

## VIEWPOINT

# The tracheal tube: gateway to ventilator-associated pneumonia

Parjam S Zolfaghari<sup>1\*</sup> and Duncan LA Wyncoll<sup>2</sup>

### Abstract

Ventilator-associated pneumonia (VAP) is a major healthcare-associated complication with considerable attributable morbidity, mortality and cost. Inherent design flaws in the standard high-volume low-pressure cuffed tracheal tubes form a major part of the pathogenic mechanism causing VAP. The formation of folds in the inflated cuff leads to microaspiration of pooled oropharyngeal secretions into the trachea, and biofilm formation on the inner surface of the tracheal tube helps to maintain bacterial colonization of the lower airways. Improved design of tracheal tubes with new cuff material and shape have reduced the size and number of these folds, which together with the addition of suction ports above the cuff to drain pooled subglottic secretions leads to reduced aspiration of oropharyngeal secretions. Furthermore, coating tracheal tubes with antibacterial agents reduces biofilm formation and the incidence of VAP. In this Viewpoint article we explore the published data supporting the new tracheal tubes and their potential contribution to VAP prevention strategies. We also propose that it may now be against good medical practice to continue to use a 'standard cuffed tube' given what is already known, and the weight of evidence supporting the use of newer tube designs.

### Introduction

Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring in a mechanically ventilated patient after 48 hours of endotracheal intubation [1]. Despite significant advances in managing intubated patients, VAP remains a common and occasionally fatal complication in the ICU [2]. A systematic review of published data since

1990 showed the incidence of VAP to be 10 to 20%, with a possible two-fold increase in mortality attributable to VAP [3]. The ICU length of stay was also significantly increased by a mean of 6.1 days with an attributable cost of \$10,019 per case [3]. A recent Canadian study estimated an additional 4.3 ICU days attributable to VAP, occupying 2% of all ICU days and an estimated national cost of CAN\$43 million per year [4]. Similar findings were reported by a North American study with increased unadjusted ICU length of stay and mortality in patients with VAP (50% mortality in VAP patients versus 34% in non-VAP) with an estimated \$11,897 attributable cost [5]. Furthermore, the burden of VAP takes up a significant portion of antibiotic dispensing in the ICU [6] and may well be a contributor to the development of multi-resistant bacteria [7].

Importantly, many units are recently reporting a reduction in VAP incidence following implementation of various prevention measures, as well as programs that increase compliance with such care bundles [8-10].

