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Technology Assessment Unit of the McGill University Health Centre (MUHC)

Subglottic Secretion Drainage Endotracheal Tubes for Prevention of Ventilator-Associated Pneumonia

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by

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PRINCIPAL MESSAGES

- A considerable body of evidence suggests that a modified endotracheal tube for subglottic secretion drainage (SSD ETT) can reduce the incidence of ventilation-associated pneumonia, The possibility cannot be excluded that this benefit might be the result of bias or confounding .
- In spite of this the available evidence of benefit is sufficiently convincing to serve as the basis for MUHC policy in the case of this relatively low-cost, apparently harmless intervention, until stronger evidence is available,
- Used for an estimated 500 cases per year the available evidence suggests that it would result in a reduction of 20 cases of ventilation-associated pneumonia and an associated 86 days of intensive-care unit occupancy per year with a budget impact of $9,250.
- It is recommended that SSD ETT should be approved for use in those patients who are expected to be mechanically ventilated in the intensive-care unit for at least 3 days.

LIST OF ABBREVIATIONS

CI	Confidence Intervals
CrI	Credible Intervals (Bayesian analysis)
ETT	Endotracheal Tube
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IHI	Institute of Health Information
MGH	Montreal General Hospital
MUHC	McGill University Health Centre
MV	Mechanical Ventilation
RCT	Randomized Controlled Trial
RR	Risk Ratio
RVH	Royal Victoria Hospital
SD	Standard Deviation
SSD	Subglottic Secretion Drainage
VAP	Ventilator-Associated Pneumonia

EXECUTIVE SUMMARY

Background

Ventilator-associated pneumonia (VAP) is a common nosocomial infection in mechanically ventilated patients. Intubation with a modified endotracheal tube (ETT) that allows subglottic secretion drainage (SSD) may reduce incidence of VAP. The Technology Assessment Unit was asked to evaluate the efficacy, cost and cost-effectiveness of such a device in reducing the risk of VAP in the adult intensive care units of the McGill University Health Centre (MUHC).

Method

A systematic literature search was conducted using the following online databases: PubMed, Medline, Embase, the International Network of Agencies for Health Technology Assessment, and the Centre for Reviews and Dissemination. Systematic reviews and randomized controlled trials (RCTs) comparing subglottic secretion drainage endotracheal tubes (SSD ETTs) to standard endotracheal tubes were selected. Efficacy of SSD ETT for prevention of VAP was estimated using Bayesian meta-analysis. Sub-group analyses were conducted to study the efficacy of the Hi-Lo Evac tube (Covidien) and the efficacy in cardiac surgery patients. Efficacies of SSD ETT in prevention of early-onset VAP and in postponement of VAP were also estimated. The net budget impact of routine use of SSD ETT and its cost-effectiveness compared to standard ETT were estimated.

Results

Literature review

Three systematic reviews were included. We identified only one additional RCT, which provided information on early-onset VAP. The sample size of the 14 included RCTs ranged from 18 patients to 714 patients. All but one of the RCTs were found to have possible methodological defects that could have led to bias. Eight RCTs reported using the Hi-Lo Evac tube and two RCTs included cardiac surgery patients only. Only two studies reported that they were known to be supported by the manufacturer.

Efficacy

SSD ETT significantly reduced either the frequency of VAP or early onset VAP in 11 of 14 studies. The pooled risk ratio (RR) for the decrease in frequency of VAP was 0.53 (95% Credible Interval (CrI) 0.43, 0.64) based on 13 studies. Meta-analysis of the 8 RCTs using the Hi-Lo Evac tube gave similar results (RR 0.59 (95% CrI 0.44, 0.78). Meta-analysis of 8 RCTs that reported risk ratios for prevention of early-onset VAP (within 5-7 days) gave a pooled RR of 0.24 (95% CrI 0.13, 0.42). The pooled RR in the two studies of cardiac surgery patients was 0.64 (95% CrI 0.16, 2.64). The

RR in the one study we considered to have the lowest risk of bias was 0.57(0.36, 0.88).

Safety

Only four of the 14 studies mentioned adverse events. Two studies reported that there were no complications associated with SSD ETT. One study reported that a few intervention group patients developed laryngeal oedema after extubation, while another study found slightly more intervention group patients developed laryngeal dyspnea postextubation.

Budget impact and cost effectiveness

Annually about 500 patients at the MUHC are intubated for 3 or more days, and therefore suitable candidates for SSD ETT. The estimated incidence rate of VAP at the MUHC is 8.3/1000 patient days. We assumed that patients receive mechanical ventilation for a median duration of 10 days, that the unit cost of SSD ETT is $18.50, and that the cost of ICU stay is $1,217 per day. We estimated that using SSD ETT would avoid 20 VAP cases (95% CrI 15, 24) in 500 target patients with a theoretical cost saving of approximately $202 per patient. Although this reflects increased efficiency, the beds made available would be used for other purposes and no actual budget saving would result. There would in practice be a budget impact on the MUHC (via the ICU cost centre) of $9,250.

Conclusions

- Twelve of 14 randomised controlled trials found a statistically significant reduction of VAP or early onset of VAP associated with use of SSD ETT. The average reduction based on all 14 studies is 47% (95% credible interval 36%, 53%).
- The possibility cannot be excluded that this benefit might be the result of bias or confounding due to other therapeutically effective co-interventions. Thus, further more methodically rigourous trials are very desirable.
- In spite of this, until stronger evidence is available, the available evidence of benefit is sufficiently convincing to serve as the basis for MUHC policy in the case of this relatively low-cost, apparently harmless intervention**.**
- Based on the efficacy as defined in this study, application of this technology to an estimated 500 patients per year would result in:
    - Prevention of 20 cases of VAP per year.

- An estimated reduction in ICU occupancy due to VAP of 86 bed days (95% credible interval 65days, 103 days), with an equivalent increase in the number of other patients treated.
- The budget impact of this intervention (the cost of the necessary equipment) would be $9,250.

Recommendations

SSD ETT is an efficacious intervention that should be approved for use in those patients who are expected to be mechanically ventilated in the ICU for at least 3 days.

SOMMAIRE

Contexte

La pneumonie associée à la ventilation assistée (PAVA) est une infection courante chez les patients ventilés mécaniquement. Mais l'intubation à l'aide d'un tube endotrachéal modifié permettant le drainage des sécrétions sous-glottiques pourrait réduire l'incidence des PAVA. L'Unité d'évaluation des technologies (« Technology Assessment Unit ») fut contacté pour évaluer l'efficacité, les coûts et le coût-efficacité d'un tel dispositif qui réduirait les risques de PAVA chez les patients adultes admis aux unités de soins intensifs du Centre universitaire de santé McGill (CUSM).

