New Endotracheal Tubes Designed to Prevent Ventilator-Associated Pneumonia: Do They Make a Difference?

Steven Deem MD and Miriam M Treggiari MD PhD MPH

Introduction
Pathogenesis of Ventilator-Associated Pneumonia: The Role of the Endotracheal Tube
Strategies for Preventing Ventilator-Associated Pneumonia
Continuous Suctioning of Subglottic Secretions
Polyurethane-Cuffed Endotracheal Tubes
Antibacterial-Coated Endotracheal Tubes
Other Miscellaneous Tubes and Devices
Cost Concerns With Modified Endotracheal Tubes
Summary

Ventilator-associated pneumonia (VAP) is a pervasive and expensive nosocomial infection that is largely related to instrumentation of the airway with an endotracheal tube (ETT), followed by microaspiration of contaminated secretions. VAP prevention will probably be most effective via a multifaceted approach, which includes meticulous attention to basic infection-control methods during patient care, proper patient positioning, oral hygiene, and removal of the ETT as soon as indicated. Modification of the ETT to reduce microaspiration and/or biofilm formation may also play an important role in VAP prevention. However, despite numerous studies of various such interventions, there is insufficient evidence upon which to base strong recommendations, and important safety concerns remain regarding the use of some devices. Most importantly, cost-effectiveness data are lacking for modified ETTs designed to prevent VAP. It is critical that future studies of ETTs designed to prevent VAP be adequately powered to demonstrate efficacy on important patient outcomes and safety, in addition to cost-effectiveness. *Key words: nosocomial pneumonia; infection; subglottic; endotracheal tube; ventilator-associated pneumonia; VAP; mortality; morbidity*. [Respir Care 2010;55(8):1046–1055. © 2010 Daedalus Enterprises]

Introduction

Nosocomial pneumonia is a common complication in critically ill patients. A large multicenter study conducted in European intensive care units (ICUs) and involving more than 10,000 patients identified pneumonia as by far the most common nosocomial infection, with an overall prev-

Steven Deem MD and Miriam M Treggiari MD PhD MPH are affiliated with the Anesthesiology Department, Harborview Medical Center, University of Washington, Seattle, Washington.

Dr Deem presented a version of this paper at the 25th New Horizons Symposium, "Airway Management: Current Practice and Future Directions," at the 55th International Respiratory Congress of the American Association for Respiratory Care, held December 5–8, 2009, in San Antonio, Texas.

The authors have disclosed no conflicts of interest.

Correspondence: Steven Deem MD, Anesthesiology Department, Harborview Medical Center, Box 359724, 325 Ninth Avenue, Seattle WA 98104. E-mail: sdeem@u.washington.edu.

alence of 10%.[1] Mechanical ventilation has been consistently identified as the greatest risk factor for the development of nosocomial pneumonia.[2-6] Indeed, ventilator-associated pneumonia (VAP) accounts for 80–90% of cases of nosocomial pneumonia in ICU patients.[4,7,8] This observation is probably due to factors associated with translaryngeal intubation rather than simply an effect of patient susceptibility from severity of illness (see below under "Pathogenesis"). The quoted incidence of VAP ranges widely, between 5% and 67%, depending on the patient population studied and the diagnostic criteria used.[9] The 6 largest studies, involving a mixed population of more than 5,500 patients and a variety of diagnostic techniques, identified VAP incidences between 9% and 28%.[10-15] The risk of VAP is highest in the first few days of intubation, with a daily hazard rate of approximately 3% at day 5 of intubation, decreasing to 1% per day by day 15.[16] Cumulative risk continues to accrue for the duration of mechanical ventilation.

VAP appears to be independently associated with increased morbidity, as measured by increased duration of mechanical ventilation, ICU stay, and hospital stay.[17-19] A retrospective analysis of 4,543 patients at 59 United States hospitals found that mortality associated with VAP was 29%, compared to 19% and 10% for hospital-acquired and community-acquired pneumonia, respectively.[20] In the largest studies that reported mortality, the mortality figures associated with VAP ranged from 24% to 54%.[11-14,18] Because the likelihood of VAP also increases with severity of illness, the mortality attributable to VAP is difficult to separate from the mortality related to other aspects of the patient's illness. Studies using case-control design suggest that the mortality attributable to VAP is between 15% and 48%, and may be higher in the presence of multiple-drug-resistant pathogens.[6,17,18,21,22] The increased intensity and duration of care for patients with VAP is also associated with increased cost of care.[20] Papazian et al observed that the incremental costs associated with VAP were generated even in the absence of significantly increased duration of mechanical ventilation, ICU stay, or hospital stay.[19] A conservative estimate of the increased costs due to VAP, using matched controls and based on an average increased stay of 10 days, was approximately $12,000 (inflation-adjusted to 1992 United States dollars).[23] A more recent study found that hospital charges were $48,500 (inflation-adjusted to 1996 United States dollars) greater in patients with VAP, compared to matched controls.[24]

Several strategies to prevent VAP have been investigated, and are reviewed in depth elsewhere.[25,26] Prevention of VAP has focused primarily on:

- Reduction of digestive tract, airway, and endotracheal tube (ETT) colonization with pathogenic bacteria[27-32]
- Improvement of pulmonary secretion clearance by rotational therapy[25,33]
- Prevention of microaspiration of oropharyngeal contents by semi-recumbent positioning[34-36]
- Prevention of microaspiration via alterations in ETT design
- Prevention of ETT bacterial colonization by coating the ETT lumen with silver chloride[32]

Several approaches have been found promising, but are associated with measurable or potential costs.[25,32] The remainder of this review will focus on the role of the ETT in the pathogenesis of VAP, and how modification of the ETT may help prevent VAP.

Pathogenesis of Ventilator-Associated Pneumonia: The Role of the Endotracheal Tube

A compelling argument can be made that it is the ETT, and not the ventilator, that increases susceptibility to pneumonia in ICU patients.[37] Placement and maintenance of a tube through the glottis predisposes to nosocomial pneumonia via several possible mechanisms:

- Aspiration of oropharyngeal secretions during tracheal intubation, as illustrated by the increased risk of VAP associated with re-intubation[38,39]
- Trauma and mechanical forces on the tracheal wall that decrease mucosal integrity and reduce mucociliary clearance of secretions
- Microaspiration of secretions around the inflated ETT cuff
- Biofilm formation and bacterial colonization inside the ETT lumen.