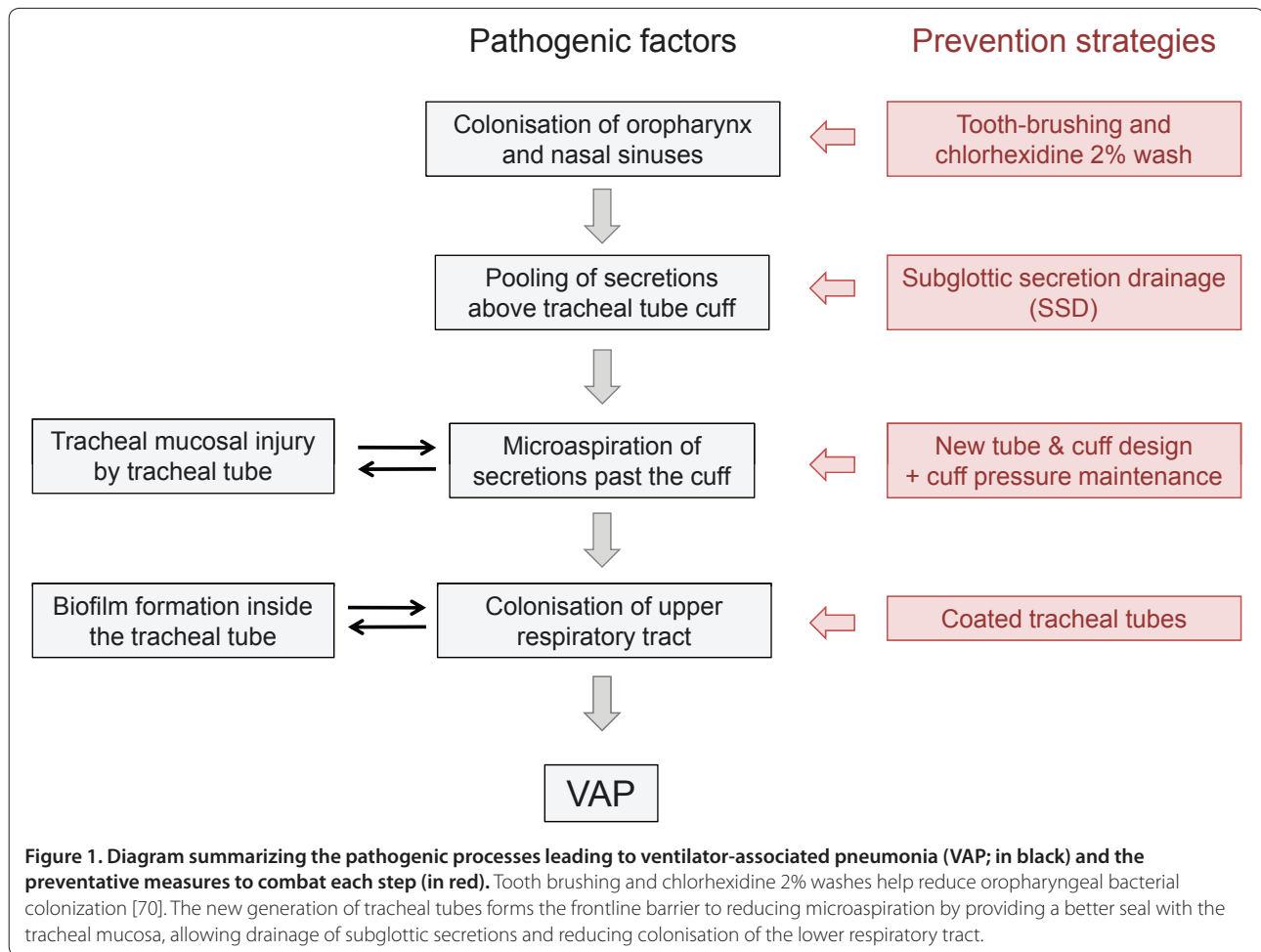
### Pathogenesis

The pathogenesis of VAP mainly stems from the introduction of microbial pathogens by microaspiration past the tracheal tube cuff and into the lower respiratory tract (Figure 1). Subsequent colonization and overwhelming of the host mechanical, humoral and cellular defence mechanisms lead to the development of VAP [11]. The tracheal tube forms the essential first part of this mechanistic pathway by breaching the anatomic barriers formed by the glottis and larynx. Suppression of the cough reflex as a result of sedation further hampers natural reflexes [2]. The oropharynx, nasal sinuses and the stomach have been proposed as potential reservoirs of infective material [11]. Furthermore, bacterial biofilm formation on the inner aspect of the tracheal tube is another potential portal of bacteria [12]. But perhaps more importantly, this biofilm formation, which takes place within days of intubation, functions to maintain bacterial colonization of the trachea [13]. The biofilm is inaccessible to antibiotic therapy unless aerosolised, which likely reduces bacterial shedding, but does not lead to full eradication and may even promote antibiotic

\*Correspondence: [parjamz@yahoo.co.uk](mailto:parjamz@yahoo.co.uk)

<sup>1</sup>London Deanery, Guy's and St Thomas' NHS Trust, Lambeth Palace Road, London SE1 7EH, UK

Full list of author information is available at the end of the article



**Figure 1. Diagram summarizing the pathogenic processes leading to ventilator-associated pneumonia (VAP; in black) and the preventative measures to combat each step (in red).** Tooth brushing and chlorhexidine 2% washes help reduce oropharyngeal bacterial colonization [70]. The new generation of tracheal tubes forms the frontline barrier to reducing microaspiration by providing a better seal with the tracheal mucosa, allowing drainage of subglottic secretions and reducing colonisation of the lower respiratory tract.

resistance [14]. The fact that the NASCENT trial, using a silver-coated tracheal tube, showed a significant reduction in microbiologically diagnosed VAP suggests that intraluminal biofilm and the intratracheal route of infection contribute significantly to the aetiology of VAP [15].