Méthodologie

Une recherche systématique de la littérature fut menée à partir des bases de données suivantes : PubMed, Medline, Embase, l'*International Network of Agencies for Health Technology Assessment* (INAHTA) et le *Centre for Reviews and Dissemination* (CRD). Les revues systématiques et les études randomisées comparant les tubes endotrachéaux avec drainage sous-glottique (TEDSG) et les tubes endotrachéaux standards furent choisies. L'efficacité des TEDSG dans la prévention des PAVA fut évaluée à partir d'une méta-analyse bayésienne. Les analyses des sous-groupes furent réalisées pour étudier l'efficacité du tube Hi-Lo Evac (Covidien) et son efficacité chez les patients ayant subi une chirurgie cardiaque. L'efficacité des TEDSG dans la prévention de l'apparition précoce et le report de la PAVA fut aussi évaluée. Enfin, l'impact budgétaire net de l'utilisation courante des TEDSG et son coût-efficacité comparé aux tubes endotrachéaux standards furent évalués.

Résultats. 3Revue de la littérature

Revues systématiques – Rapports d'évaluation des technologies

Trois revues systématiques furent retenues et nous avons identifié uniquement une seule étude randomisée supplémentaire qui fournissait de l'information sur l'apparition précoce de la PAVA. Le nombre de patients des 14 études randomisées retenues variait de 18 à 714 patients. Toutes les études randomisées, sauf une, furent soupçonnées d'une faiblesse méthodologique qui aurait pu entraîner un biais. Huit études randomisées mentionnaient l'utilisation des tubes endotrachéaux Hi-Lo Evac et deux études randomisées ne comprenaient que des patients ayant subi une chirurgie cardiaque. Seulement deux études ont rapporté le support financier d'un manufacturier.

Efficacité clinique

Les TEDSG diminuaient de façon significative la fréquence des PAVA ou leur apparition précoce dans 11 des 14 études. Le risque relatif sommatif (RR) pour la diminution du nombre de PAVA était de 0,53 (95% Intervalle de crédibilité (Icr) 0,43 - 0,64) basé sur 13 études. La méta-analyse des 8 études randomisées portant sur le tube endotrachéal Hi-Lo Evac fournit des résultats similaires (RR 0,59 (95% Icr 0,44-0,78). La méta-analyse des 8 études randomisées qui mentionnaient des RR reliés à la prévention de l'apparition précoce des PAVA (en deçà de 5 à 7 jours) fournit un RR sommatif de 0,24 (95% Icr 0,13-0,42). Le RR sommatif des deux études portant sur les patients ayant subi une chirurgie cardiaque était de 0,64 (95% Icr 0,16-2,64). Le RR de la seule étude qui avait le risque le plus faible était de 0,57 (95% Icr 0,36-0.88).

Innocuité

Seulement 4 des 14 études retenues mentionnèrent des évènements indésirables. Deux études ont souligné l'absence de toute complication avec les TEDSG tandis qu'une troisième mentionnait que quelques patients du groupe interventionnel avaient développé un œdème du larynx après extubation. Enfin, la dernière étude rapportait qu'un peu plus de patients du groupe interventionnel avaient développé une dyspnée laryngée postextubation.

Impact budgétaire et coût-efficacité

Environ 500 patients par année sont intubés au CUSM pour une durée de 3 jours ou plus et sont, par le fait même, des candidats pouvant recevoir un TEDSG. L'estimation du taux d'incidence de développer une PAVA au CUSM est de 8,3/1000 jours-patients. Pour évaluer l'impact budgétaire relié à l'utilisation des TEDSG, nous avons présumé que les patients sont ventilés mécaniquement pour une durée moyenne de 10 jours, que le coût unitaire d'un TEDSG est de 18,50 $ et que le per diem pour un lit aux soins intensifs est de 1 217 $ par jour. Nous avons ainsi estimé que l'utilisation des TEDSG nous permettrait d'éviter 20 cas de PAVA parmi 500 patients ciblés, se traduisant par des économies budgétaires théoriques d'environ 202 $ par patient. De façon pratique, ces économies ne permettent pas une réduction des dépenses mais reflètent une plus grande efficacité où les lits disponibles peuvent être utilisés à d'autres fins. En fait, il y aurait un impact budgétaire de 9 250 $ au niveau du budget des soins intensifs du CUSM.

CONCLUSIONS

- Parmi les 14 études randomisées retenues, douze études ont démontré une diminution statistiquement significative des PAVA ou d'une apparition précoce

reliée à l'utilisation des TEDSG. La diminution moyenne basée sur ces 14 études est de 47% (95% Icr 36%-53%).

- Par contre, l'on ne peut exclure la possibilité que ce bénéfice cache l'influence de biais reliés à d'autres interventions thérapeutiques qui se sont montrées efficaces. Ainsi, d'autres études rigoureuses s'imposent.

- Malgré ceci et en attendant que des preuves plus solides soient disponibles, les preuves actuelles montrant un certain bénéfice sont suffisamment convaincantes pour servir de base à une politique générale au CUSM en regard de cette intervention peu coûteuse et vraisemblablement inoffensive.

- En se basant sur l'efficacité clinique telle que définie dans cette étude, l'application de cette technologie chez environ 500 patients par année se traduirait par :
    - La prévention de 20 cas de PAVA, annuellement;
    - Une diminution de 86 jours-lits dans l'achalandage des lits de soins intensifs due aux PAVA (95% Icr 65 jours-lits – 103 jours-lits), impliquant une disponibilité pour un nombre équivalent de patients traités pour d'autres pathologies;
    - Un impact budgétaire de 9 250 $ dû à l'achat de ce dispositif.

RECOMMANDATIONS

Le TEDSG est une technologie dont l'utilisation devrait être approuvée chez les patients soupçonnés d'être ventilés mécaniquement aux soins intensifs pour une durée d'au moins 3 jours.

Subglottic Secretion Drainage Endotracheal Tubes for Prevention of Ventilator-associated Pneumonia

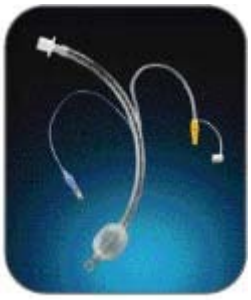
1. BACKGROUND

Ventilator-associated pneumonia (VAP), a common nosocomial infection, is a leading cause of morbidity and mortality in intensive care units (ICUs)(1). One European study estimated that cases of VAP accounted for almost half of all ICU infections (2). The mortality attributable to VAP is estimated to be between 15-50%(3). The estimated cost of an episode of VAP is $ 10,000 to $ 13,000(4).