The following discussion will focus on microaspiration, biofilm formation, and colonization.

VAP appears to be preceded by bacterial colonization of the trachea in most cases.[9,26,40-43] The major source of colonization is probably contaminated oropharyngeal secretions that leak through folds of the inflated ETT cuff into the trachea.[41,44-46] Microaspiration occurs in virtually 100% of inflated high-volume, low-pressure ETT cuffs.[44,46] Microaspiration is reduced but still present in the semi-recumbent, compared to the supine, position.[34,35] Oropharyngeal bacterial colonization increases the risk of developing VAP, and there is concordance between oropharyngeal colonizing flora and the causative organisms of VAP, as diagnosed by invasive techniques.[47,48] Furthermore, interventions that reduce oropharyngeal colonization (topical oropharyngeal antiseptics, selective digestive decontamination) or reduce tracheal microaspira-

tion (semirecumbent positioning) reduce the incidence of VAP.[27-29,31,36]

Another way the ETT may contribute to VAP is through bacterial colonization and subsequent biofilm formation in the lumen of the tube. This process occurs within a few days of tracheal intubation, and there is remarkable concordance between the organisms within the biofilm and tracheal-suctioning samples from patients with VAP.[49,50] A biofilm is a structured community of bacterial cells in a self-produced polymeric matrix and adherent to an inert or living surface.[51] Biofilms appear to confer resistance to antibiotics by creating a microenvironment that favors bacterial proliferation and makes the bacteria inaccessible to antimicrobials.[52] A biofilm adhering to the surface of the ETT may act as a continuous source of bacterial contamination of the lower respiratory tract. On the other hand, the ETT appears to become colonized with bacteria after the lower respiratory tract.[42] This observation suggests that microaspiration of contaminated secretions may be the primary event in the causal pathway for VAP, but that biofilm formation plays a role in maintaining tracheal bacterial colonization.

Strategies for Preventing Ventilator-Associated Pneumonia

Considering the mechanisms leading to VAP, it would appear that efforts to reduce microaspiration of contaminated secretions and biofilm formation within the ETT lumen would be beneficial in preventing VAP. One obvious approach to prevention of VAP is to avoid instrumentation of the airway by using noninvasive ventilation when appropriate. A meta-analysis by Hess found that the use of noninvasive ventilation conferred a reduction in the relative risk of VAP of 76–85%, in comparison with invasive mechanical ventilation.[53] A recent analysis of over 6,000 cases of nosocomial pneumonia from 400 German hospitals found a nearly 5-fold increase in the mean incidence density of pneumonia in patients undergoing invasive ventilation, compared to noninvasive ventilation.[54] These data further support the role of airway violation by the ETT in the causal pathway for VAP.

In terms of other interventions to minimize microaspiration and airway colonization, limited evidence suggests that reduction of microaspiration by using semi-recumbent positioning reduces the risk of VAP[36,55,56]; likewise, decontamination of the oropharynx with topical chlorhexidine may also reduce the risk of VAP.[31] However, given that neither of these interventions has been conclusively shown to prevent VAP, alternative and/or multi-modality approaches could further minimize the risk of VAP. The following section reviews modifications of the design of the ETT that aim to reduce microaspiration, and a variety of techniques designed to limit biofilm formation on the lumen of the ETT (Table 1).[57-65]

Continuous Suctioning of Subglottic Secretions

One innovation in ETT design is the placement of an orifice just above the tube cuff, connected to an externalized lumen that allows intermittent or continuous suctioning of subglottic secretions (Fig. 1).[57] The principle behind this technique is that secretions pool in the space between the laryngeal aperture and the ETT cuff, and that removal of these secretions may prevent or minimize microaspiration, tracheal colonization with bacteria, and ultimately VAP. Nine randomized trials and one prospective observational trial have investigated ETTs that allow subglottic suctioning.[38,60,66-72] Suction was applied continuously or intermittently via the suction port to remove subglottic secretions. A meta-analysis examined the data from five of these studies and estimated that subglottic suctioning gave an approximately 50% overall reduction in the risk of VAP, based on the pooled results (relative risk 0.51, 95% CI 0.37–0.71).[57] The time to onset of VAP was delayed by 3.1 days (95% CI 2.7–3.4) with the use of subglottic suctioning. When examined on an intention-to-treat basis, the relative risk of death in patients receiving subglottic suctioning from the 4 studies reporting mortality was 1.13 (95% CI 0.84–1.53).[67-70] Likewise, there were no significant effects of subglottic suctioning on duration of mechanical ventilation, ICU stay, or hospital stay. However, when per-protocol analysis was performed, there were significant reductions in duration of mechanical ventilation and ICU stay.

Of the remaining studies investigating the role of subglottic suctioning in VAP prevention, one small randomized trial published only in the Chinese language reported a significant reduction in VAP, duration of mechanical ventilation, and ICU stay in association with the intervention.[71] Another small randomized trial found a significant reduction in VAP in patients who were intubated with a polyurethane-cuffed subglottic-suctioning ETT, but no effect on other outcomes.[60] A third small trial found no effect of subglottic suctioning on tracheal bacterial colonization or VAP,[73] and a prospective, observational study of 250 patients found no effect of subglottic suctioning on the risk of VAP.[72]

The largest single study of subglottic suctioning to prevent VAP randomized 740 patients undergoing major cardiac surgery to intubation with a subglottic-suctioning ETT and continuous subglottic suctioning in the ICU, versus intubation with a conventional ETT.[38] The subglottic-suctioning ETT did not reduce the incidence of VAP or the duration of mechanical ventilation, ICU stay, hospital stay, or mortality. The subglottic-suctioning ETT was associ-