This article explores the contribution of the tracheal tube to the development of VAP and looks at how the emergence of new designs may help prevent this complication. A question is posed: is it good medical practice to continue to use a 'standard cuffed tube' given what is already known?

### The contribution of the tracheal tube cuff

The main function of the tracheal tube cuff is to produce a seal between the tube and the tracheal mucosa in order to allow the institution of positive pressure ventilation. It has become apparent, however, that pooling and leakage around the endotracheal tube cuff leads to aspiration of contaminated oropharyngeal secretions, stomach contents and bacteria into the trachea and the lower respiratory tract [16]. This is supported by the finding that persistent

intra-cuff pressures of  $<20$  cmH<sub>2</sub>O in intubated patients are independently associated with pneumonia [17]. Furthermore, frequent microaspiration of stomach contents as evidenced by the presence of pepsin in sequential tracheal aspirates is an independent predictor of pneumonia in intubated patients [18]. These findings highlight the importance of adequate sealing of the lower respiratory tract from soiling by oropharyngeal secretions.

Some small studies have looked at the use of automated devices to control cuff pressures but have produced varying results. In an 'underpowered' randomised controlled trial where cuff pressures were maintained either by an automatic device at 25 to 30 cmH<sub>2</sub>O, or 8-hourly nurse-adjusted cuff pressures, no difference in the incidence of VAP was observed [19]. Conversely, a more recent proof of concept study showed reduced pepsin and micro-aspiration in the tracheal samples and lower microbiologically confirmed VAP in patients where an automated device was used to maintain cuff pressures [20].

Interestingly, despite correctly pressurised cuffs in commonly used standard high-volume low-pressure

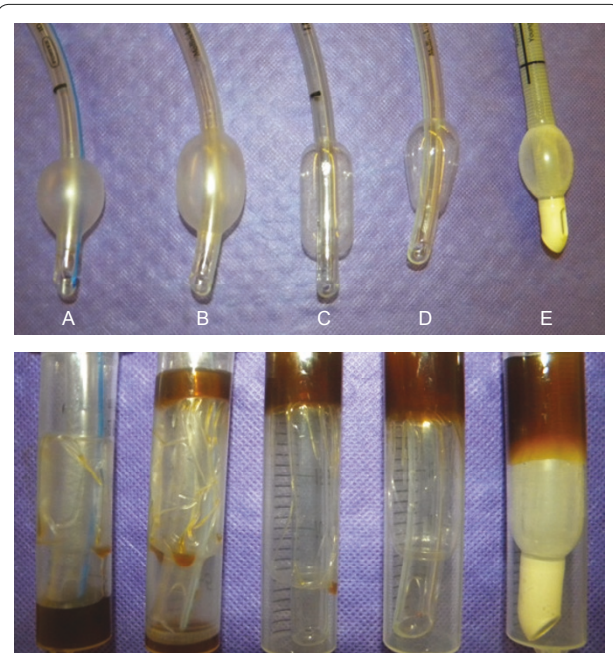
tubes, microaspiration often takes place [21-23]. This stems from the basically flawed design of these cuffs. The diameter of the fully inflated cuff is up to twice as large as the diameter of the tracheal lumen, so that once inflated to the correct pressure in the trachea, these cuffs remain only partially inflated and result in the formation of folds along the cuff that then channel oropharyngeal secretions into the trachea [21]. Bench studies have clearly demonstrated these findings (Figure 2) and identified major design features that influence the size of these leaky folds and channels.