VAP is defined as a hospital-acquired pneumonia that develops more than 48 to 72 hours after endotracheal intubation, as a result of mechanical ventilation (MV)(1). The infection results from microbial invasion of the lower respiratory tract and lungs(1). The main source of bacterial entry into the lower respiratory tract is drainage of contaminated secretions from above the endotracheal tube (ETT), also known as micro-aspiration of secretions(1). The primary focus of this report is to examine the efficacy of a modified ETT that allows for continuous subglottic secretion drainage.

The first commercially manufactured SSD ETT was the Hi Lo Evac tube (Covidien (previously Mallinckrodt), Dublin, Ireland), which was developed in 1992(1;4). The Hi Lo Evac tube has an additional lumen that stops above the tracheal cuff and connects to an external suctioning port that suctions the liquid that collects above the ETT cuff(4). Hi Lo Evac is intended for continuous aspiration of secretions(4). However, secretions can also be drained intermittently, or by manual aspiration using the same subglottic secretion drainage technology (4).

Figure 1 Subglottic Secretion Drainage Endo Tracheal Tube*



*** Hi-Lo Evac Tube (courtesy Covidien)**

Although there is evidence to suggest there is a benefit due to subglottic secretion drainage, uptake of the practice in routine care has been slow (4). One study from 2003 found that nurses performed subglottic secretion suction only 17.6% of the time(4). A study from 2000 surveyed the critical care practice of Canadian and French university-affiliated hospitals and found that less than 5% reported performing continuous aspiration of subglottic secretions(1). Currently, the American

Thoracic Society recommends the continuous aspiration of subglottic secretions as a preventive intervention (4),

The incidence rate of VAP in the Royal Victoria Hospital was 8.3 per 1000 ventilator days for the year 2010-2011(5). This is higher than the VAP rate of 5.4 per 1000 ventilator days published by the National Nosocomial Infections Surveillance (NNIS) Systems Report in the United States(6), based on voluntary reports from participating hospitals. The TAU was approached by Gary Stoopler , Administrative Director of the Medical Mission, MUHC, to evaluate the utility of SSD ETT in reducing the VAP rate at the MUHC, and the costs associated with its use.

2. OBJECTIVES

The objectives of this report are:

- To determine the efficacy of SSD ETT in reducing the risk of VAP in patients undergoing mechanical ventilation.
- To estimate the budget impact of using this technology at the MUHC.
- To estimate its cost effectiveness from the point of view of the MUHC

3. METHODS

3.1 Literature search and quality assessment

A systematic literature search of articles was performed using online databases of PubMed, Medline (1948-2011), Embase (1980-2011), the International Network of Agencies for Health Technology Assessment (INAHTA), and the Centre for Reviews and Dissemination (CRD) to identify health technology assessment (HTA) reports, systematic reviews and randomized controlled trials (RCTs). Three systematic reviews were identified, the most recent, published in 2011. Because it was not possible to determine the efficacy of the instrument of interest to the MUHC, the Hi-Lo Evac model of SSD ETT, and because we wished to reassess the risk of bias in each study and identify any possible new studies published since April 2010, we carried out a systematic review of published RCTs. No limits were applied for language or year of publication. We used the following key words and MeSH terms: ("Supraglottic" OR "Subglottic") AND ("endotracheal tube" OR "Intratracheal" OR "Intubation") AND ("ventilator-associated pneumonia" OR "VAP"). A further search was conducted by tracking references in publications identified. The date of the last literature search was September 9, 2011. The literature search was performed by two reviewers, working first independently and subsequently reviewing outstanding or conflicting issues together (IN and XX).

3.2 Inclusion criteria

We included HTAs and systematic reviews of the efficacy of SSD ETT if they were published in 2000 or later and if the authors reported a systematic approach to identify, select and synthesize the available evidence.

We included RCTs that met the following criteria: i) they compared SSD ETT to standard ETT in studies of adults (or a majority of adults) who required mechanical ventilation (MV), ii) they reported the number of patients randomized to each group and those experiencing VAP in each group.

3.3 Data extraction

English articles were reviewed by all authors. Data extraction was performed by one reviewer (XX) and independently verified by the other reviewer (IN). Chinese articles were read by one reviewer only (XX), though the data extraction was verified by the second reviewer (IN). We extracted conclusions and sources of evidence (e.g. RCTs included) for the HTAs and systematic reviews. We extracted the following information from RCTs when available: risk of VAP, risk of early-onset VAP, time to VAP, risk of adverse safety events associated with SSD ETT, type of SSD ETT, industry support and co-interventions. Early-onset VAP refers to VAP diagnosed within 5-7 days of mechanical ventilation (MV) (7;8). If the authors conducted both intention to treat (ITT) analysis and per-protocol analysis, we extracted data from the ITT analysis.

3.4 Risk of bias in RCTs

The nature of the SSD ETT intervention increases the risk of a number of well-recognized biases in RCTs. It is not possible to blind physicians and nurses to the group to which a patient has been randomized. Further, the eligibility of a patient for the trial is based on the physician's subjective judgement as to how long the patient will be ventilated. Even the diagnosis of VAP involves some degree of subjectivity.

The lack of blinding of caregivers gives rise to the possibility of intervention group patients receiving better quality of care, particularly co-interventions, e.g. placing the patient in a semi-recumbent position, that are known to decrease the risk of VAP. Lack of blinding of those who evaluate outcome increases the chances of detection bias in diagnosing VAP. The physician's role in determining eligibility increases the risk of selection bias. Thus it is very important for studies to have an appropriate randomization strategy with concealment of treatment allocation until the time that patient eligibility is determined. In addition, in the absence of blinding of outcome evaluation the diagnosis of VAP should be based as far as possible on recorded objective criteria.

We used a quality tool previously developed by TAU to assess the risks of bias of non-medical RCTs. This instrument estimates the presence or absence of potential

bias in four domains 1) *Selection bias* (including randomization strategy and allocation concealment), 2) *Detection bias*, (blinded assessment of VAP, or, in the absence of blinding, the use of objective diagnostic criteria), 3) *Attrition Bias* . (absence of dropouts, or if present evidence, that they are not treatment-related with adequate adjustment of dropouts when the percentage of dropouts is high). and 4) *Substantial conflict of interest* (See Appendix 1). Potential bias was judged to be either absent or present in each domain, irrespective of whether there were one or more reasons to suspect bias in that domain. Failure to describe appropriate methodology was considered to be equivalent to describing defective methodology. Thus the number of domains judged to be susceptible to bias varied from 0 to 4. The risk of bias in English articles was assessed by two reviewers (XX and ND) independently, while the Chinese articles were scored by one reviewer only (XX). Any disagreements were resolved by discussion.

