CRITICAL CARE

REVIEW

Novel preventive strategies for ventilator-associated pneumonia

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Introduction

Ventilator-associated pneumonia (VAP) is a complication of mechanical ventilation and is defined as the occurrence of pneumonia in patients undergoing mechanical ventilation for at least 48 hours. Clinical suspicion of VAP arises when new infiltrates are present on chest x-ray, and at least one of the following is present: Fever, leukocytosis, or purulent tracheo-bronchial secretions.

The incidence of VAP reported in the literature ranges from 15 to 20% [1]. However, the real incidence of VAP is difficult to assess, given the extreme variability of the diagnostic criteria for pneumonia, which often rely on bronchoscopic procedures. The specific mortality attributable to VAP is also debated. The reported VAP-associated mortality ranges from 20 to 70%. Patients with VAP are often critically ill, and survival may be affected both by underlying conditions and the new-onset VAP. A recent study demonstrated a relatively limited attributable intensive care unit (ICU)-mortality of VAP, about 1–1.5%, when adjusting for severity of co-existing diseases [2]. In the last few years, various strategies have been investigated in order to reduce the incidence of VAP. Reducing the duration of intubation, oral and endotracheal tube (ETT) care, positioning, and ETT modifications are aspects that may have a role in the prevention of VAP. Many of these strategies have been incorporated into 'VAP bundles', a set of treatments implemented simultaneously to reduce VAP incidence. Recent studies suggest that the use of bundle treatments can result in substantial reductions in rates of VAP [3].

In this chapter, we will present some novel VAP prevention strategies, explaining the possible mechanisms by which they may be clinically beneficial in reducing the incidence of VAP. A summary of these novel strategies is given in Table 1.

Reduce duration of intubation

The risk of developing VAP increases with prolonged intubation, and reintubation is a known risk factor [4]. This fact suggests that the presence of the ETT, although necessary for the survival of the patient, interferes with the normal physiological mechanisms that maintain the airways free of bacterial contamination. When the ETT is in place, the cough reflex is impaired and normal mucociliary flow is blocked by the inflated cuff. The ETT itself allows bacteria to drain into the trachea and distal airways leading to pneumonia. Intubated patients may be more prone to develop VAP as compared to tracheostomized patients because the ETT keeps the trachea and the oropharynx in communication, acting as a bridge for bacteria to move toward the dependent airways. Aspiration of pathogens from the oropharynx in patients with subglottic dysfunction may occur both during extubation and reintubation. The rate of reintubation can be reduced by a variety of measures, including avoiding accidental removal of the ETT, improving planned extubations with weaning protocols designed to improve extubation success, and use of non-invasive ventilation (NIV).

On the basis of the observation that the ETT creates a communication between the oropharynx and airways, early tracheostomy has been advocated as one of the possible preventive measures for VAP. Although tracheostomy reduces duration of ventilation and ICU stay [5], a recent randomized trial failed to demonstrate a reduction in VAP incidence when early tracheostomy (6–8 days after intubation) was performed [6].

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Table 1. Most relevant clinical studies supporting the use of novel strategies to prevent ventilator-associated pneumonia (VAP)

First Author [ref]	Journal, Year	Implemented strategy	Summary
Morris [3]	Crit Care Med, 2011	VAP bundle	Before-and-after study, showing that implementation of a 4 item bundle (head elevation, oral chlorhexidine gel, sedation interruptions and a ventilator weaning protocol) reduced VAP rate
Terragni [6]	JAMA, 2010	Tracheostomy	Randomized trial showing that VAP incidence was not significantly different comparing early (7 days after intubation) to late (14 days) tracheostomy
Nseir [20]	Am J Respir Crit Care Med, 2011	Control of ETT cuff pressure	Randomized trial showing VAP rate reduction using a pneumatic device to maintain ETT cuff inflating pressure constant
Lacherade [22]	Am J Respir Crit Care Med, 2010	Intermittent SSD system	Randomized trial; the use of a SSD system resulted in a significant reduction of VAP incidence, including late-onset VAP
Kollef [27]	JAMA, 2008	Silver coated ETT	Randomized trial showing that VAP rates were lower with silver coated ETTs, as compared to standard ETTs
Miller [33]	J Crit Care, 2011	Polyurethane ETT cuff	Retrospective assessment of VAP rate with polyurethane vs. PVC cuffed ETTs, favoring the use of polyurethane ETT cuff
Siempos [44]	Crit Care Med, 2010	Probiotics	Meta-analysis of randomized controlled trials showing an association between the use of probiotics and reduced VAP incidence

ETT, endotracheal tube; SSD, subglottic secretion drainage.