#### Excess cuff material and shape of the cuff

Newer tracheal tube cuff designs such as the Lo-Trach™ (Intravent) low-volume low-pressure cuff and the Microcuff™ tube (Kimberly-Clark) have shown promising results with significant reduction in leakage of fluid placed above the cuffs [24-26]. The Microcuff™ tube has an elongated cylindrical-shaped cuff that results in a fully inflated cuff *in situ* with minimal excess cuff material at acceptable intracuff pressures of 20 to 30 cmH<sub>2</sub>O. The fully inflated cuff leads to limited or even absence of channel formation and the shape of the cuff results in a larger surface area in contact with the trachea. Microaspiration of blue dye placed above the cuff (as demonstrated by bronchoscopy) was also shown to be reduced and delayed in patients intubated with the Mallinckrodt/Covidien SealGuard™ tube with an inverted pear-shaped (conical) cuff [27]. This pear-shaped design was first described in 1999 by Young and Blunt [28], and subsequently shown to provide better sealing properties across a wider range of tracheal diameters when compared to the cylindrical-shaped cuff [29].

#### Tracheal tube cuff material

A major advance in the tracheal tube cuff design has been the introduction of thinner (7 μm thick) polyurethane (PU) material [29]. These cuffs have consistently been shown to form narrower folds/channels with reduced leakage than tubes with thicker (50 μm) polyvinyl chloride (PVC) cuffs [21,25,30]. Clinical studies have also confirmed reduced leakage of subglottic material [27], reduced pepsin levels in tracheal secretions [31], and lower rates of nosocomial post-operative pneumonia in patients following cardiac surgery randomised to endotracheal tubes with cuffs made from PU [32]. A retrospective analysis of intubated patients following the introduction of tracheal tubes with PU cuffs showed a reduction in VAP from 5.3 to 2.8 per 1,000 ventilator days [33]. In an elegant *in vitro* study of six commercially available tracheal tubes, Zanella and colleagues [30] showed that all cuffs made from PVC (be they conical or cylindrical in shape) demonstrated significant leakage over a 24-hour period, except when a positive



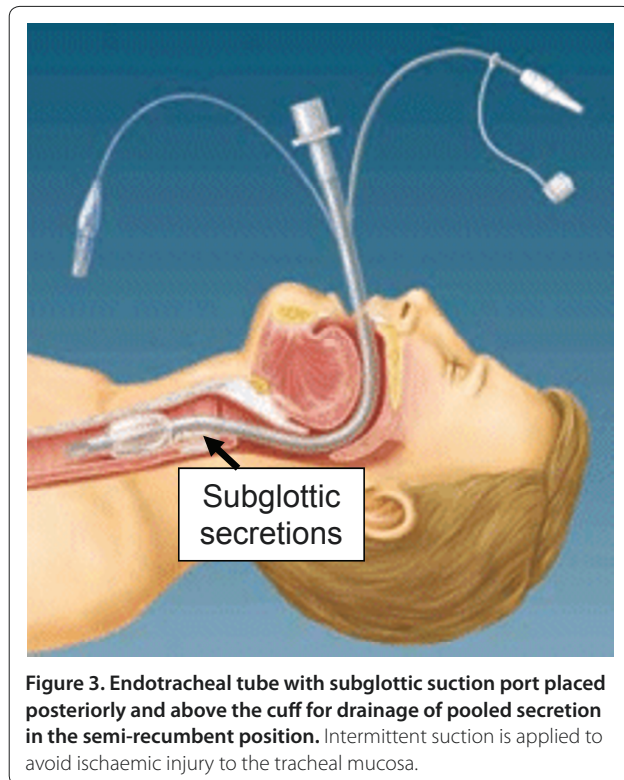
**Figure 2. Photograph of various bench tested tracheal tubes of different designs showing the internal channels created and the leak of liquid material past the cuff.** Tube cuffs A and B are made from polyvinyl chloride, and cuffs C and D with thin polyurethane (C has an elongated cylindrical shape and D is a tapered cuff design). Tube E is the LoTrach™ ET tube. (Photograph courtesy of Dr Peter Young, Kings Lynn, UK.)