3.4 Meta-analysis of RCTs

The primary outcome of interest was the efficacy of SSD ETT for the prevention of VAP. In particular, we focused on estimation of the between-study variability and some sub-group analyses that had not been carried out in the earlier systematic reviews. One previous review (9) had identified two studies among cardiac surgery patients as being of high quality and both studies had reported a statistically non-significant result despite being large. We were interested in the efficacy within the following sub-groups: i) studies using the Hi-Lo Evac model of SSD ETT, ii) studies that did or did not receive manufacturer support, and iii) studies of cardiac surgery patients, iv) studies with a low risk of bias. In secondary analyses, we estimated the efficacy of SSD ETT to prevent early-onset VAP. We used Bayesian hierarchical models with low information prior distributions(10) to estimate the pooled and predicted risk ratio (RR) of VAP and early onset VAP (11). We reported the posterior median and 95% credible interval (95% CrI) of the parameters of interest.

3.5 Cost effectiveness analysis

Our primary interest was to estimate the cost-effectiveness of the use of SSD ETT compared to standard ETT. Our analysis considered two costs: the cost of the SSD ETT device and the cost of VAP treatment. We assumed that resource consumption was balanced in both arms with the exception of these two costs. For simplicity, we ignored clinical outcomes (e.g. VAP mortality) whose cost is difficult to estimate. The estimate of the baseline risk of VAP was obtained from data provided by the Infection Control Department, MUHC(5). The estimated efficacy of SSD ETT was based on the predicted risk ratio from our meta-analysis. We obtained an estimate of the increase in ICU length of stay attributable to VAP and the daily cost of antibiotics from a Canadian cost-effectiveness analysis carried out in 2008 (12). We used MUHC surveillance data from the Department of Finance for the estimate of the cost of admission to ICU (primarily personnel cost and supplies). We estimated the

median (95% Crl) of the incremental cost of SSD ETT compared to standard ETT. We also estimated the net annual budget impact of adopting SSD ETT at the MUHC.

Meta-analyses and cost-effectiveness analysis were performed using Winbugs 1.4 and SAS 9.2 for Windows, respectively (13;14). Monte Carlo simulations were used to obtain the credible intervals.

4. RESULTS OF SYSTEMATIC REVIEW

4.1 Health technology assessment reports/systematic reviews

We identified three systematic reviews and meta-analyses published in 2005, 2010, and 2011 (4;9;15), all of which concluded that SSD ETT is efficacious and safe. The results of the three systematic reviews are summarized in end-of-text Table 2. The most recent systematic review by Muscedere et al included 13 RCTs (2442 patients) (7;8;16-26) and concluded that SSD ETT reduced the risk of VAP by nearly half (pooled RR (95% Confidence Interval (CI)): 0.55(0.46, 0.66).

Muscedere et al. 2011 also reported on the efficacy of SSD ETT for several secondary outcomes. They found that SSD ETT did not significantly reduce ICU mortality, hospital mortality, or risk of adverse events. SSD ETT was associated with significantly reduced length of stay in ICU, reduced duration of mechanical ventilation and longer time to first episode of VAP, but there was substantial between-study heterogeneity in these outcomes.

4.2 Randomized controlled trials

Our literature search retrieved 137 citations, and from these 15 articles were selected for full-text review. Fourteen studies(7;8;16-27) met our inclusion criteria, including one study(27) not included in the most recent review (9). The additional study, by Liu SH et al (27), reported results of early-onset VAP only. The sample sizes of the 14 included studies ranged from 18 in Girou et al (21) to 714 in Bouza et al (24). Five out of 14 studies were written in Chinese (19;22;25-27) with English abstracts.

The percentage of ventilated cases who developed VAP was highly variable, ranging from 5.1% (22) to 71.4% (15). Likewise, the maximum duration of mechanical ventilation was also highly variable across studies ranging from 10 days(21) to 65 days(22).

SSD ETT significantly reduced either the frequency of VAP or of early onset VAP in 12 of 14 studies and the time to the first episode of VAP in 6 of 10 studies. For detailed results see Figure2 and Table 3. Information on the types of SSD ETT used,

types of co-interventions used, adverse events reported and source of financial support is summarized in the end-of-text Table 4.

4.2.1 Potential for bias

Five studies reported using semi-recumbency positioning as a cointervention. In three of these it was carried out in both intervention and control groups(25-27), but in two it was in the intervention group only(21;22). Since the semi recumbent position is associated with a reduced risk of pneumonia (28;29). This must be considered a likely source of confounding error.

Based on our risk of bias assessment, Lacherade et al (7) was the only study with no apparent risk of bias in any of the domains considered (Table 5). The pooled risk ratio for prevention of VAP based on this study was 0.57(0.36, 0.88). Five studies (8;22;24;25;27) had a risk of bias in 1 domain, 5 studies (17;18;20;21;23) in 2 domains and 3 studies (16;19;26) in ≥3 domains. Only Lacherade et al (7) described performing the appropriate randomization strategy and using concealed allocation of treatment. Two studies (16;26) were judged to suffer from detection bias. Four studies (16;19;23;26) did not report applying an analytic method to adjust for incomplete outcomes. It should be noted that of the 52 "defects" recorded in Table 5, all but 8 were failures to record appropriate methodology rather than reports of defective methodology.