Since the ETT is believed to be involved in the pathogenesis of VAP, many clinicians avoid intubation when possible. The early use of NIV with the aim of avoiding intubation may be worth considering, particularly in fragile patients. Although a reduction in VAP incidence has not been demonstrated, the early use of continuous positive airway pressure (CPAP) reduced the need for ICU admission and ventilatory support in a randomized trial in 40 patients with hematological malignancies [7].

Another strategy to indirectly prevent the occurrence of VAP is the reduction of sedative administration. Reduced administration of sedatives is associated with shorter ICU stays and fewer days of intubation. Although no data are currently available to prove that VAP occurrence is decreased by reduced sedative administration, daily suspension of sedative drugs has been suggested as a preventive measure. Similarly, the implementation of a protocol for ventilator weaning may be useful to prevent VAP, as a result of the reduction in unneeded days on the ventilator and need for reintubation [8].

Oral care

After prolonged intubation, tracheal colonization is frequently demonstrated, and the gastric enzyme, pepsin, may be detected in trachea-bronchial aspirates. In patients affected by VAP, the same bacteria are often present in the distal airways and in the stomach or oropharynx [9]. This suggests that the draining of saliva or gastric contents to below the ETT cuff determines the colonization of the tracheal mucosa, possibly leading to pneumonia.

The use of acid-suppressive medications and the subsequent increase in gastric pH allows bacterial growth in the stomach, increasing the risk of colonization in case of aspiration of gastric contents. A cohort study of more than 60,000 patients showed an increased risk of hospital-acquired pneumonia when acid-suppressive medications were used [10]. However, no definitive recommendation can be pro vided about the use of acid-suppressive medications in relation to VAP in the ICU setting, and stress-ulcer prophylaxis is still suggested as part of the bundle treatments for VAP prevention published by the Institute for Healthcare Improvement.

To reduce the bacterial load of the fluids that drain into the airways when the ETT is in place, selective digestive tract decontamination (SDD) has been proposed. Decontamination with antibiotics reduces the incidence of VAP [11], but it is not currently recommended because of concern for possible selection of resistant bacteria. Oropharyngeal rinse with chlorhexidine was shown to be effective in reducing tracheal colonization and VAP incidence in a randomized, placebo-controlled study on nearly 400 patients [12], and is now widely used as standard of care for the intubated patient.

Airway care

Draining of secretions around the ETT cuff is not the only way for bacteria to reach the distal airways and, therefore, lead to pneumonia. Another possible mechanism is the inoculation of bacteria through the inner lumen of the tube. To reduce this occurrence, proper hand hygiene by healthcare workers is a preventive measure that should always be implemented when treating intubated patients [13]. With time and despite routine suctioning, the inner surface of the ETT becomes covered by a layer of mucus and cells soon after

intubation, which increases with duration of ETT use. This layer of 'biofilm' is an optimal environment for growth of a wide range of bacterial species [14], through which antibiotics penetrate with difficulty. Biofilm forms on both the internal and the external surface of the ETT. The presence of biofilm is particularly marked in proximity to the cuff, where secretions accumulate. Bacteria in the biofilm may detach to inoculate the lower airways leading to the development of pneumonia [15]. The importance of biofilm in the pathogenesis of VAP is suggested by the finding that about 70% of patients with VAP show the same pathogens isolated from the biofilm and the tracheal secretions [16].

Tube care

Care of the inner lumen of the ETT might be a new strategy to prevent VAP. The Mucus Shaver is a device able to keep the ETT free of secretions and biofilm by mechanically removing the deposits. Recently, a randomized clinical study confirmed the efficacy of the device in intubated patients, showing a marked reduction of secretions and contaminants in the treatment group [17]. Although the removal of biofilm with this device may be helpful, no data are yet available showing a reduction in VAP incidence.

Cuff care

Maintaining adequate cuff pressure is vital to reduce draining of oropharyngeal and gastric secretions around the ETT. An inflating cuff pressure less than 20 cmH_2O may favor secretion drainage, while a pressure greater than 30 cmH_2O may result in mucosal injury [18]. Despite routine cuff pressure controls, variations in ETT cuff pressure frequently occur, exposing patients to increased risk of VAP [19]. Several devices have been developed to constantly monitor and adjust the ETT cuff inflating pressure. A recent randomized study of 122 patients showed lower levels of pepsin in the tracheal aspirates of the group treated with a device maintaining the cuff pressure constant, confirming the effectiveness of these devices in reducing micro-aspiration. Moreover, the treatment group had lower VAP rate as compared to controls, with no evident adverse effects [20].