end-expiratory pressure (PEEP) of 15 cmH<sub>2</sub>O was applied in addition. On the other hand, double-layered cuffs made of Guayule-latex and PU cuffs provided significantly improved performances with minimal leakage at zero PEEP and none at 5 cmH<sub>2</sub>O. Interestingly, there was no difference in performance between the cylindrical and conically shaped cuffs made from PU (Microcuff™, cylindrical versus Mallinckrodt/Covidien SealGuard™, conical).

#### Subglottic secretion drainage and ventilator-associated pneumonia

Removal of oropharyngeal secretions that have pooled above the tracheal tube cuff by subglottic secretion drainage (SSD) further reduces microaspiration [34-37] (Figure 3). Specially designed tracheal tubes are widely available, with a separate lumen or lumens that open above the cuff and allow intermittent or continuous drainage of the pooled secretions. In 2005, a meta-analysis examining five prospective studies using SSD showed a 50% reduction in the incidence of pneumonia in patients randomised to SSD [38]. This effect was more pronounced in those who were intubated for more than 72 hours and for early onset VAP. A reduction in the length of mechanical ventilation and ICU stay (2 and





3 days, respectively) makes this a favourable intervention, and has now been included in many national VAP prevention bundles [39]. Further convincing evidence has also been published since this 2005 meta-analysis [34,36,37].

However, the uptake of SSD into clinical practice has been slow [40], and this is likely because of (i) conflicting clinical trial evidence, (ii) safety concerns surrounding laryngeal/tracheal damage caused by the stiffer nature of these tubes, (iii) suction damage to the tracheal mucosa, (iv) the higher cost of the tubes, and (v) the fact that the studies often only show that early VAP is reduced. Of nine prospective, randomised controlled studies of SSD, six did not look at adverse effects of SSD, two reported no adverse events and one reported a significant increase in the risk of laryngeal oedema requiring re-intubation in patients intubated with an SSD tube [13,41]. Furthermore, Dragoumanis and colleagues [42] described herniation of tracheal mucosa into the dorsal SSD suction port of the first generation Hi-Lo<sup>®</sup> Evac endotracheal tube (Hi-Lo Evac, Mallinckrodt, Athlone, Ireland), resulting in failure of subglottic suction and the risk of mucosal injury due to tissue ischaemia. Of concern also is the fact that in sheep, significant tracheal mucosal injury has been observed with continuous aspiration of subglottic secretions [43].

These observations have encouraged the development of second and third generation tube designs, which have

overcome some of these concerns. In some tubes the position of the SSD suction port has been placed adjacent to the tracheal tube cuff, lifting its opening away from the tracheal mucosa. Also, improved cuff designs that produce a better tracheal seal (tapered/conical PU or low-volume controlled-pressure cuffs) have allowed hourly intermittent suctioning, instead of continuous suction [37]. Avoiding continuous suctioning strongly suggests that ischaemic lesions of the posterior tracheal wall can now be avoided. The LoTrach<sup>™</sup> tube has further addressed these concerns by incorporating three subglottic suction ports adjacent to the tracheal tube cuff, making subglottic suctioning more efficient and less traumatic. Furthermore, its flexible design conforms to the shape of the upper airway, potentially reducing laryngeal injury [24].

In order to accommodate the SSD channel into the wall of the tracheal tube, the outer diameter of the tube in some of the designs has had to be enlarged by approximately 1 mm on average and some designs are slightly stiffer. This needs to be taken into consideration when sizing these tracheal tubes in order to avoid laryngeal injuries, and is a potential area for future refinement in design.