Table 1. Selected Endotracheal Tubes and Related Devices for Prevention of VAP

Device	Proposed Mechanism	Comments
Hi-Lo Evac	Extra lumen allows continuous suctioning of subglottic secretions to prevent microaspiration	Appears to reduce early-onset VAP, but cost-effectiveness and safety not clear[57]
Microcuff	Polyurethane cuff to prevent microaspiration	Limited data suggest less short-term microaspiration, but effect on VAP not clear[58]
SealGuard	Polyurethane cuff to prevent microaspiration	One RCT suggested efficacy in preventing postoperative pneumonia, but cost-effectiveness not clear[59]
SealGuard Evac	Combination continuous suctioning of subglottic secretions plus polyurethane cuff to prevent microaspiration	One RCT showed efficacy in preventing VAP, but cost-effectiveness not clear[60]
TaperGuard Evac	Combination continuous suctioning of subglottic secretions plus tapered cuff to prevent microaspiration	No published data available
LoTrach	Combination low-volume, low-pressure cuff and continuous suctioning of subglottic secretions to prevent microaspiration	Limited data suggest less short-term microaspiration, but effect on VAP not clear.[61] Not available in the United States.
Agento IC	Silver-coated lumen to prevent biofilm formation	One RCT showed efficacy in preventing VAP,[32] but cost-effectiveness and safety not clear. High acquisition cost.
Mucus Slurper	Extra lumen allows suctioning of secretions from tip of endotracheal tube	Prevents mucus buildup in vitro,[62,63] but no published clinical data
Mucus Shaver	Inflatable silicone-rubber "razor" to remove mucus and biofilm from endotracheal tube lumen	Reduces mucus buildup in vitro,[64,65] but no published clinical data

VAP = ventilator-associated pneumonia
RCT = randomized controlled trial

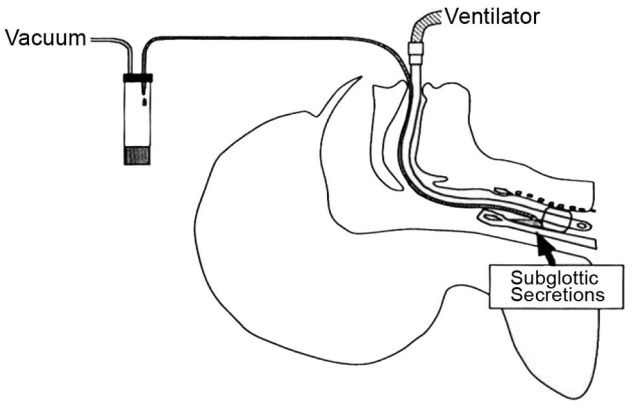

Fig. 1. Subglottic secretion drainage. The endotracheal tube has a dorsal lumen (black arrow) above the cuff, which is connected to suction to remove the secretions that pool above the cuff in the subglottic space. (From Reference 57, with permission.)

ated with less antibiotic use and less VAP in a subset of the population intubated for more than 48 hours.

Based on the literature reviewed above, there is no clear evidence about the efficacy and effectiveness of subglottic suctioning in reducing the development of VAP. Moreover, there are several limitations in the data from the randomized trials that reduce their strength and generalizability:

Patient Selection and Lack of Intention-to-Treat Analysis. Each of the studies that have shown a significant effect of subglottic suctioning selected patients who were expected to require mechanical ventilation for 2–3 days or more, and yet the criteria for making that determination were not explicit in any study.[66,68-71] In 2 studies, patients who were ventilated less than 3 days were excluded from analysis, invalidating the randomization process.[69,70] The lack of intention-to-treat analysis and vagaries in study selection process limits the ability to make inference to a larger, mixed population of patients requiring emergency tracheal intubation with no knowledge of the anticipated duration of ventilation.

Practically, it is difficult to introduce a device into practice when the criteria for patient selection and identification of the target population likely to benefit from the intervention are not explicit. In practice, it is often difficult to predict duration of ventilation at the time of intubation in the emergency setting. Approximately 60% of the variability in duration of mechanical ventilation is explained by patient characteristics, and duration of ventilation can be at least in part predicted using multiple logistic regression techniques.[74] Therefore, it is likely that practical implementation of subglottic suctioning would require insertion of the subglottic-suctioning ETT in an unselected population of patients requiring mechanical ventilation of

variable duration. A large-scale implementation of tracheal intubation with subglottic-suctioning-equipped ETTs has not been proven efficacious. Additionally, inefficiencies associated with widespread insertion of the subglottic-suctioning ETT may reduce the cost-effectiveness of the device (see discussion below).

Lack of Application of Other Strategies to Reduce VAP. None of the positive studies of subglottic suctioning systematically applied concomitant strategies known to reduce the risk of microaspiration and VAP, such as semi-recumbent positioning.

Lack of Cost-Effectiveness Data. In addition to the methodological issues and limitations in the available studies, the cost related to subglottic suctioning has not been adequately addressed by previous investigations.

Safety Concerns Associated With the Subglottic-Suctioning ETT. Important safety concerns regarding the use of the subglottic-suctioning ETT and subglottic suctioning exist. Subglottic suctioning may lead to mucosal drying and trauma and thus predispose the airway to injury more than intubation with a conventional ETT, as demonstrated in a recent in vivo study.[75] Sheep that were intubated with a subglottic-suctioning ETT and subjected to continuous subglottic suctioning and mechanical ventilation for 3 days all exhibited severe tracheal mucosal injury, including necrosis and exposure of tracheal cartilage.[75] Animals intubated with a conventional ETT had no tracheal injury. A recent clinical study raises additional concerns about the potential for subglottic suctioning to cause tracheal injury; in 17 (43%) of 40 patients undergoing subglottic suctioning who were evaluated endoscopically, herniation of the tracheal mucosa into the subglottic suctioning lumen was evident.[76]

Another concern is that in order to maintain competency of the suction lumen the subglottic-suctioning ETT is thicker and more rigid than conventional ETTs, which may lead to an increase in airway-related complications. The outside diameter of a 7.5-mm inner-diameter subglottic-suctioning ETT (Hi-Lo Evac, Mallinckrodt, St Louis, Missouri) is approximately 1 mm greater than that of a conventional tube with the same inner diameter This is concerning, given that increasing tube size is a risk factor for pharyngeal and laryngeal injury.[77,78] A case report described the occurrence of a tracheal-innominate artery fistula associated with use of a Hi-Lo Evac Tube, following which the authors confirmed the increased rigidity of the tube in a bench model.[79]