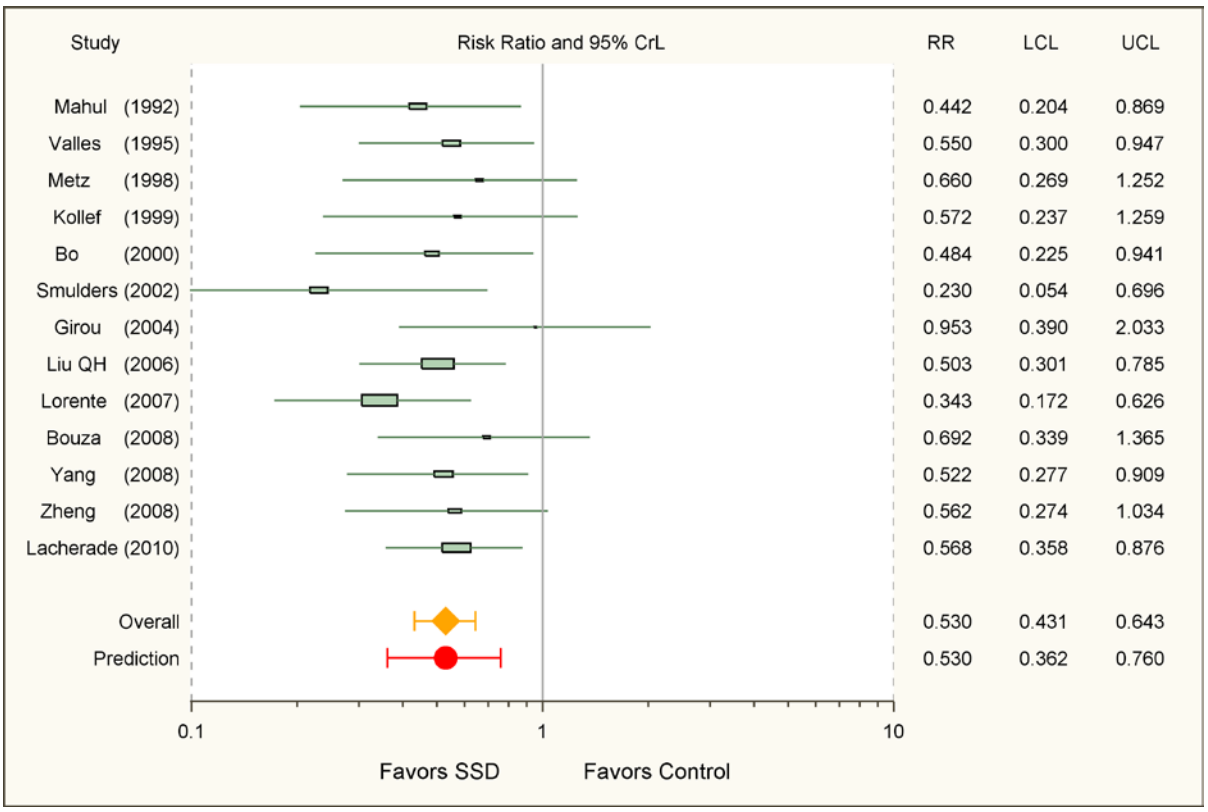
Two studies (17;18) were supported in part by the manufacturer, and neither of these reported statistically significant results. Eight (7;8;22-27) of the 14 studies declared either that there were no conflicts of interests, or that they were supported by public research grants. The other 4 studies (16;19-21) did not report sources of financing.

4.2.2 Efficacy of SSD ETT for prevention of VAP

Our estimate of the pooled risk ratio (RR) for prevention of VAP was similar to that obtained by the previous review of Muscedere et al. as it was based on 13 of the 14 studies (Pooled RR (95% Credible Interval (CrI)) 0.53 (0.43, 0.64)) (Figure 2).

The between-study standard deviation in the log risk ratio (0.09 (95% CrI 0.006, 0.36)) was relatively low, indicating little heterogeneity between studies. Further, the predicted RR for an individual study was 0.53 (95% CrI 0.36, 0.76), supporting the observation that there was very little heterogeneity between the results of individual studies for this outcome.

Figure 2 Results of meta-analysis of the efficacy of sub-glottic suction drainage endotracheal tubes (SSD ETT) on prevention of ventilation-associated pneumonia (VAP)



Type of SSD ETT

Ten studies reported the type of SSD ETTs used (7;8;16-19;21;23-25). Yang et al (25) used EVAC^{tm} (OHMEDA, USA) suction system. Lorente et al (23)used the SealGuard Evac tube that is made up of two portions : the polyurethane cuff and the subglottic secretion drainage. The other 8 studies (7;8;16-19;21;24) used a Hi-Lo Evac tube (Covidien, previous Mallinckrodt, Ireland). It should be noted that these 8 studies described the SSD ETT only briefly and it is unclear whether they used an identical device. Meta-analysis of these 8 RCTs resulted in a pooled RR of 0.59 (95% CrI 0.44, 0.78), comparable to the median pooled RR from all 13 studies.

Cardiac surgery

The subgroup analysis performed on patients who require mechanical ventilation after Cardiac surgery, consisting of 2 RCTs (18;24), with relatively large sample sizes, did not show that SSD ETT significantly reduced the risk of VAP (pooled RR (95% Confidence Interval (CI)): 0.64(0.16, 2.64). Following cardiac surgery radiological lung shadows may be observed for reasons other than pneumonia and when associated with pyrexia might lead to misdiagnosis. It is therefore uncertain whether one should conclude that SSD is ineffective in post-cardiac surgical cases,

or whether statistical significance could not be reached because of "noise" due to overdiagnosis.

4.3.2 Efficacy of SSD ETT for preventing early-onset VAP

Eight RCTs (7;8;17-19;22;23;27) reported the efficacy of SSD ETT for prevention of early-onset VAP (onset within 5-7 days). With the exception of the study by Metz et al. (17) (which had a small sample size of 24 patients), the other 7 studies found a statistically significant risk reduction in early-onset VAP in the intervention group. In total, 22 out of 679 patients in the SSD ETT group and 93 out of 706 patients in the control group had early-onset VAP, respectively. The pooled and predicted RRs were 0.24 (95% CrI 0.13, 0.42) and 0.24 (95% CrI 0.06, 0.84), respectively. The between-study standard deviation in the log risk ratio was 0.34 (95% CrI 0.02, 1.3), indicating some heterogeneity between studies.

4.3.3 Efficacy of SSD ETT for postponing the onset of VAP

Ten RCTs (7;8;16-19;23;25-27) reported the impact of SSD ETT on time to VAP among VAP patients. The average time to VAP ranged from 4.4(17) to 16.2(16) days in the intervention group, and 2.9(18) to 9.3(7) days in the control group. Five of the 10 studies found a statistically significant difference of time to VAP between the intervention and control groups (8;16;18;19;27).

4.4 Safety

Only four of the 14 studies mentioned adverse events. Kollef et al(18) and Bouza et al(24), reported that there were no complications associated with SSD ETT. In Girou et al (21), 2 patients developed laryngeal oedema after extubation in the SSD ETT group, but it was not clear whether it was related to the intervention. Lacherade et al. (7) reported episodes of postextubation laryngeal dyspnea (inspiratory dyspnoea associated with stridor) in 8/79 (10.1%) of the SSD ETT group versus 4/89 (4.5%) in the control group.

5. ESTIMATION OF COSTS AND COST-EFFECTIVENESS

5.1 ASSUMPTIONS

- Patients in need of mechanical ventilation for at least 3 days would be candidates for intubation with SSD ETT. Dr. Jayaraman estimated that 200 patients at the RVH site and 300 patients at the MGH site would be eligible each year.

