and benefits of the various types of specialized ETTs used in the care of the critically ill patient.

DISCUSSION

The goal of this study was to examine the effectiveness of subglottic secretion aspiration in reducing the occurrence of VAP. The findings of this systematic review demonstrated a 50% reduction in VAP rates when an ETT with SSD was compared with an ETT without SSD. Across studies, subjects in the experimental group did experience a shorter duration of MV by approximately 2 days compared with control subjects.

Subglottic secretion drainage did not have a significant impact on mortality rates. Individuals requiring MV have underlying medical conditions, which may have a greater impact on mortality rates than the more subtle impact of the use of an ETT with the capabilities for SSD. Several investigators have established the positive relationship of VAP and mortality rates, which may well have a more direct causal relationship than the use of an ETT that facilitates removal of subglottic secretions.

Critically ill patients who received subglottic drainage were in the ICU at an average of 3 days less that those who did not. This is likely related to the fact that they were extubated an average of 2 days sooner. Thus, transfer from the ICU was likely linked to extubation. There was no difference in hospital length of stay. Critically ill patients who require MV represent the "sicker of the sick" among critically ill patients. It is likely that this underlying illness has greater impact on length of ICU stay than the type of ETT used is a more subtle cofactor. Thus, a larger sample would be needed for this smaller effect size as the impact is likely more subtle.

CONCLUSION

The results of this systematic review support level 1 recommendation[58] for use of ETTs with SSD for reducing the incidence of VAP.

Acknowledgments

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