### Tracheal tube biofilm management

Microbial biofilms are present on the luminal surface of endotracheal tubes of all patients ventilated in the ICU and form within hours of tracheal intubation, becoming abundant at 96 hours [12,44,45]. Whilst the exact sequence of tube colonisation and infection is unclear, it is thought that the microbial biofilm may act as a reservoir of pathogens causing recurrent infections [45]. Adair and colleagues [12] showed that 70% of patients with VAP had the identical pathogen isolated from their tracheal tube and lower respiratory tract. Furthermore, biofilms are associated with developing microbial bacterial resistance [46].

Endotracheal tubes coated with anti-microbial silver hydrogel showed delayed and reduced bacterial colonisation in a mechanically ventilated animal model [47]. In one of the largest multi-centre prospective studies of VAP prevention (NASCENT study), Kollef and colleagues [15] compared rates of VAP in 2,003 patients randomised to intubation with either a silver-coated tube (Agento IC, CR Bard Inc., Covington, GA, USA) or the Hi-Lo Endotracheal Tube (Mallinckrodt, St Louis, MO, USA). This study showed a statistically significant relative risk reduction of 36% in the occurrence of VAP in patients intubated with silver-coated tubes, but failed to show a reduction in length of mechanical ventilation, ICU stay or mortality. Interestingly, the VAP rates in this study were lower than previously quoted rates (5 to 10% versus the 10 to 20% in other studies frequently quoted).

### **Tracheotomies and ventilator-associated pneumonia**

Another frequently debated point is the influence of the timing of tracheotomy on the development of VAP. While Rumbak and colleagues [48] showed a significant reduction in the development of VAP with early tracheotomy (within 48 hours of mechanical ventilation) versus delayed tracheotomy (after 14 to 16 days), a later but larger multicentre study showed no difference in the rate of pneumonia in patients that underwent early tracheotomy versus patients who had more prolonged endotracheal intubation [49]. The largest multicentre study on this question showed no difference in the incidence of VAP with early tracheotomy (after 6 to 8 days of tracheal intubation) versus later tracheotomy (after 13 to 15 days) [50]. One interpretation of these observations is that while a patient has any artificial cuffed airway in place (whether endotracheal or tracheostomy tube), this predisposes to some degree of microaspiration and biofilm formation on the inner lumen, which increases the risk for VAP. However, many of the novel design features already mentioned are also now being incorporated into new tracheostomy tubes.

### **Other strategies**

It is clear that reducing the incidence of VAP requires new strategies incorporating guidelines, resources, education and leadership [51,52]. Patient positioning, sedation holds, adequate and frequent oral hygiene, SSD, maintenance of cuff pressures and guidelines on stress ulcer prophylaxis are listed in a high impact care bundle to prevent VAP that has recently been published [39]. The integration of new and proven technology into this strategy will further improve its success. Current evidence highlighting the role of tracheal tubes in the pathogenic processes leading to the development of VAP may be ethically difficult to ignore. The newer tracheal tubes with tapered or cylindrical cuffs made from thin PU material and incorporating subglottic ports for intermittent suction of subglottic secretions should be an addition to this VAP bundle. Furthermore, automating cuff pressures using devices such as the disposable Portex PressureEasy® cuff controller or the Venner™ PneuX PY™, comprising the Venner tracheal seal monitor device in conjunction with the LoTrach™ ET Tube and LoTrach™ T Tube, would limit exposure to low (<20 cmH<sub>2</sub>O) and high (>30 cmH<sub>2</sub>O) cuff pressures (that is, by continuous monitoring and maintaining of cuff pressure). Interestingly, in a study discussed earlier, using a constant cuff pressure controller device failed to show statistically significant reduction in VAP when compared to an 8-hourly nurse monitored method (22% VAP in intervention group versus 29% in control group) [19]. However, the investigators used the leaky PVC high-volume

low-pressure cuffed tubes for both groups, and highlight the point that using single interventions to reduce VAP is unlikely to be as successful as multiple interventions [53].