Complications related to the subglottic-suctioning ETT were not mentioned in 6 of the 9 prospective randomized trials of subglottic suctioning. In 2 trials the absence of complications was reported, but in those trials the duration of mechanical ventilation was relatively short.[38,67] It is not clear if airway complications were systematically sought in these or any of the other trials. However, concern regarding the safety of the subglottic-suctioning ETT and subglottic suctioning was raised in the study by Girou et al, who reported laryngeal edema requiring re-intubation in an exceedingly high proportion (25%) of patients undergoing subglottic suctioning.[73] This compares to an incidence of re-intubation due to stridor and upper-airway obstruction of approximately 1–2% when conventional tubes are used.[80,81]

It is conceivable that the limited benefit of subglottic suctioning on duration of mechanical ventilation, stay, and mortality in prospective trials might be due to an increased incidence of airway-related complications that result in the need for re-intubation or prolonged intubation that offset the benefits of preventing VAP. Future trials should include more systematic evaluation of safety issues associated with subglottic suctioning and the subglottic-suctioning ETT.

Given the above discussion, it is evident that there are insufficient efficacy data and concerns regarding the safety of subglottic suctioning and the subglottic-suctioning ETT; these concerns warrant caution in widely deploying this intervention for the prevention of VAP. Despite this apprehension, both the Center for Disease Control (Level II recommendation)[82] and the American Thoracic Society (Level I recommendation)[83] recommend subglottic suctioning of tracheal secretions as a VAP-preventive measure.

Polyurethane-Cuffed Endotracheal Tubes

Recently, efforts have focused on modifying the ETT cuff composition and design to prevent channel formation within the inflated cuff and consequent microaspiration. Several studies have found that tracheal tube cuffs composed of polyurethane or silicone prevent leakage of dye around the cuff, in comparison to conventional cuffs composed of polyvinylchloride, both in vitro and in vivo (Fig. 2).[58,84-86] A small randomized trial in patients undergoing cardiac surgery found that tracheal intubation with a polyurethane-cuffed tube was associated with a reduced incidence of early postoperative pneumonia, compared to intubation with a traditional polyvinyl-chloride cuffed tube (23% vs 42%).[59] Preliminary results from a study comparing VAP rates before and after introduction of a polyurethane-cuffed tube found that VAP rates were reduced from 5.5/1,000 to 2.8/1,000 ventilator days.[87] Another randomized trial compared a tube that features both a polyurethane cuff and a subglottic suctioning port to a conventional tracheal tube in medical-surgical ICU patients and found a significant reduction in VAP among patients who used the specialized tube (22% vs 8%).[60] However, it is

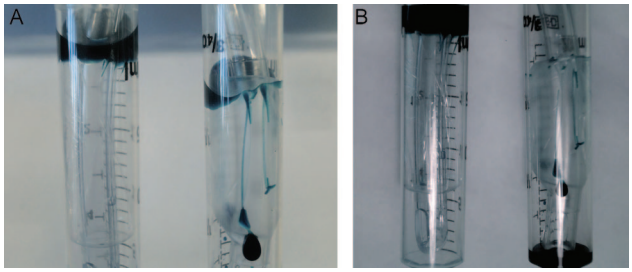

Fig. 2. A: Polyurethane-cuffed (left) and polyvinylchloride-cuffed (right) endotracheal tubes with 2 mL of dye above the inflated cuff. Note that channels in the polyvinylchloride-cuff allow leakage of dye from above to below the cuff. B: Fifteen minutes later all the dye has leaked past the polyvinylchloride cuff, but remains above the polyurethane cuff.

unclear if the benefit seen was related to the tube cuff, subglottic suctioning, or a joint effect of both ETT modifications. Neither of the above randomized trials detected a difference in duration of mechanical ventilation, ICU stay, or mortality between the groups. Cost-effectiveness data for these devices have not been reported. Thus, further evidence is needed before polyurethane-cuffed ETTs can be recommended as a widespread VAP prevention measure.

Two commercially available ETTs with polyurethane cuffs are available: Microcuff (Kimberley Clark, San Antonio, Texas) and Sealguard (Mallinckrodt, Covidien-Nellcor, Boulder, Colorado). There are no studies directly comparing these 2 tubes, and insufficient evidence upon which to base conclusions as to their relative efficacy.

No safety issues have been raised regarding polyurethane-cuffed ETTs, and there are no known theoretical concerns as to these tubes posing an added safety risk. However, safety data on the use of polyurethane-cuffed tubes are limited.

Antibacterial-Coated Endotracheal Tubes

In an effort to limit bacterial colonization and biofilm formation on the lumen of the ETT, investigators have studied tubes coated or impregnated with silver, silver sulfiadiazine, and silver sulfadiazine plus chlorhexidine.[88-90] Because of concerns about hypersensitivity reactions to chlorhexidine-impregnated devices, this agent has fallen out of favor as a tube coating.[91] Silver sulfadiazine coating has been shown to prevent bacterial colonization of the ETT lumen in the experimental setting and in short-term intubation of patients; however, there are no data available on the efficacy of this intervention in preventing VAP.[88,90]

Silver-coating of the ETT lumen is the best-studied of the antibacterial interventions. Pre-clinical and small clinical trials have documented a reduction in bacterial colonization of tubes internally coated with silver.[89,92,93] Subsequently, a large, multicenter trial randomized 2,003 patients to tracheal intubation with either a conventional ETT or a tube coated with silver.[32] The incidence of VAP was lower in the group of patients intubated for $\geq$ 24 hours who used the silver-coated ETT (4.8% vs 7.5%, $P = .03$). The difference was smaller when all intubated patients were considered (3.8% vs 5.8%, $P = .04$). More importantly, and as might be expected given the relatively low incidence of VAP in that study, there was no effect of silver-coated ETT on other meaningful clinical outcomes, such as duration of mechanical ventilation, or ICU stay, or hospital stay. Furthermore, there was a worrisome trend toward increased mortality in patients randomized to the silver-coated ETT (30.9% vs 27.3%, $P = .08$). The mechanism for a paradoxical effect on mortality of the silver-coated ETT was not addressed in the paper. Given these results and the lack of cost-effectiveness data on the use of this very expensive device, the silver-coated ETT cannot be recommended as a standard VAP-preventive intervention, and further investigation is warranted.