- The efficacy of SSD ETT was estimated by the predicted RR from the Bayesian meta-analysis (RR 0.53 (95% CrI 0.43, 0.76)).
- Incidence of VAP at the MUHC was assumed to be 8.3 per 1000 ventilator days (based on data from Infection Control Department, MUHC). The median duration of mechanical ventilation was assumed to be 10 days among patients ventilated for a minimum of 3 days (based on data from Infection Control Department, MUHC). Therefore, the approximate risk of VAP for an individual patient was estimated as 8.3%(5).
- The unit cost of SSD ETT was assumed to be $18.50 based on a quotation from the manufacturer (Covidien). We assumed that the unit cost is fixed and that each patient receives one SSD ETT.
- We assumed that the increase in the length of ICU stay attributed to VAP was 4.3 days (95% CI, 1.5-7 days) (12).
- The estimated cost of ICU stay was based on MUHC data, $1,217 per day (Department of Finance, MUHC).
- Costs of antibiotics were estimated to be $49.80 (29.30-70.30) per day for 10 days(12).

We assumed that both the length of increased ICU stay and cost of antibiotics follow a Gamma distribution whose 95% credible interval matched the ranges given above. All costs were expressed in 2011 Canadian dollars (30).

5.2 Cost and cost-effectiveness of SSD ETT

The estimated cost of using SSD ETT for all 500 eligible patients would be $9,250. Based on our assumptions this would be cost-effective (Table 1), since it would help avoid roughly 20 VAP cases in 500 target patients with a theoretical cost reduction of $202 (95% CrI 72, 388) per patient or $100,900 (95% CrI 36140, 193800) per year. Note, however, that in practice any ICU beds saved as a result of this intervention would be used for other patients. Thus, this intervention would result in increased efficiency, but not in budget saving. There would in practice be a budget impact on the MUHC (via the ICU cost centre) of $9,250 .

Table 1 Cost-effectiveness of subglottic secretion drainage (SSD) endotracheal tube (ETT) for prevention of ventilator-associated pneumonia (VAP)*

	Expected number of VAP in 500 patients	Expected Number of VAP avoided in 500 patients	Cost per patient ($)	Incremental cost per patient ($)
Standard ETT	42	--	481 (257, 820)	--
SSD ETT	22 (15, 31)	20 (10, 26)	274 (142, 501)	-202 (-388, -72)

*All results are expressed as median (95% Credible Interval).

Sensitivity analysis showed that even if the duration of mechanical ventilation is as low as 5 days, use of SSD ETT still results in cost savings of $ 92 (27, 185) per patient. If the incidence of VAP declined to 5/1000 days then the cost saving per patient would be $114 (36, 226).

6. DISCUSSION

The estimated efficacy (RR 0.53 (95% CrI 0.43, 0.76)) arrived at in this meta-analysis strongly suggests that SSD ETT is an efficacious intervention to prevent VAP that could potentially lead to substantial cost reduction for the MUHC. However, this result must be interpreted with caution. Only 1 of the 14 RCTs we included can be considered to have low risk of bias. Due to the nature of the intervention, it was not possible to blind caregivers to the group to which a patient had been randomized. Therefore, we cannot completely eliminate the possibility that the reported benefit of SSD ETT in these studies is attributable to the intervention group patients receiving better quality care than their control group counterparts, thus biasing the results in favour of SSD ETT.

Other risk factors for VAP and the ventilator bundle

Though the focus of this report has been SSD ETT, it should be noted, that it is only one of many available interventions that have been proposed for the prevention of VAP. Moreover, some have observed that compliance with a ‘bundle’ of multiple such interventions is necessary for any of them to be effective in clinical practice (28;29). As described in Appendix 2, a number of observational studies have reported successful reduction in VAP rates following the implementation of a bundle of interventions. These bundles did not always include SSD ETT.

7. CONCLUSIONS

- Twelve of 14 randomised controlled trials found a statistically significant reduction of VAP or early onset of VAP associated with use of SSD ETT. The average reduction based on all 14 studies is 47% (95% credible interval 36%, 53%).
- The possibility cannot be excluded that this benefit might be the result of bias or confounding due to the occurrence of other therapeutically effective co-interventions. Thus, further more methodically rigourous trials are very desirable.
- In spite of this, until stronger evidence is available, the available evidence of benefit is sufficiently convincing to serve as the basis for MUHC policy in the case of this relatively low-cost, apparently harmless intervention
- Based on the efficacy defined in this study, application of this technology to an estimated 500 patients per year would result in:
    - Prevention of 20 cases of VAP per year.
    - An estimated reduction in ICU occupancy due to VAP of 86 bed days (95% credible interval 65days, 103 days), with an equivalent increase in the number of other patients treated.
    - The budget impact of this intervention (the cost of the necessary equipment) would be $9,250.

RECOMMENDATIONS

SSD ETT is an efficacious intervention that should be approved for use in those patients who are expected to be mechanically ventilated in the ICU for at least 3 days.

Tables

Table 2 **Conclusions of systematic reviews of subglottic secretion drainage endotracheal tube for prevention of ventilator-associated pneumonia**

Author (year)	**Conclusions**	**Source of evidence**
Muscedere (2011)(9)	The use of endotracheal tubes with subglottic secretion drainage is effective for the prevention of ventilator-associated pneumonia and may be associated with reduced duration of mechanical ventilation and intensive care unit length of stay.	13 RCTs: Mahul (16), Valles(8), Metz(17), Kollef(18), Bo(19), Smulders(20), Girou(21), Liu QH(22), Lorente(23), Bouza(24), Yang(25), Zheng(26), Lacherade(7)
Scherzer (2010) (4)	Subglottic secretion aspiration is both a safe and effective therapy.	6 RCTs: Mahul (16), Valles(8), Kollef(18), Smulders(20), Lorente(23), Bouza(24)
Dezfulian (2005)(15)	Subglottic secretion drainage appears effective in preventing early-onset ventilator associated pneumonia among patients expected to require >72 hours of mechanical ventilation.	5 RCTs: Mahul (16), Valles(8), Kollef(18), Bo(19), Smulders(20)

RCT: Randomized Controlled Trial

Table 3. Summary of primary outcomes of the selected randomized controlled trials (RCTs) of subglottic secretion drainage (SSD) endotracheal tube (ETT) for prevention of ventilator-associated pneumonia (VAP)