Tube modifications

A number of approaches have been investigated to reduce VAP incidence through modifications of the ETT. These efforts have focused on systems for drainage of subglottic secretions, coating of the ETT with antibacterial materials, and the sealing capacity of the cuff.

Subglottic secretion drainage

Despite tracheal suctioning, secretions tend to accumulate around the ETT cuff, where they cannot be removed. Subglottic secretion drainage systems usually consist of an accessory aspiration conduit opening above the ETT cuff and a vacuum source. Secretions may be continuously or intermittently removed from the subglottic space. Continuous aspiration has been shown to cause mucosal injuries in animal models [21], therefore intermittent aspiration systems are generally preferred. Use of an ETT equipped with a subglottic secretion drainage system has been associated with a reduction in VAP incidence. A multicenter study of more than 300 patients showed a decrease in VAP rate in the group treated with intermittent secretion drainage [22]. The beneficial effects of secretion drainage lasted over time, with no significant adverse events. A recent meta-analysis including nearly 2500 patients confirmed the efficacy of ETTs equipped with subglottic secretion drainage systems in preventing VAP, shortening ICU stay and reducing days of ventilation [23].

A different method of secretion drainage is the Mucus Slurper, a modified tube equipped with multiple aspirating holes opening on the tip of the ETT. Secretions are aspirated intermittently in the early expiratory phase, keeping the ETT lumen and the proximal trachea free from secretions [24]. However, no clinical data are available and the effectiveness of this device in VAP prevention remains to be determined.

ETT coating

The inner surface of coated ETT tubes may be covered by a thin layer of anti-microbial agent(s), to prevent the formation of biofilm and bacterial colonization. Among several coating agents, silver seems to be feasible: It is biologically compatible, easy to employ, and effective in reducing tracheal colonization and bacterial growth in animal models [25]. The silver coating has bacteriostatic properties: Silver ions penetrate into the microbial membrane interfering with DNA synthesis, thereby preventing cell replication. Other agents have shown even greater *in vitro* antibacterial activity as compared to silver, but their clinical use remains to be investigated [26].

Several clinical trials have been conducted evaluating the efficacy of VAP prevention using silver-coated ETTs. In the North American Silver-Coated Endotracheal Tube (NASCENT) study, the use of a silver-coated ETT was associated with lower rates of VAP and of late-onset VAP in more than 2000 patients [27]. Hence, the use of antibacterial coating seems suitable to treat patients expected to be ventilated for more than 48 hours, possibly resulting in VAP prevention and cost-effectiveness [28].

Cuff seal and shape

Modified cuffs have been proposed to improve tracheal sealing and reduce secretion drainage. Traditional hi-volume/low-pressure cuffs are made of polyvinylchloride

(PVC). The surface of a traditional ETT cuff folds when inflated in the trachea, creating potential channels through which secretions can drain and reach the subglottic space. *In vitro* models have shown passage of fluids around a traditional ETT cuff already 1 minute after the beginning of the experiment, whereas modified cuffs provided significantly better sealing [29]. The principal cuff modifications involve changes in cuff shape and materials employed. The tapered shape seems to provide better sealing as compared to the classical cylindrical shape [30], possibly because the tapered cuff maintains better contact with the tracheal wall, resulting in less folding of the cuff surface. The use of materials other than PVC, such as polyurethane, lycra, silicone or latex, also result in better sealing *in vitro* [31]; however, no definitive clinical data are available regarding the material of choice to prevent VAP. ETTs equipped with polyurethane cuffs protected against early postoperative pneumonia in a population of cardiac surgery patients, but the effect on VAP rate was not investigated [32]. A retrospective study on more than 3000 patients showed an association between the use of a polyurethane cuff and a decrease in VAP incidence [33]. A randomized clinical trial showed VAP rate reduction for patients intubated with an ETT equipped with both a subglottic secretion drainage system and a polyurethane cuff, but the contribution of the polyurethane cuff to preventing VAP in this combined system is unclear [34].

Positioning

Positioning of the intubated patient is believed to be a relevant factor for the development of VAP. The 45° semi-recumbent position is widely recommended, but recent data suggest that the lateral position may be superior to prevent VAP.