Other Miscellaneous Tubes and Devices

Other interventions designed to prevent or reduce VAP include modification of the ETT cuff shape and inflation characteristics, and devices designed to reduce mucus buildup on the lumen of the ETT (mucus slurpers and shavers). Similar to using polyurethane or silicone to manufacture the ETT cuff, changing the shape and inflation characteristics of the cuff is designed to eliminate folds in the in vivo inflated cuff that otherwise allow microaspiration.[85,94] Although several ETTs with various cuff modifications are commercially available, there are insufficient clinical data to allow conclusions about their ability to prevent VAP.

The Mucus Slurper is an ETT with suction ports arranged radially around the tip of the tube, and is designed to prevent the entry and buildup of tracheal secretions in the ETT lumen.[62,63] Preclinical studies suggest that the Mucus Slurper is effective at reducing mucus buildup inside the ETT, although it had no effect on bacterial colonization of the trachea. There are no clinical reports on the use of this device. The Mucus Shaver, which shares developers with the Mucus Slurper, is an inflatable silicone-rubber "razor" that is introduced into the lumen of the ETT, thus allowing cleaning or "shaving" of material built up within the lumen.[64,65] Laboratory studies suggest that the Mucus Shaver can reduce mucus buildup within the ETT, but the safety and efficacy of this device has not been reported in human subjects, and neither are there data documenting any effect on VAP development.

The LoTrach ETT (Intavent Orthofix, Berkshire, United Kingdom) is commercially available in Europe, and, sim-

ilar to the Sealguard Evac ETT, incorporates a low-volume, low-pressure cuff designed to inflate uniformly, combined with a suction port for subglottic suctioning.[61,85] Although this dual approach appears to be effective at preventing short-term microaspiration, there are no published data on this device's effects on the incidence of VAP.

Cost Concerns With Modified Endotracheal Tubes

In terms of estimated acquisition costs for hospitals, the conventional, polyvinyl chloride-cuffed ETT costs approximately one dollar per tube, the polyurethane-cuffed ETT costs between 3 and 4 dollars per tube, the polyurethane-cuffed subglottic-suctioning ETT costs over $30 per tube, and the silver-coated ETT costs over $100 per tube. The incremental costs of the modified tubes may be well justified, depending on their relative efficacy in reducing VAP. However, the considerable increase in acquisition costs compared to that of conventional tubes prohibits their routine, unselected use in the absence of reliable cost-effectiveness data. To date, these data have not been reported for any of these devices, and modeling efforts to justify the high acquisition costs of these tubes have been severely flawed, as discussed below.

Shorr et al modeled the cost-effectiveness of using the original subglottic-suctioning ETT (Hi-Lo Evac, Mallinckrodt, Covidien-Nellcor, Boulder, Colorado) with continuous suctioning versus conventional ETTs, based on an estimated VAP relative risk reduction of 30%, an increased equipment cost of $14 per tube, and approximately $5,300 cost per case of VAP.[95] They found a cost savings of approximately $5,000 per case of VAP prevented. However, their VAP cost data were based on a predicted increased ICU stay attributable to VAP of 5 days.[18] In addition, this economic evaluation did not account for the potential airway complications associated with the use of the subglottic-suctioning ETT. The randomized trials of subglottic suctioning found no effect of this intervention on ICU stay, as confirmed by meta-analysis of intention-to-treat data.[57] Thus, the cost savings from subglottic suctioning may be limited to the cost generated by the diagnosis and treatment of VAP, which Shorr et al estimated at approximately $800.[95] This may be less than the cost of widespread use of the Hi-Lo Evac, particularly as VAP rates are reduced by other interventions, if the device is less effective than estimated, or if there are any complications associated with its use (see previous safety discussion). These concerns are even greater given that the manufacturer plans to replace the Hi-Lo Evac with the considerably more expensive polyurethane-cuffed Sealguard Evac.

Likewise, Shorr et al modeled the cost effectiveness of the silver-coated ETT (Agento IC, CR Bard, Murray Hill, New Jersey) in preventing VAP, using an assumed VAP relative risk reduction of 24%, a marginal cost of approximately $16,000 per VAP event, and an acquisition cost of $90 per tube for the Agento IC.[96] They predicted a savings of $12,840 per case of VAP prevented, which persisted in multivariate sensitivity analysis (95% CI $9,630–$16,356). However, similar to the previous analysis of the cost-effectiveness of the subglottic-suctioning ETT, the cost per VAP event was based on effects on multiple patient outcomes, including reduced duration of ventilation and hospital stay,[97] none of which were affected by use of the silver-coated ETT in the previously discussed randomized controlled trial.[32] Given the current extremely high acquisition cost of the silver-coated ETT, it is unlikely that this device would be cost saving if it has not been shown to be effective in improving patient outcomes related to VAP. At Harborview Medical Center in Seattle, Washington, where over 1,000 emergency intubations are performed per year, widespread and unselected use of the silver coated ETTs would add over $100,000/year to the budget for respiratory therapy equipment, an amount that is prohibitive, barring more conclusive cost-effectiveness data.

Summary

VAP is a pervasive and expensive nosocomial infection that is largely related to instrumentation of the airway with an endotracheal tube, followed by microaspiration of contaminated secretions. VAP prevention will probably be most effective via a multifaceted approach, which includes meticulous attention to basic infection-control methods during patient care, proper patient positioning, oral hygiene, and removal of the ETT as soon as indicated. Modification of the ETT to reduce microaspiration and/or biofilm formation may also play an important role in VAP prevention. However, despite numerous studies of various such interventions, there is insufficient evidence upon which to base strong recommendations, and important safety concerns remain regarding the use of the subglottic-suctioning ETT and the silver-coated ETT. Most importantly, cost-effectiveness data are lacking for these device-associated VAP-preventive measures. It is critical that future studies of ETTs designed to prevent VAP be adequately powered to demonstrate efficacy on important patient outcomes and safety, in addition to cost-effectiveness. These studies need to be conducted in a setting reproducing the clinical situation of emergency tracheal intubation, and in the context of a bundled approach to the prevention of VAP.