		Number of VAP / Total N (%)			Time to VAP: mean (SD) days		
Author (year)	**Inclusion criteria**	**SSD ETT**	**Standard ETT**	**P value**	**SSD**	**Control**	**P value**
Mahul (1992) (16)	Expected MV duration > 3 days	9/70 (12.8)	21/75 (29.1)	<0.05	16.2 (11)	8.3 (5)	<0.05
Vallés (1995) (8)	Expected MV duration > 3 days	14/76 (18.4) Early onset: 3/76 (3.9)!	25/77 (32.5) Early onset: 21/77 (27.3)!	<0.046‡ Early onset: <0.001	12 (7.1)	5.9 (2.1)	<0.001
Metz (1998) (17)	Expected MV duration > 3 days	5/10 (50) Early onset: 3/10 (30)	10/14 (71.4) Early onset: 3/14 (21.4)	>0.05 Early onset: 0.6653‡	4.4 (1.14) ‡	5.1 (0.88) ‡	0.208‡
Kollef (1999) (18)	Require MV after cardiac surgery	8/160 (5) Early onset: 2/160 (1.3)	15/183 (8.2) Early onset: 15/183 (8.2)	0.238 Early onset: 0.005‡	5.6 (2.3)	2.9 (1.2)	0.006
Bo (2000) (19)	MV duration > 3 days	8/35 (23) Early onset: 2/35 (6)!	15/33 (45) Early onset: 10/33 (30)!	<0.05 Early onset: <0.01	14 (8)	6 (4)	<0.05
Smulders (2002) (20)	Expected MV duration > 3 days	3/75 (4)	12/75 (16)	0.014	NR	NR	NR
Girou	Expected MV	5/8 (62.5)	6/10 (60)	1.00‡	Median: 4	Median: 12	NR

		Number of VAP / Total N (%)			Time to VAP: mean (SD) days		
Author (year)	**Inclusion criteria**	**SSD ETT**	**Standard ETT**	**P value**	**SSD**	**Control**	**P value**
(2004) (21)	duration > 5 days						
Liu SH (2006)(27)	MV duration > 2 days	Early onset: 3/48 (6.3)	Early onset: 10/50 (20)	Early onset: 0.045	7.7 (3.2)	4.6 (2.1)	0.002
Liu QH (2006)@ (22)	Expected MV duration > 2 days	14/41 (34.1) Early onset: 2/41 (4.9)	30/45 (66.7) Early onset: 9/45 (20)	<0.01 Early onset: <0.05	NR	NR	NR
Lorente (2007)* (23)	Expected MV duration > 1 day	11/140 (7.9) Early onset: 5/140 (3.6)	31/140 (22.1) Early onset: 15/140 (10.7)	0.001 Early onset: 0.02	10.5 (11.1)	7.2 (5.3)	0.36
Bouza (2008) (24)	Require MV after cardiac surgery	13/345 (3.8)	19/369 (5.1)	0.178‡	NR	NR	NR
Yang (2008) (25)	Expected MV duration > 2 days	12/48 (25)	20/43 (46.5)	0.032	7.3 (4.2)	5.1 (3)	0.1
Zheng (2008) (26)	Expected MV duration > 2 days	9/30 (30)	16/31 (51.6)	<0.05	6.5 (1.3)	5.5 (0.6)	>0.05
Lacherade (2010) (7)	Expected MV duration > 2 days	25/169 (14.8) Early onset: 2/169 (1.2)	42/164 (25.6) Early onset: 10/164 (6.1)	0.02 Early onset: 0.02	9.1 (5.1) +	9.3 (5.6) +	0.884‡

SSD: Subglottic Secretion Drainage; ETT: Endotracheal Tubes; VAP: Ventilator-Associated Pneumonia; N: Number; MV: Mechanical Ventilation; SD: standard deviation; VAP (< 5 days); NR: Not Reported.

‡: Authors did not state the p value. We used Chi Square test, Fisher's exact test or T test for two independent samples to calculate the p value.

!: Definition of early-onset VAP: ≤ 7 days.

@: Authors reported results of the early-onset VAP only, and did not report the total number of VAP events for each group. But, authors stated that there are no statistical differences between SSD and control in late-onset VAP without further details. We judged that the statistics of the mean and SD of the time to VAP were based on all VAP cases.

*: The experimental group had two interventions, the polyurethane cuff and subglottic secretion drainage. Polyurethane cuff can reduce channel formation and fluid leakage from the subglottic area.

+: This article did not report the time to VAP. We obtained the information from Muscedere's review, which included some unpublished data.

Table 4 Summary of type of subglottic secretion drainage tube used, adverse events reported and funding received in each of the selected randomized controlled trials

Author (year)	Type of SSD device	Adverse events associated with SSD ETT	Co-interventions	Financial Support
Mahul (1992) (16)	Hi-Lo Evac tube	NR	Patients in both groups randomly received either antacid (aluminum hydroxide) in 20 ml/6 h, or sucralfate (cytoprotective agent) in 1 g/6 h.	NR
Vallés (1995) (8)	Hi-Lo Evac tube	NR	None specified	Public research grant (partial)
Metz (1998) (17)	Hi-Lo Evac tube	NR	None specified	Manufacturer (partial)
Kollef (1999) (18)	Hi-Lo Evac tube	No adverse events were associated with SSD.	None specified	Manufacturer (partial)
Bo (2000) (19)	Hi-Lo Evac tube*	NR	None specified	NR
Smulders (2002) (20)	NR	NR	None specified	NR
Girou (2004) (21)	Hi-Lo Evac tube	In SSD, 2 developed laryngeal oedema after extubation.	SSD group: Patients were placed in semirecumbent position (30º) in the bed; control group: in supine position.	NR
Liu SH (2006)(27)	NR	NR	The head of bed was elevated 30º - 45º in both groups.	Public research grant
Liu QH (2006)@ (22)	NR	NR	SSD group: Patients were placed in semirecumbent position (30º - 45º), and received Mosapride 5mg tid (gastroprokinetic agent).	Public research grant

Author (year)	Type of SSD device	Adverse events associated with SSD ETT	Co-interventions	Financial Support
Lorente (2007) (23)	SealGuard Evac tube	NR	SSD group: additional polyurethane cuff of the tube.	Authors had no financial relationship with the company, but, who supported this RCT was unclear.
Bouza (2008) (24)	Hi-Lo Evac tube	No complications were rated to SSD.	None specified	No significant conflicts of interest#
Yang (2008) (25)	EVAC suction system @	NR	If applicable, the head of bed was elevated 30º - 45º in both groups.	Public research grant
Zheng (2008) (26)	NR	NR	Patients were placed in semi recumbent position in the bed in both groups.	Public research grant
Lacherade (2010) (7)	Hi-Lo Evac tube	Similar compliance between two groups; postextubation laryngeal dyspnea: 8/79 (10.1%) in SSD vs. 4/89 (4.5%) in control (p-value=0.25); Reintubation: 4 cases in SSD vs. 2 in control.	None specified	Public research grant , no conflicts of interest

NR: Not Reported

*: Authors did not report the type of SSD, but reported the manufacturer, Covidien, Ireland. We judged that this study used Hi-Lo Evac tube.