Semi-recumbent position

The rationale for keeping patients in the semi-recumbent position is that elevation of the head above the stomach reduces the aspiration of gastric reflux. A clinical cross-over trial demonstrated a greater amount of gastric content in the airways when patients were kept supine compared to a period of head elevation [35]. A later randomized trial showed the effectiveness of the semi-recumbent position in reducing VAP incidence as compared to the supine position [36]. On the basis of these data, many guidelines recommend the semi-recumbent position as a preventive measure for VAP. Recently, however, some investigators have questioned whether this position is optimal for VAP prevention [37,38]. In the semi-recumbent position, aspiration of subglottic secretions across the tracheal cuff is not prevented and secretions in the lower respiratory tract cannot be cleared. The effects of gravity on aspiration in the semi-recumbent position may be most pronounced in patients intubated for a prolonged period and especially during suctioning because of the pressure drop within the respiratory system with this maneuver. Interestingly, a study using an animal model of long term mechanical ventilation showed that mucus flow was reversed toward the lungs in the semi-recumbent position and that it could be drained out of the lungs in the horizontal position [39]. The animals did not develop VAP if the tracheal tube and trachea were maintained slightly below horizontal. A pilot study of 10 intubated patients placed in the lateral horizontal position compared to 10 patients in the semi-recumbent position showed that the lateral position was feasible and did not cause serious adverse events [40]. Furthermore, the authors found more ventilator free days and a trend toward a lower incidence of VAP in the lateral horizontal position group. A multinational trial is currently ongoing to corroborate these benefits [41].

Kinetic therapy

Immobility of the intubated critically ill patient may impair mucociliary clearance [42]. Mechanical rotation of patients with 40° turns (kinetic therapy) may improve pulmonary function more than the improvement in function achieved via standard care (i.e., turning patients every 2 hours). Kinetic therapy is believed to improve movement of secretions and to avoid the accumulation of mucus in dependent lung zones. A meta-analysis of 10 studies found that kinetic therapy reduced VAP incidence but did not reduce the duration of mechanical ventilation, ICU stay or mortality [43]. Many of the studies of kinetic therapy are limited by small sample sizes and VAP diagnoses made on a clinical basis without microbiological cultures. In addition, many of the patients in studies of kinetic therapy had complications, which might be associated with the therapy, including intolerance to rotation, unplanned extubation, loss of vascular access and arrhythmias. Based on the limitations of the existing studies and potential complications, a definitive recommendation regarding the use of kinetic therapy cannot be made at this time.

Other measures

Probiotics

Probiotics are commercially available preparations of live non-pathogenic microorganisms administered to improve microbial balance resulting in health benefits for the host. Administration of probiotics has been advocated as a means of preventing a variety of infections including VAP in the ICU. The potential beneficial effect of probiotics in prevention of VAP may be in their competition with VAP-producing microorganisms in the oropharynx and stomach. In addition, it has been suggested

that the benefits of probiotics might be explained by their immunomodulatory properties. A recent meta-analysis of randomized controlled trials comparing probiotics to control in patients undergoing mechanical ventilation found a lower incidence of VAP in the probiotics group compared with control [44]. Administration of probiotics was also found to be beneficial in reducing length of stay in the ICU and colonization of the respiratory tract by *Pseudomonas aeruginosa*.

Early and enteral feeding

Enteral feeding may predispose to aspiration of gastric contents and the subsequent development of VAP. It has been suggested that placement of a post-pyloric feeding tube might reduce the risk of aspiration and VAP. A meta-analysis of seven studies found that post-pyloric feeding showed a trend toward lower incidence of VAP and mortality than gastric feeding [45]; however, the differences were not statistically significant. A more recent randomized trial showed a similar non-significant trend [46]. Therefore, a definitive recommendation regarding the routine use of post-pyloric feeding cannot be made. The timing of initiation of enteral feeding has also been reported to be associated with the development of VAP. In a large retrospective multicenter analysis, early feeding (i.e., within 48 hours of onset of mechanical ventilation) was found to be associated with an increased risk of VAP, although ICU and hospital mortality were decreased in the early feeding group [47].

Conclusion

Many factors contribute to the development of VAP. A number of strategies have been proposed for VAP prevention; however, only a few have been demonstrated to be effective, and many others still need evaluation in large randomized clinical trials before definitive recommendations can be made. Among others, modifications to the ETT (e.g., subglottic secretion drainage systems, antimicrobial coating, alternative cuff shapes and materials), continuous maintenance of proper cuff inflating pressures, ETT secretion removal, patient positioning in the lateral horizontal position, kinetic therapy, and administration of probiotics are measures worthy of consideration and further study in the ongoing battle to reduce the rates of VAP.

Abbreviations

CPAP, continuous positive airway pressure; ETT, endotracheal tube; ICU, intensive care unit; NASCENT, North American Silver-Coated Endotracheal Tube; NIV, non-invasive ventilation; PVC, polyvinylchloride; SDD, selective digestive tract decontamination; SSD, subglottic secretion drainage; VAP, ventilator-associated pneumonia.

Competing interests

The authors declare that there are no competing interests.

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