REFERENCES

1. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 1995;274(8):639-644.

2. Celis R, Torres A, Gatell JM, Almela M, Rodriguez-Roisin R, Agusti-Vidal A. Nosocomial pneumonia. A multivariate analysis of risk and prognosis. Chest 1988;93(2):318-324.
3. Langer M, Cigada M, Mandelli M, Mosconi P, Tognoni G. Early onset pneumonia: a multicenter study in intensive care units. Intensive Care Med 1987;13(5):342-346.
4. Chevret S, Hemmer M, Carlet J, Langer M. Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European Cooperative Group on Nosocomial Pneumonia. Intensive Care Med 1993;19(5): 256-264.
5. Cross AS, Roup B. Role of respiratory assistance devices in endemic nosocomial pneumonia. Am J Med 1981;70(3):681-685.
6. Cunnion KM, Weber DJ, Broadhead WE, Hanson LC, Pieper CF, Rutala WA. Risk factors for nosocomial pneumonia: comparing adult critical-care populations. Am J Respir Crit Care Med 1996;153(1): 158-162.
7. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. Crit Care Med 1999;27(5):887-892.
8. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in combined medical-surgical intensive care units in the United States. Infect Control Hosp Epidemiol 2000;21(8):510-515.
9. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165(7):867-903.
10. Cook DJ, Walter SD, Cook RJ, Griffith LE, Guyatt GH, Leasa D, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 1998;129(6):433-440.
11. Fagon JY, Chastre J, Domart Y, Trouillet JL, Pierre J, Darne C, Gibert C. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. Am Rev Respir Dis 1989;139(4):877-884.
12. Fagon JY, Chastre J, Vuagnat A, Trouillet JL, Novara A, Gibert C. Nosocomial pneumonia and mortality among patients in intensive care units. JAMA 1996;275(11):866-869.
13. Langer M, Mosconi P, Cigada M, Mandelli M. Long-term respiratory support and risk of pneumonia in critically ill patients. Intensive Care Unit Group of Infection Control. Am Rev Respir Dis 1989; 140(2):302-305.
14. Mosconi P, Langer M, Cigada M, Mandelli M. Epidemiology and risk factors of pneumonia in critically ill patients. Intensive Care Unit Group for Infection Control. Eur J Epidemiol 1991;7(4):320-327.
15. Eggimann P, Hugonnet S, Sax H, Touveneau S, Chevrolet JC, Pittet D. Ventilator-associated pneumonia: caveats for benchmarking. Intensive Care Med 2003;29(11):2086-2089.
16. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. N Engl J Med 1998; 338(12):791-797.
17. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 1993;94(3): 281-288.
18. Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun-Buisson C. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. Am J Respir Crit Care Med 1999;159(4 Pt 1):1249-1256.
19. Papazian L, Bregeon F, Thirion X, Gregoire R, Saux P, Denis JP, et al. Effect of ventilator-associated pneumonia on mortality and morbidity. Am J Respir Crit Care Med 1996;154(1):91-97.
20. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. Chest 2005;128(6):3854-3862.
21. Bercault N, Boulain T. Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit: a prospective case-control study. Crit Care Med 2001;29(12):2303-2309.
22. Craig CP, Connelly S. Effect of intensive care unit nosocomial pneumonia on duration of stay and mortality. Am J Infect Control 1984; 12(4):233-238.
23. Kappstein I, Schulgen G, Beyer U, Geiger K, Schumacher M, Daschner FD. Prolongation of hospital stay and extra costs due to ventilator-associated pneumonia in an intensive care unit. Eur J Clin Microbiol Infect Dis 1992;11(6):504-508.
24. Baker AM, Meredith JW, Haponik EF. Pneumonia in intubated trauma patients. Microbiology and outcomes. Am J Respir Crit Care Med 1996;153(1):343-349.
25. Collard HR, Saint S, Matthay MA. Prevention of ventilator-associated pneumonia: an evidence-based systematic review. Ann Intern Med 2003;138(6):494-501.
26. Kollef MH. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. Crit Care Med 2004;32(6):1396-1405.
27. D'Amico R, Pifferi S, Leonetti C, Torri V, Tinazzi A, Liberati A. Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. BMJ 1998; 316(7140):1275-1285.
28. DeRiso AJ 2nd, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest 1996; 109(6):1556-1561.
29. Nathens AB, Marshall JC. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. Arch Surg 1999;134(2):170-176.
30. Cook DJ, Laine LA, Guyatt GH, Raffin TA. Nosocomial pneumonia and the role of gastric pH. A meta-analysis. Chest 1991;100(1):7-13.
31. Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis. Crit Care Med 2007;35(2):595-602.
32. Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, et al. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial. JAMA 2008;300(7):805-813.
33. Ahrens T, Kollef M, Stewart J, Shannon W. Effect of kinetic therapy on pulmonary complications. Am J Crit Care 2004;13(5):376-383.
34. Orozco-Levi M, Torres A, Ferrer M, Piera C, el-Ebiary M, de la Bellacasa JP, Rodriguez-Roisin R. Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. Am J Respir Crit Care Med 1995;152(4 Pt 1):1387-1390.
35. Torres A, Serra-Batlles J, Ros E, Piera C, Puig de la Bellacasa J, Cobos A, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann Intern Med 1992;116(7):540-543.
36. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 1999; 354(9193):1851-1858.
37. Pneumatikos IA, Dragoumanis CK, Bouros DE. Ventilator-associated pneumonia or endotracheal tube-associated pneumonia? An approach to the pathogenesis and preventive strategies emphasizing the importance of endotracheal tube. Anesthesiology 2009;110(3):673-680.