#: This study was partly supported by Ciber de Enfermedades Respiratorias (CIBERES) and by the Rafael del Pino Foundation. The authors have declared that “no significant conflicts of interest exist”.

@: They used EVAC^{tm} suction system, OHMEDA, USA.

Table 5 Risk of bias in the selected randomized controlled trials

	Selection bias[1]		Detection bias[2]		Attrition Bias[3]			Absence of major conflict of interest[4]	Domains with potential bias
	Randomization appropriate	Allocation concealed	Outcome evaluation blinded	Defined objective outcome	Dropout rates <5% in both arms	Difference in dropout rates <5%. Not treatment related	Analytic method adequate		
Mahul (16)	NR	NR	NR	NR	NO	NR	NR	NR	4
Vallés (8)	NR	NR	YES	YES	NO	YES	--	YES	1
Metz (17)	NR	NR	NR	YES	YES	--	--	NO	2
Kollef (18)	NO	NO	YES	YES	YES	--	--	NO	2
Bo (19)	NR	NR	NR	YES	NR#	NR#	NR#	NR	3
Smulders (20)	NR	YES	YES	YES	YES	--	--	NR	2
Girou (21)	NR	NR	NR	YES	YES	--	--	NR	2
LiuSH (27)	YES	NR	NR	YES	NO	YES#	--	YES	1
LiuQH (22)	NR	NR	NR	YES	YES	--	--	YES	1
Lorente (23)	YES	NR	YES	YES	NR	NR	NR	YES	2
Bouza (24)	NR	YES	NR	YES	YES	--	--	YES	1
Yang (25)	YES	NR	NR	YES	NO	YES#	--	YES	1
Zheng (26)	YES	NR	NR	NR	NR!	NR#	NR#	YES	3
Lacherade (7)	YES	YES	YES	YES	YES	--	--	YES	0

1: Absence of Selection Bias Patients are appropriately randomized **AND** randomization is concealed until treatment commences.

2: Absence of Detection Bias.Blinded assessment of outcomes **OR** There is a defined objective outcome.

3: Absence of Attrition Bias. There are <5% dropouts **OR** If > 5%, dropout rates in each arm differ by <5%, **OR** The reasons for dropouts are given and are not treatment related, **OR** if outcome data are incomplete, they are analysed by appropriate statistical methods (e.g. survival analysis, multiple imputation, Crossovers analysed by Intention To Treat).

4: Absence of Major Conflict of Interest. Not entirely or largely supported by manufacturer. Not contract research. No industry participation in design, execution, or writing. No receipt by authors of substantial personal benefit. No equity interest.

For further explanation of method, see Appendix.

NR = Not reported.

#: Evidence of exclusion of patients following randomization without sufficient information.

APPENDIX 1: EVALUATION OF RISK OF BIAS IN RCTS

	NO
Selection bias	
Allocation was adequate and concealed?[1]	☐
Detection bias.	
Blinding was adequate and appropriate?[2]	☐
Attrition Bias	
There were no dropouts/exclusions that could have been treatment related[3] that were not adequately addressed,[4] Any crossovers were analysed by ITT?	☐
Conflict of Interest	
There is no evidence of substantial[5] conflict of interest?	☐

NOTES

This tool is intended as a guide to assist the evaluation of the validity of randomised controlled trials. Before use, one should add, subtract, or modify items, and review definitions to ensure they are appropriate for the trials under consideration.

1. Randomization method is clearly described and appropriate. There are no substantial (>10%), unexplained, differences between study arms.

2. Appropriate. The importance of blinding evaluators, subjects, and treaters will vary with intervention and outcome. First define appropriate blinding for the study in question. Do not score unachievable/inappropriate items. Only penalise failure to blind *treater* if this is likely to lead to *performance* bias.

3. Dropouts/Exclusions are an *unlikely* source of bias unless they are *treatment related*. So reasons should be given. Suspect a relationship to treatment when there is unexplained *inequality* (>5%) in the two arms of the study.

4. Adequate methods, (including statistical approaches such as survival analysis in studies recording time to event data or multiple imputation in studies that record outcomes only at the end of the study) should be used for handling incomplete outcome data.

5. Substantial conflict of interest. First define "substantial", in the context of the study. Suggestion: *Industry sponsorship, industry authorship (employment of an author by industry), contract research, receipt by authors of substantial personal financial benefit search (>$ 5,000), equity interest* constitute significant conflict of interest.

APPENDIX 2: VENTILATOR BUNDLE FOR PREVENTION OF VAP

Several other modifiable causes of VAP, besides miro-aspiration of secretions, have been identified including supine patient positioning, gastric over-distension, contamination of ventilator circuits, frequent patient transfers, and inadequate tube cuff pressure(31). These in turn have lead to numerous suggestions for prevention strategies (31). In an attempt to increase compliance with evidence-based guidelines for reducing risk of VAP, the Institute for Healthcare Improvement (IHI) proposed a simplified, four-component ventilator bundle for patients on mechanical ventilation(28;29). The four components proposed by them are: raising the head of the patient's bed by 30-40°, giving prophylaxis to prevent stomach ulcers, giving prophylaxis to prevent blood clots, and daily sedation interruption and assessment of readiness to extubate(28;29). Moreover, this initiative requires 95% compliance to each of the components (32).

Individual centers have extended or modified this bundle to suit their local requirements. A recent review by Klompas(33) listed 16 studies that had evaluated a VAP bundle, each study using different combinations of 13 possible components. Fourteen of these studies reported a reduction in VAP ranging from 37% to 100%. Only 6 of these reported aspiration of subglottic secretions as a component of the bundle. A 2009 systematic review included four studies implementing the original IHI bundle (that does not include SSD ETT) and reported that the incidence of VAP was reduced from the range of 2.7-13.3 cases to 0.0-9.3 cases per 1000 MV days(34). Of the four included studies only two reported compliance rates. One study reported 100% compliance (34), while the second study, of 35 hospital centers, reported that only 60% of centers had adherence rates greater than 95%(34). Both the reviews by Klompas(33) and Zilberberg(34) identified multiple shortcomings in the ventilator bundle research published so far, including the problems with the before-after design that does not control for a secular trend, the lack of published research, the potential of publication bias since the overwhelming majority of recent articles reported only positive results, the possibility of selection bias due to the absence of blinding and problems in defining and diagnosing VAP. Zillerberg and collegues concluded there was insufficient evidence to support the use of the ventilator bundle since the instrument's internal validity as an intervention to reduce VAP rates has not been evaluated using rigorous methodology(34).

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