### **Attributable mortality and ventilator-associated pneumonia**

Some clinicians remain concerned about the lack of effect on mortality in the published studies of VAP reduction interventions. Mortality is clearly the hardest end-point for clinical trials in the critically ill, but softer outcomes such as VAP should not be ignored [54]. It is important to distinguish the consequences of VAP from the progression of an underlying illness, and a key variable is the attributable mortality of developing VAP. The literature is not clear in answering this question, since it may well depend on the severity of underlying disease and acute respiratory failure as a result of pneumonia [55,56], the case-mix of the population [57], the adequacy of initial empiric treatment [58], and the infecting agent [59]. Methodological differences, such as variables and covariates used to match control patients in the various studies, add to this uncertainty [3].

The attributable mortality of VAP is widely quoted as 0 to 36% [60-63]. By way of illustration, let us consider a hypothetical VAP trial involving 800 patients, and a proposed new intervention that reduces VAP by 50%. In this population the control arm event rate (VAP) is about 20%, and the 28-day mortality is also about 20%. If the trial showed that VAP was reduced to 10% in the intervention arm (a 50% reduction), and if it was assumed that the attributable mortality due to VAP is about 10%, then at very best mortality could only be reduced by a statistically non-significant (but clinically important) four patients. Hence the reason why so many of the current studies are not powered for mortality.

### **Should the newer tubes be used for all intubated patients admitted to the ICU?**

The incidence of VAP increases with length of mechanical ventilation [64,65], and the evidence presented above points towards more benefit being gained by patients intubated for prolonged periods [15,38]. Various tools have been proposed to predict length of mechanical ventilation, but these are only applicable at 24 to 48 hours following institution of mechanical ventilation [66,67]. It could therefore be argued as reasonable to intubate all patients admitted to the ICU who are expected to be intubated for longer than 24/48 hours with a newer generation tracheal tube.

### **Can we justify the higher cost of the newer tubes?**

When compared to the old generation (leaky) tubes without subglottic suction, which cost about \$2 each, and considering that each new case of VAP leads to an

increased estimated cost of approximately \$5,000 to \$26,000 [5], then it would be financially beneficial to pay a lot more for the 'interface' (that is, the tube) between the ventilator and the patient - an 'interface' that can potentially contribute to or prevent VAP. A cost-analysis performed by Shorr and colleagues [68] found a \$12,840 reduction in hospital costs per single case of VAP prevented as a result of introducing \$90 silver-coated tubes compared to using standard \$2 non-coated tubes, making this a very financially viable intervention. In fact, the break-even cost of the silver-coated tubes was calculated to be \$388. Even 'back of the envelope' conservative calculations that assume the cost of a VAP to be just \$5,000 would support an investment of \$49 per patient in a new intervention if it merely reduces the rate of VAP by just 1% absolute!

## Conclusion

In a recent editorial, Valles, Blanch and Respiratorias [69] applied Sutton's law to interventions that prevent VAP. Willy Sutton was a prolific bank robber, having stolen \$2 million over his career. When asked by a reporter why he continued to rob banks, he replied, 'Because that is where the money is'. Application of Sutton's law - 'Go where the money is' - to the paradigm of VAP prevention strongly favours multi-faceted strategies aimed at reducing aspiration of oropharyngeal secretions. With the increasing weight of evidence pointing at the role of the tracheal tube design and maintenance of adequate cuff pressures, is it really good medical practice to continue to use 'standard cuffed tubes'?

## Abbreviations

PEEP, positive end-expiratory pressure; PU, polyurethane; PVC, polyvinyl chloride; SSD, subglottic secretion drainage; VAP, ventilator-associated pneumonia.

## Competing interests

PSZ has no competing interests. In the past 3 years, DW has acted as a paid consultant or given lectures on VAP for Covidien, Kimberly-Clark and Bard.

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## Author details

<sup>1</sup>London Deanery, Guy's and St Thomas' NHS Trust, Lambeth Palace Road, London SE1 7EH, UK. <sup>2</sup>Guy's and St Thomas' NHS Trust, Lambeth Palace Road, London SE1 7EH, UK.

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