38. Bouza E, Perez MJ, Munoz P, Rincon C, Barrio JM, Hortal J. Continuous aspiration of subglottic secretions in the prevention of ventilator-associated pneumonia in the postoperative period of major heart surgery. Chest 2008;134(5):938-946.
39. Torres A, Gatell JM, Aznar E, el-Ebiary M, Puig de la Bellacasa J, Gonzalez J, et al. Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. Am J Respir Crit Care Med 1995;152(1):137-141.
40. Johanson WG Jr, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with gram-negative bacilli. The significance of colonization of the respiratory tract. Ann Intern Med 1972;77(5): 701-706.
41. Cardenosa Cendrero JA, Sole-Violan J, Bordes Benitez A, Noguera Catalan J, Arroyo Fernandez J, Saavedra Santana P, Rodriguez de Castro F. Role of different routes of tracheal colonization in the development of pneumonia in patients receiving mechanical ventilation. Chest 1999;116(2):462-470.
42. Feldman C, Kassel M, Cantrell J, Kaka S, Morar R, Goolam Mahomed A, Philips JI. The presence and sequence of endotracheal tube colonization in patients undergoing mechanical ventilation. Eur Respir J 1999;13(3):546-551.
43. Bonten MJ, Gaillard CA, van Tiel FH, Smeets HG, van der Geest S, Stobberingh EE. The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. Chest 1994; 105(3):878-884.
44. Blunt MC, Young PJ, Patil A, Haddock A. Gel lubrication of the tracheal tube cuff reduces pulmonary aspiration. Anesthesiology 2001;95(2):377-381.
45. Pavlin EG, VanNimwegan D, Hornbein TF. Failure of a high-compliance low-pressure cuff to prevent aspiration. Anesthesiology 1975; 42(2):216-219.
46. Seegobin RD, van Hasselt GL. Aspiration beyond endotracheal cuffs. Can Anaesth Soc J 1986;33(3 Pt 1):273-279.
47. Torres A, el-Ebiary M, Gonzalez J, Ferrer M, Puig de la Bellacasa J, Gene A, et al. Gastric and pharyngeal flora in nosocomial pneumonia acquired during mechanical ventilation. Am Rev Respir Dis 1993; 148(2):352-357.
48. Garrouste-Orgeas M, Chevret S, Arlet G, Marie O, Rouveau M, Popoff N, Schlemmer B. Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. A prospective study based on genomic DNA analysis. Am J Respir Crit Care Med 1997;156(5):1647-1655.
49. Sottile FD, Marrie TJ, Prough DS, Hobgood CD, Gower DJ, Webb LX, et al. Nosocomial pulmonary infection: possible etiologic significance of bacterial adhesion to endotracheal tubes. Crit Care Med 1986;14(4):265-270.
50. Adair CG, Gorman SP, Feron BM, Byers LM, Jones DS, Goldsmith CE, et al. Implications of endotracheal tube biofilm for ventilator-associated pneumonia. Intensive Care Med 1999;25(10):1072-1076.
51. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science 1999;284(5418):1318-1322.
52. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet 2001;358(9276):135-138.
53. Hess DR. Noninvasive positive-pressure ventilation and ventilator-associated pneumonia. Respir Care 2005;50(7):924-931.
54. Kohlenberg A, Schwab F, Behnke M, Geffers C, Gastmeier P. Pneumonia associated with invasive and noninvasive ventilation: an analysis of the German nosocomial infection surveillance system database. Intensive Care Med 2010;36(6):971-978.
55. Alexiou VG, Ierodiakonou V, Dimopoulos G, Falagas ME. Impact of patient position on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. J Crit Care 2009;24(4):515-522.
56. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, Joore HC, van Schijndel RJ, van der Tweel I, Ramsay G, Bonten MJ. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. Crit Care Med 2006;34(2):396-402.
57. Dezfulian C, Shojania K, Collard HR, Kim HM, Matthay MA, Saint S. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. Am J Med 2005;118(1):11-18.
58. Dullenkopf A, Gerber A, Weiss M. Fluid leakage past tracheal tube cuffs: evaluation of the new Microcuff endotracheal tube. Intensive Care Med 2003;29(10):1849-1853.
59. Poelaert J, Depuydt P, De Wolf A, Van de Velde S, Herck I, Blot S. Polyurethane cuffed endotracheal tubes to prevent early postoperative pneumonia after cardiac surgery: a pilot study. J Thorac Cardiovasc Surg 2008;135(4):771-776.
60. Lorente L, Lecuona M, Jimenez A, Mora ML, Sierra A. Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. Am J Respir Crit Care Med 2007;176(11): 1079-1083.
61. Fletcher AJ, Ruffell AJ, Young PJ. The LoTrach system: its role in the prevention of ventilator-associated pneumonia. Nurs Crit Care 2008;13(5):260-268.
62. Kolobow T, Li Bassi G, Curto F, Zanella A. The Mucus Slurper: a novel tracheal tube that requires no tracheal tube suctioning. A preliminary report. Intensive Care Med 2006;32(9):1414-1418.
63. Li Bassi G, Curto F, Zanella A, Stylianou M, Kolobow T. A 72-hour study to test the efficacy and safety of the "Mucus Slurper" in mechanically ventilated sheep. Crit Care Med 2007;35(3):906-911.
64. Kolobow T, Berra L, Li Bassi G, Curto F. Novel system for complete removal of secretions within the endotracheal tube: the Mucus Shaver. Anesthesiology 2005;102(5):1063-1065.
65. Berra L, Curto F, Li Bassi G, Laquerriere P, Baccarelli A, Kolobow T. Antibacterial-coated tracheal tubes cleaned with the Mucus Shaver: a novel method to retain long-term bactericidal activity of coated tracheal tubes. Intensive Care Med 2006;32(6):888-893.
66. Bo H, He L, Qu J. [Influence of the subglottic secretion drainage on the morbidity of ventilator associated pneumonia in mechanically ventilated patients]. Zhonghua Jie He He Hu Xi Za Zhi 2000;23(8): 472-474. *Article in Chinese.*
67. Kollef MH, Skubas NJ, Sundt TM. A randomized clinical trial of continuous aspiration of subglottic secretions in cardiac surgery patients. Chest 1999;116(5):1339-1346.
68. Mahul P, Auboyer C, Jospe R, Ros A, Guerin C, el Khouri Z, et al. Prevention of nosocomial pneumonia in intubated patients: respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. Intensive Care Med 1992;18(1):20-25.
69. Smulders K, van der Hoeven H, Weers-Pothoff I, Vandenbroucke-Grauls C. A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. Chest 2002;121(3):858-862.
70. Valles J, Artigas A, Rello J, Bonsoms N, Fontanals D, Blanch L, et al. Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. Ann Intern Med 1995;122(3):179-186.
71. Zheng RQ, Lin H, Shao J, Chen QH, Lu NF, Yu JQ. [A clinical study of subglottic secretion drainage for prevention of ventilation associated pneumonia]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2008; 20(6):338-340. *Article in Chinese.*
72. Rello J, Diaz E, Roque M, Valles J. Risk factors for developing pneumonia within 48 hours of intubation. Am J Respir Crit Care Med 1999;159(6):1742-1746.
73. Girou E, Buu-Hoi A, Stephan F, Novara A, Gutmann L, Safar M, Fagon JY. Airway colonisation in long-term mechanically ventilated patients. Effect of semi-recumbent position and continuous subglottic suctioning. Intensive Care Med 2004;30(2):225-233.

74. Seneff MG, Zimmerman JE, Knaus WA, Wagner DP, Draper EA. Predicting the duration of mechanical ventilation. The importance of disease and patient characteristics. Chest 1996;110(2):469-479.
75. Berra L, De Marchi L, Panigada M, Yu ZX, Baccarelli A, Kolobow T. Evaluation of continuous aspiration of subglottic secretion in an in vivo study. Crit Care Med 2004;32(10):2071-2078.
76. Dragoumanis CK, Vretzakis GI, Papaioannou VE, Didilis VN, Vogiatzaki TD, Pneumatikos IA. Investigating the failure to aspirate subglottic secretions with the Evac endotracheal tube. Anesth Analg 2007;105(4):1083-1085.
77. Santos PM, Afrassiabi A, Weymuller EA Jr. Risk factors associated with prolonged intubation and laryngeal injury. Otolaryngol Head Neck Surg 1994;111(4):453-459.
78. Jaensson M, Olowsson LL, Nilsson U. Endotracheal tube size and sore throat following surgery: a randomized-controlled study. Acta Anaesthesiol Scand 2010;54(2):147-153.
79. Siobal M, Kallet RH, Kraemer R, Jonson E, Lemons D, Young D, et al. Tracheal-innominate artery fistula caused by the endotracheal tube tip: case report and investigation of a fatal complication of prolonged intubation. Respir Care 2001;46(10):1012-1018.
80. Deem S. Limited value of the cuff-leak test. Respir Care 2005; 50(12):1617-1618.
81. Francois B, Bellissant E, Gissot V, Desachy A, Normand S, Boulain T, et al. 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial. Lancet 2007;369(9567):1083-1089.
82. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep 2004;53(RR-3):1-36.
83. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171(4):388-416.
84. Lucangelo U, Zin WA, Antonaglia V, Petrucci L, Viviani M, Buscema G, et al. Effect of positive expiratory pressure and type of tracheal cuff on the incidence of aspiration in mechanically ventilated patients in an intensive care unit. Crit Care Med 2008;36(2): 409-413.
85. Young PJ, Pakeerathan S, Blunt MC, Subramanya S. A low-volume, low-pressure tracheal tube cuff reduces pulmonary aspiration. Crit Care Med 2006;34(3):632-639.
86. Young PJ, Burchett K, Harvey I, Blunt MC. The prevention of pulmonary aspiration with control of tracheal wall pressure using a silicone cuff. Anaesth Intensive Care 2000;28(6):660-665.
87. Miller MA, Arndt JL, Konkle M, Chenoweth CE, Flaherty KR, Hyzy RC. Polyurethane cuff endotracheal tube to prevent ventilator-associated pneumonia in an academic hospital (abstract). Am J Respir Crit Care Med 2009:179;A1731. http://ajrccm.atsjournals.org/cgi/reprint/179/1meetingabstracts/a1731.pdf. *Accessed May 21, 2010.*
88. Berra L, Curto F, Li Bassi G, Laquerriere P, Pitts B, Baccarelli A, Kolobow T. Antimicrobial-coated endotracheal tubes: an experimental study. Intensive Care Med 2008;34(6):1020-1029.
89. Berra L, De Marchi L, Yu ZX, Laquerriere P, Baccarelli A, Kolobow T. Endotracheal tubes coated with antiseptics decrease bacterial colonization of the ventilator circuits, lungs, and endotracheal tube. Anesthesiology 2004;100(6):1446-1456.
90. Berra L, Kolobow T, Laquerriere P, Pitts B, Bramati S, Pohlmann J, et al. Internally coated endotracheal tubes with silver sulfadiazine in polyurethane to prevent bacterial colonization: a clinical trial. Intensive Care Med 2008;34(6):1030-1037.
91. US Food and Drug Administration. Public health notice: potential hypersensitivity reactions to chlorhexidine-impregnated medical devices. March 11, 1998. http://www.fda.gov/medicaldevices/safety/alertsandnotices/publichealthnotifications/ucm062306. *Accessed June 8, 2010.*
92. Rello J, Afessa B, Anzueto A, Arroliga AC, Olson ME, Restrepo MI, et al. Activity of a silver-coated endotracheal tube in preclinical models of ventilator-associated pneumonia and a study after extubation. Crit Care Med 2010;38(4):1135-1140.
93. Rello J, Kollef M, Diaz E, Sandiumenge A, del Castillo Y, Corbella X, Zachskorn R. Reduced burden of bacterial airway colonization with a novel silver-coated endotracheal tube in a randomized multiple-center feasibility study. Crit Care Med 2006;34(11):2766-2772.
94. Young PJ, Basson C, Hamilton D, Ridley SA. Prevention of tracheal aspiration using the pressure-limited tracheal tube cuff. Anaesthesia 1999;54(6):559-563.
95. Shorr AF, O'Malley PG. Continuous subglottic suctioning for the prevention of ventilator-associated pneumonia: potential economic implications. Chest 2001;119(1):228-235.
96. Shorr AF, Zilberberg MD, Kollef M. Cost-effectiveness analysis of a silver-coated endotracheal tube to reduce the incidence of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 2009;30(8): 759-763.
97. Warren DK, Shukla SJ, Olsen MA, Kollef MH, Hollenbeak CS, Cox MJ, et al. Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center. Crit Care Med 2003;31(5):1312-1317.